MMP-032

New Jersey Department of Health
Medicinal Marijuana Program
PO 360
Trenton, NJ 08625-0360

MEDICINAL MARIJUANA PETITION
(N.J.A.C. 8:64-5.1 et seq.)

INSTRUCTIONS

This petition form is to be used only for requesting approval of an additional medical condition or treatment thereof as a "debilitating medical condition" pursuant to the New Jersey Compassionate Use Medical Marijuana Act, N.J.S.A. 24:6I-3. Only one condition or treatment may be identified per petition form. For additional conditions or treatments, a separate petition form must be submitted.

NOTE: This Petition form tracks the requirements of N.J.A.C. 8:64-5.3. Note that if a petition does not contain all information required by N.J.A.C. 8:64-5.3, the Department will deny the petition and return it to petitioner without further review. For that reason the Department strongly encourages use of the Petition form.

*This completed petition **must** be postmarked **August 1 through August 31, 2016** and sent by **certified mail** to:*

New Jersey Department of Health
Office of Commissioner - Medicinal Marijuana Program
Attention: Michele Stark
369 South Warren Street
Trenton, NJ 08608

Please complete each section of this petition. If there are any supportive documents attached to this petition, you should reference those documents in the text of the petition. If you need additional space for any item, please use a separate piece of paper, number the item accordingly, and attach it to the petition.

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1. **Petitioner Information**

Name: [redacted]
Street Add
City, State
Telephone
Email Add

2. **Identify the medical condition or treatment thereof proposed. Please be specific. Do not submit broad categories (such as "mental illness").**

Multisystem Atrophy (MSA); Complex Tremors;Neurogenic bladder and bowel:Ataxia (wheelchair with three point (see attached.)

3. **Do you wish to address the Medical Marijuana Review Panel regarding your petition?**

☒ Yes, in Person
☐ Yes, by Telephone
☐ No

4. **Do you request that your personally identifiable information or health information remain confidential?**

☐ Yes
☒ No

If you answer "Yes" to Question 4, your name, address, phone number, and email, as well as any medical or health information specific to you, will be redacted from the petition before forwarding to the panel for review.

RECEIVED
SEP 2 2016
OFFICE OF THE CHIEF OF STAFF

5. **Describe the extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition.**

   MSA is a fully accepted condition by neurology and ENT department. ICD 10 code G90.3

6. **If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, describe the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition.**

   Suprapubic catheter causing severe bladder spasm resulting in excruciating pain. Medications: Oxybutnin 5 mg every 6 hour for spasm; Pain medicine: Percocet. Vicodan, Tyleno #3 all have limited efficacy. Belladonna and Opium suppositories has long range efficacy but results in 18-24 hours of sleeping.

7. **Describe the extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living.**

   Besides above statement severe tremors interfere with all aspects of activities of daily living (ADL), e.g., eating, drinking, dressing, bathing, mobility, loss of voice, unable to use augmented communiation devices. Need constant care.

8. **Describe the availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof.**

   There are no available conventional medical therapies.

9. **Describe the extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof.** *[**Note:** You may attach articles published in peer-reviewed scientific journals reporting the results of research on the effects of marijuana on the medical condition or treatment of the condition and supporting why the medical condition should be added to the list of debilitating medical conditions.]*

   There are numerous articles supporteing the use of cannabinoids for intractable paing and tremors in Parkinson's Disease and Multiple sclerosis. These share common root causes such as dysfunction of the nigrastriatal pathway. My disease (cerebellar degeneration) is too rare for large studies (<7000 in US)

   Articles in supprot of Cannabinoids for control of pain and tremors included.

10. **Attach letters of support from physicians or other licensed health care professionals knowledgeable about the condition. List below the number of letters attached and identify the authors.**

.Letter attached from Dr. Kevin Hunter, Neurologist.

I certify, under penalty of perjury, that I am 18 years of age or older; that the information provided in this petition is true and accurate to the best of my knowledge; and that the attached documents are authentic.

[redacted] Date 5/31/16

AtlantiCare

A MEMBER OF GEISINGER HEALTH SYSTEM

318 S. Chris Gaupp Drive
Galloway, NJ 08205
609-404-9900 Phone
609-404-3653 Fax

[redacted]

8/29/2016

To whom it may concern,

[redacted] is a patient of mine he suffers from multiple system atrophy - a parkinsonian condition causing tremor, polyneuropathy and migraine headache. The patient also informs me that she suffers from pain due to various nonneurologic conditions including postsurgical pain and bladder spasms. Her pain is been refractory to multiple medications. She may benefit from use of cannabinoid treatment of pain.

Please do not hesitate to contact me should there be any further questions in this regard

Sincerely,

Kevin E. Hunter, MD
Director, Division of Neurology
Atlanticare Physicians Group

Editorial

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MMP-032
Correspondance

Marijuana in Pain Management

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Editorial

Marijuana, the magic herb, has always reaped the attention of public, medicals and scientists as well. Since ages, this herb was employed in multiple medicinal aspects from headache to surgery. The effects of the psychoactive properties verged with a magical power [1].

There are certain types of pain, especially chronic types, that has no pain cure and if present, they may have debilitating side effects. Therefore, new and safer pain relievers are needed. The ancient complementary medicine always provides a library to search. Marijuana can be a promising source for analgesic medications.

Marijuana or Cannabis sativa contains numerous compounds labelled as cannabinoids, in addition to terpenoids and flavonoids. It offers a set of advantages, compared to opiates. It lacks the un-preferable side effects and the tolerance liability. It was first traced when Davies et al. discovered that a distillate of Cannabis plant extract is more potent than morphine at intravenous administration to rats [2, 3].

There are other cannabinoids which are synthetic cannabinoids, such as nabilone, WIN55, 212-2, and ajulemic acid, that similarly bind to CBR and the endogenous cannabinoids or namely endocannabinoids, which are endogenously synthesized in the brain. A new class has been introduced, which include inhibitors of the endocannabinoid breakdown responsible enzymes (FAAH, MGL) [4].

Clinical reports showed the effectiveness of isolated THC in reducing pain sensation and even reports have shown that pain may be present at the same intensity but in less important and discomforting way. Chronic pain syndromes, such as multiple sclerosis and paraplegia were first approved to be treated with medical cannabis. Cannabinoids reduce nausea, vomiting, and appetite loss as well as pain. The euphoric effects could benefit people with anxiety-producing painful disorders such as AIDS or cancer [5-7].

It is implicated that the action of cannabinoids is receptor mediated centrally and peripherally, where CBRs are abundantly distributed in the nociceptive periaqueductal grey matter and along the spinal cord. Moreover kappa opioid receptors were found to be involved in the anti-nociceptive actions. Endocannabinoids are released in fear or stress conditions to suppress pain. Researchers have hypothesized that pathological pain can arise, at least in part, from a dysfunction of the endocannabinoid system.

The two major cannabinoids, THC and CBD, do not modulate COX-1 or COX-2 at therapeutic dosages so skipping the deleterious side effects of non-steroidal anti-inflammatory drugs (NSAIDS), e.g., gastrointestinal ulceration and bleeding. Besides, no abuse incidents were reported with the use of approved medications such as Sativex.

Currently, there are a number of approved medical cannabinoids either synthetic e.g. nabilone or cannabis extract (Sativex) or the active ingredient, THC (Marinol).

In the late nineties, seizure disorders like epilepsy and multiple sclerosis were introduced as cannabis-treatable conditions. It was until 2010 to be widely approved in many states and countries for multiple sclerosis, HIV/AIDS, cancer and spastic diseases. Parkinson disease and spinal cord tissue damage were added to the medical indications [8].

NMDA mediated pain conditions such as migraine could have benefit from cannabinoids, where THC was found to reduce NMDA response and NMDA-produced secondary hyperalgesia. Additionally, THC was demonstrated to stimulate β-endorphins thus acting by two different pathways. In addition, other cannabis constituents showed bonus pain reducing activities such as cannabichromene, cannabigerol, myrcene, or even aromatic terpenoids [9].

Relying on the fact that factors such as anxiety, mood, and personality can all influence pain intensity, cannabis can have an outstanding action in this perspective.

Cannabinoids 2016;11(special issue):1-18

Review

Review on clinical studies with cannabis and cannabinoids 2010-2014

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Abstract

In 2010 a review by Hazekamp and Grotenhermen covered controlled clinical trials of the years 2006-2009 on cannabis-based medicines, which followed the example of the review by Ben Amar (2006). The current review reports on the more recent clinical data available from 2010-2014. A systematic search was performed in the scientific database of PubMed, focused on clinical studies that were randomized, (double) blinded, and placebo-controlled.

The key words used were: cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador, nabiximols and Sativex. For the final selection, only properly controlled clinical trials were retained. Open-label studies were excluded, except if they were a direct continuation of a study discussed here.

Thirty-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Based on the clinical results, cannabinoids present an interesting therapeutic potential mainly as analgesics in chronic neuropathic pain and spasticity in multiple sclerosis. But a range of other indications also seem promising. CBD (cannabidiol) emerges as another valuable cannabinoid for therapeutic purposes besides THC.

Keywords: cannabinoids, cannabis, therapeutic potential, controlled clinical trial, efficacy, safety, cannabidiol

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Introduction and Method

This review presents an overview of clinical trials performed with cannabis or cannabinoids in the period 2010-2014. It is a follow-up of a previous review on clinical studies done in the period 2005-2009 (Hazekamp and Grotenhermen 2010), which itself was inspired by a review by Ben Amar (2006) covering the period 1975 to June 2005. The current review presents large studies with several hundreds of participants, but also small controlled studies on new indications, such as Crohn's disease. It also highlights the new interest in the therapeutic value of CBD (Cannabidiol), a non-psychotropic plant-derived cannabinoid.

The methodology of this review has been adopted from Ben Amar (2006) and Hazekamp and Grotenhermen (2010). In order to assess the current knowledge on the therapeutic potential of herbal Cannabis, isolated phyto-cannabinoids, and medicinal preparations directly inspired by phyto-cannabinoids, a systematic search was performed in the scientific database of *PubMed*. Hosted by the U.S. National Library of Medicine, this database contains about 20 million scientific publications from the field of life sciences and biomedical information.

The period screened was from January 1, 2010 up to December 31, 2014. The search focused on clinical studies that were randomized, (double) blinded,

Table 1. Number of studies and patients reviewed

Pathology	Number of studies found	Total number of patients included
Chronic pain	11	1211
Multiple sclerosis	6	1515
Irritable bowel syndrome	3	133
Crohn's disease	1	21
Appetite and chemosensory perception	2	28
Chemotherapy-induced nausea and vomiting	1	16
Pulmonary disease	1	9
Cannabis dependence	2	207
Anxiety	3	94
Psychosis	1	42
Parkinson's disease	1	21
Total	**32**	**3297**

and placebo-controlled or controlled by a standard medication. The keywords used were: *cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador, nabiximols* and *Sativex*.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded, except when they were a direct continuation of a clinical trial discussed in this paper. The research included the works and data available in English. No papers in other languages were found or excluded. Studies are presented per indication, in chronological order.

A range of different cannabis-based products are described in the studies presented in this review. For the ease of the less experienced reader, these preparations are briefly discussed below:

Inhaled cannabis refers to the dried flowers (buds) of the female plant of Cannabis. This herbal product is also commonly known as marijuana or marihuana. The main way to administer cannabis as a recreational drug is by smoking, which is also the way most medicinal users consume it. For clinical trials, most often these materials are analyzed for their content (in % of dry weight) of THC and in some studies inhalation was performed by using a vaporizer.

THC, or delta-9-tetrahydrocannabinol, or dronabinol, is the pharmacologically and toxicologically most relevant constituent found in the Cannabis plant, producing a myriad of effects in animals and humans (Hazekamp and Grotenhermen 2010). Pure THC (dronabinol) can be derived from natural sources (extraction from cannabis plants) or produced synthetically. Chemically, THC belongs to a group of closely related compounds known as cannabinoids, and they are commonly considered the main bioactive components of Cannabis. Up to date, more than 100 different cannabinoids have been described, but only a few of the major ones have been characterized for their biological activities, including cannabidiol (CBD, see below), cannabinol (CBN), and tetrahydrocannabivarin (THCV) (ElSohly and Gul 2014).

Dronabinol is the INN (international non-proprietary name) of the isomer of delta-9-tetrahydrocannabinol that is present in the cannabis plant, the (-)-trans-isomer. This is the only naturally occurring of the four possible isomers.

CBD, or cannabidiol, is the major non-psychotropic cannabinoid found in Cannabis. It has shown anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and anti-psychotic activity and (when co-administered) may reduce the psychoactive effects of THC (Russo and Guy 2006; Grotenhermen et al. 2015).

Marinol® (Solvay Pharmaceuticals, Belgium) is a synthetic version of dronabinol. It is formulated as a capsule containing synthetic dronabinol in sesame oil. In the US it is indicated for the treatment of anorexia associated with weight loss in patients with AIDS, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments. The patent on Marinol expired in 2011, which opened the way for generic preparations of dronabinol, which are now available.

Nabilone (Valeant Pharmaceuticals International, USA) is a synthetic analogue of THC which binds to the cannabinoid type 1 receptor (CB1r). In Canada, the United States, the United Kingdom and Mexico, Nabilone is marketed as Cesamet®. It is registered for treatment of chemotherapy-induced nausea and vomiting in patients that have not responded to conventional anti-emetics. It is also used for other medical conditions.

Sativex® (United States Adopted Name (USAN), nabiximols) (GW Pharmaceuticals, UK) is a cannabis-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in approximately a 1:1 ratio, delivered in an oromucosal (into the mouth) spray. Because of the use of whole extracts, ballast components are also present, such as minor cannabinoids and terpenes. Sativex has been approved in Canada as adjunctive treatment for

spasticity and neuropathic pain in adults with multiple sclerosis (MS) and in cancer pain. Sativex has been approved in most European countries for the treatment of spasticity in adult patients with MS. Each spray contains 2.7 mg THC and 2.5 mg CBD.

Cannador® (Society for Clinical Research, Germany, and Weleda, Switzerland) is an oral capsule containing a whole plant extract, with standardized THC content and a CBD amount controlled to lie within a fixed narrow range with a THC:CBD ratio of about 2:1. It has been used in several clinical trials. It has been clinically tested for reduction of muscle stiffness, spasms and associated pain in Multiple Sclerosis, for cachexia in cancer patients and for post-operative pain management. The development of Cannador as an approved medication has now been abandoned and no further clinical studies are planned.

Summary of clinical trials

1. Chronic pain

1.1. Oral cannabis

Compared to the years 2005-2009, a significant increase could be observed in the number of patients studied with regard to the impact of oral cannabis on chronic pain. The two extracts used were Sativex (THC/CBD oromucosal spray containing nearly equal amounts of CBD and THC) and a similar cannabis extract mainly containing THC (THC oromucosal spray). The analgesic effects were not always clearly visible in these studies. Selvarajah et al. (2010) investigated the effects of the THC/CBD oromucosal spray on 30 patients with painful diabetic peripheral neuropathy (DPN) in a placebo-controlled, double-blind, between-group study. After 12 weeks of treatment with divided doses up to four times a day no significant difference in pain scores could be observed between THC/CBD oromucosal spray and placebo, although both groups responded to treatment. Depression was suggested as a possible confounder, since depressed patients displayed higher baseline pain scores, as well as a more profound placebo effect, compared to other subjects. As a result, it was suggested that depression should be taken into account when designing future clinical studies into DPN.

In contrast, another between-group study with 177 patients (Johnson et al. 2010) found that THC/CBD oromucosal spray was effective in chronic cancer pain relief when added to standard opioid therapy. Specifically, the Intent-To-Treat (ITT; all randomized participants who received at least one dose of the medication and displayed efficacy data) responder analysis indicated that doses of THC/CBD oromucosal spray up to 48 sprays a day in a period of 2 weeks resulted in about twice as many patients displaying at least 30% reduction in pain intensity scores (generally considered to represent a clinically important difference in chronic pain trials), as compared to placebo and THC-only oromucosal spray. Treatment-related adverse events (AEs) were tolerable and mainly included somnolence, dizziness and nausea. No treatment-related serious adverse events (SAEs) were observed. In sum, it was concluded that the synergy between THC and CBD results in higher analgesic efficacy than THC alone.

Based on the promising results, an open-label follow-up study was conducted (Johnson et al. 2013) in order to evaluate the long-term safety and tolerability of THC/CBD oromucosal spray and THC oromucosal spray in patients with terminal cancer-related pain. In total 43 subjects who completed the randomized controlled trial described above (Johnson et al. 2010) took part in this multi-center experiment – 39 subjects received THC/CBD oromucosal spray for a median of 25 days and 4 received THC oromucosal spray for a median of 151.5 days. The medication doses were self-titrated by the patients, with a maximum of 48 sprays per day. Consequently, due to the variability of conditions present in this study, data regarding the comparison of the drugs' efficacy should be treated with caution. In spite of that, the results showed that up to 5 weeks of treatment with THC/CBD oromucosal spray was effective for pain reduction and sleep quality improvement. In addition, out of the patients receiving THC/CBD oromucosal spray, 10% of subjects administered the study medication for more than 6 months and 5% administered it for over a year without any need to increase the dosage. As a result, it was suggested that THC/CBD oromucosal spray remains effective and tolerable for some patients for an extended period of time. As for treatment-related AEs, the most frequently observed in the THC/CBD oromucosal spray group were dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. In the four patients administered THC oromucosal spray, AEs included dizziness, headache, and an episode of memory impairment. Only three (8%) subjects from the THC/CBD oromucosal spray condition experienced a SAE that was considered to be related to study medication.

A different between-group study focusing on the impact of different doses of Sativex on chronic cancer pain only partially confirmed the analgesic effect of the THC/CBD spray as an add-on to standard opioid therapy (Portenoy et al. 2012). Specifically, none of the doses administered (low: 1-4 sprays a day; medium: 6-10 sprays a day; high: 11-16 sprays a day) was able to achieve 30% pain score reduction during the 5-week treatment phase, compared to placebo. However, the secondary responder analysis of mean daily pain from baseline to end of the trial pointed to a general analgesic effect of Sativex. Analysis of the individual treatment conditions showed that this effect was present only in the low and medium dose groups, but, surprisingly, not in the high dose group. In addition, the AEs were particularly problematic in case of the high dose condition. Out of 90 patients from this group, only 59 (66%) were able to finish the study.

However, this was partially also due to the fact that the study population was terminally ill, resulting in the death of 20.9% patients in the nabiximols condition and 17.6% in the placebo group. None of these deaths was considered to be medication-related.

Sativex produced mixed results in the treatment of neuropathic pain due to multiple sclerosis according to a between-group study with 339 patients, researchers of the Pain and Anaesthesia Research Centre of St Bartholomew's Hospital in London, UK, reported (Langford et al. 2013). Patients received the product in addition to their current medication, which failed to control their pain adequately. The trial consisted of two phases. In phase A 167 participants received the THC/CBD oromucosal spray and 172 received placebo in a double-blind manner for 14 weeks. In phase B 58 patients continued to receive either placebo or Sativex for 18 weeks to investigate maintenance of treatment effects.

In phase A 50 per cent of cannabis patients experienced pain reduction of more than 30 per cent compared to 45 per cent of placebo patients, which was not significantly different. However, during phase B Sativex was superior to placebo, with 57 per cent of patients receiving placebo failing treatment versus only 24 per cent of patients from the active treatment group. In addition, mean pain intensity and sleep quality improved in the treated group compared to placebo. Regarding AEs, during phase A 15 patients (9%) in the active condition and 12 patients (7%) in the placebo condition stopped using study medication due to, mainly, gastrointestinal and nervous system disorders. In phase B the most frequent AEs were fatigue, somnolence, vertigo, dizziness and nausea. However, in total 6 patients (10%) stopped applying their study medication due to AEs during the open-label part of phase B. Moreover, two patients from the active treatment group (10%) experienced a SAE: serious disorientation and suicidal ideation, respectively. Suicidal ideation was also observed in case of one patient (5%) from the placebo condition. Authors concluded that "the results of the current investigation were equivocal, with conflicting findings in the two phases of the study. (...) These findings suggest that further studies are required to explore the full potential of THC/CBD spray in these patients."

A between-group study by Serpell et al. (2014) was conducted to examine the efficacy of Sativex on peripheral neuropathic pain (PNP) associated with allodynia. In total 246 patients took part in the experiment, with 128 receiving THC/CBD oromucosal spray and 118 receiving placebo for 14 weeks. The dosage was self-titrated with a maximum of 24 sprays per day. The main analysis included two sets of subjects: the ITT and per protocol (PP; participants who displayed no protocol deviations from the primary parameter) analysis sets. The ITT analysis demonstrated at least 30% reduction in pain intensity scores in 34 patients (28%) in the active group, in contrast to 19 patients (16%) in the placebo group. This was further supported by the PP analysis, which showed the same effect in 27 subjects (36%) from the active group, compared to 18 subjects (20%) in the placebo condition. It was concluded that THC/CBD oromucosal spray produced a clinically significant improvement in average daily pain in a significantly greater percentage of patients, as compared to the placebo group. The treatment-related AEs were mostly mild to moderate in severity and included mostly nervous system, gastrointestinal, administration site and psychiatric effects. In total, 97 (76%) subjects in the active condition and 56 (47%) participants in the placebo group experienced at least one treatment-related AE. In total, 25 (20%) patients receiving THC/CBD oromucosal spray and 8 (7%) patients receiving placebo withdrew from the study due to AEs.

The latest (in the period covered by this review) investigation into the effect of Sativex on chronic pain was conducted by Lynch et al. (2014). It was a crossover study that included 16 patients with chemotherapy-induced neuropathic pain. Subjects self-administered their dose, with a maximum of 12 sprays per day. After establishing an optimal dose, it was fixed for the remainder of the study. The treatment lasted 4 weeks and was followed by a 2-week washout period before starting to use the other medication (placebo or Sativex). The results were not clear: there was no significant difference in pain scores between the two conditions. Nonetheless, five patients reported a borderline significant reduction in pain scores when receiving active treatment, compared to using placebo. Keeping in mind the small sample size and pilot nature of the study, this was considered a promising result for future studies into this topic. Although treatment-related AEs were reported by most subjects, they were not particularly problematic with fatigue, dizziness, dry mouth and nausea being the main ones.

1.2. Oral THC

Turning the attention of this review towards the study of isolated cannabinoids, a crossover experiment was conducted to directly compare the analgesic efficacy of oral THC (dronabinol) and diphenhydramine – an approved treatment for central neuropathic pain which may display some side-effects similar to those of THC (Rintala et al. 2010). Seven patients with traumatic spinal cord injury (SPI) received each medication for 8 weeks (which included a 12-day up-titration and 9-day down-titration phase at the start and end of this time period, respectively, a 7-day stabilization phase, and a 28-day maintenance phase), followed by a 7-day washout phase before starting to use the second drug. The doses started with 5 mg of THC or 25 mg of diphenhydramine per day, reaching a maximum daily dosage of 20 mg of THC or 75 mg of diphenhydramine, respectively. The results did not show any significant differences between the two treatments, while the AEs were similar for both medications. The most frequent AEs included dry mouth, constipation, fatigue, and drowsiness for both

drugs. All subjects reported fatigue at least once while using diphenhydramine, while fewer than three-fifth of the patients reported fatigue at least once after being administered THC. Infrequent reports of feeling high, dizziness, abdominal discomfort, confusion, lack of coordination, and nausea were found only in the THC condition. Only two treatment-related severe AEs were reported: one related to abdominal discomfort (THC) and the second one regarding drowsiness (diphenhydramine). It was concluded that THC was as effective as diphenhydramine for pain relief, while side-effects were comparable.

1.3. Inhaled cannabis

Regarding research into the analgesic potential of herbal cannabis, a crossover study was conducted (Ware et al. 2010) in order to investigate the safety and efficacy of smoked cannabis on chronic neuropathic pain. Twenty-one patients who completed the trial received a random dose of 25 mg cannabis material (obtained from Prairie Plant Systems Inc., and the United States National Institute of Drug Abuse) with varying potency (placebo, 2.5%, 6%, 9.4% THC), using a titanium pipe for smoking. Each dose was administered three times daily in single inhalations for the period of 5 days, followed by a 9-day washout phase before starting to use the subsequent dose. The results showed that only the 9.4% THC dose was effective at decreasing pain and improving sleep, compared to placebo. Treatment-related AEs were quite mild with headache, dry eyes, burning sensation in areas of neuropathic pain, numbness, cough and dizziness as the most common ones in the 9.4% THC condition. In addition, there were single reports on euphoria and feeling "high" in each of the active drug conditions (2.5%, 6%, 9.4% THC). It was concluded that the highest cannabis dose administered 3 times daily by inhalation may be a well-tolerated and effective treatment for chronic neuropathic pain.

Another study compared the subjective effects on pain management induced by smoked cannabis versus oral THC (Issa et al. 2014). Thirty chronic non-cancer pain patients received placebo, 10 mg or 20 mg of oral THC in a crossover manner. A separate comparison sample of 20 healthy individuals was administered smoked cannabis (1.99% and 3.51% THC) in a similar crossover manner. Both samples rated the subjective psychoactive effects induced by the drugs. The results demonstrated that the psychoactive effects of 10 mg and 20 mg oral THC were significantly greater than placebo and comparable to the subjective effects of smoked cannabis. However, there was a different pattern of peak effects (2 h with oral administration, compared to 30 min with smoking). Consequently, a similar "high" was induced by both oral THC in pain patients, and smoked cannabis in healthy subjects. There were no AEs reported.

A single study investigated the impact of cannabis on neuropathic pain using the Volcano vaporizer (Wilsey et al. 2013). Thirty-nine patients with central and peripheral neuropathic pain were administered a placebo, low-dose (1.29%), or medium-dose (3.53%) of cannabis by vaporizing. Subsequently, subjective side effects and neuropsychological performance were measured. The study found no significant difference between the two active dose groups. The number needed to treat (NNT) to obtain 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium- versus low-dose. The two active dose groups did not significantly differ in terms of analgesic efficiency. Subjective side effects were minor and easily tolerated. The results of neuropsychological testing showed that subjects in the medium-dose condition displayed lower learning and memory performance than those in the low-dose condition. However, delayed memory performance did not differ between the low-dose and placebo. Both doses produced identical effects on attentional processing, with subjects performing worse after cannabis administration. In any case, these effects were of limited duration and reversible within 1 to 2 hours. Accordingly, it was concluded that vaporized cannabis, even at low doses, may be effective in addressing treatment-resistant neuropathic pain.

2. Multiple sclerosis

2.1. Oral cannabis

Investigation into the effectiveness of oral cannabis on the treatment of multiple sclerosis (MS) included three studies with Sativex and large sample sizes and a large study with a capsulated cannabis extract (Cannador). The first one (Kavia et al. 2010) inquired into the effect of Sativex on bladder dysfunction associated with MS. Self-titrated doses (up to 48 sprays per day) of either placebo or THC/CBD oromucosal spray were randomly administered using a between-group design for the period of 8 weeks in a sample of 135 MS patients with an overactive bladder (OAB). The main variable of interest was the decrease in the daily occurrence of loss of bladder control. Although there was no significant reduction in the amount of urinary incontinence episodes, there were fewer episodes of nocturia and daytime urination in the active treatment group. As for treatment-emergent AEs, most of them were mild or moderate in severity and mostly related to CNS-type disturbances, including dizziness, disorientation, headache, dissociation, impaired balance and paraesthesia. These treatment-related AEs led to the withdrawal of ten patients from the experiment (7 from the active condition and 3 from the placebo condition). In addition, three patients reported treatment-related SAEs (2 under active treatment and 1 under placebo treatment). Moreover, a potential transient ischaemic attack was observed in case of one subject receiving Sativex 4 days after starting to use study medication. The symptoms included shaking, coordination problems and severe absence following a dose of 18 sprays in one day. The

symptoms resolved after ceasing to administer the study drug. Sativex treatment was restarted the next day but the symptoms appeared once again a day later after increasing the dose to 18 sprays.

Collin et al. (2010) examined 337 patients with MS in a between-group study regarding the effects of Sativex on symptoms of spasticity. Patients self-titrated over a period of 14 weeks (up to 24 sprays per day) and the main variable of interest was the self-reported spasticity on a 0-10 numerical rating scale (NRS) – a similar scale as the one applied in many pain studies. The PP data analysis set showed a significant decrease in spasticity NRS scores in the active condition, compared to placebo. However, the ITT data analysis set did not show any effects. The authors explained this difference with the fact that subjects who were included in the ITT set but terminated their treatment early, displayed a detrimental effect on the mean treatment response to active treatment in the ITT analysis. However, those patients who complied with the protocol showed promising beneficial effects on spasticity. In case of AEs related to the drug, the most frequent ones were urinary tract infections, nausea and vomiting. Nine (5%) participants in the Sativex group and five (3%) in the placebo condition stopped using the study medication due to AEs. In addition, 4 treatment-related SAEs were observed: one with aggression, agitation, delusions, irritability, insomnia and muscle spasms; one with depression, drug dependence and suicidal ideation; one with an acute confusional state; and one with severe urinary tract infection.

Another study also determined the impact of Sativex on spasticity in MS patients (Novotna et al. 2011). It applied a between-group study design with two phases. In the first (dose-finding) phase, 572 patients first received only THC/CBD oromucosal spray in a single-blind manner (not knowing whether they received the active drug or placebo) for the study period of 4 weeks (up to 12 sprays per day). Subsequently, 241 subjects from this phase, who displayed ≥20% improvement in spasticity, were randomized into the double-blind, placebo-controlled second phase of the investigation lasting 12 weeks (receiving the same dosage of the medication as established in the first phase). Both the ITT analysis of NRS spasticity scores and secondary endpoints (including measures of sleep disturbance, depression and overall impression of change) showed a highly significant difference in favor of Sativex treatment, compared to placebo, in the second phase of the study. The authors concluded that this clearly pointed to a beneficial effect of THC/CBD on treatment-resistant spasticity in MS patients who displayed capacity to respond to this kind of treatment. Moreover, the enriched study design allowed to identify the extent of the benefit that can be derived from the treatment with Sativex in responder subjects. The drug-induced AEs were quite mild and did not exceed 10% frequency for each type of event in both groups. The most common AEs included vertigo, fatigue, muscle spasms and urinary tract infections, which led to the exclusion of only 3% of patients in both phases of the study.

Notcutt et al. (2012) investigated the long-term maintenance of efficacy of Sativex and the effect of its withdrawal in 36 MS patients who have been using nabiximols for the treatment of spasticity for at least 12 weeks. Only subjects who were considered to tolerate and receive benefits from using the THC/CBD oromucosal spray were included in this between-group study. All eligible subjects were included in a 1-week baseline open-label phase in which they continued to use their medication at a stable dose level. Afterwards, the participants were randomized into either the nabiximols or placebo condition and asked to continue administering a stable dose of the drug (on average 7.3 sprays per day of Sativex and 9.2 of placebo). This double-blind phase of the study lasted for 4 weeks. The main variable of interest was the time to treatment failure (TTF). The results showed that 17 subjects in the placebo condition failed to complete the study (94%), compared to only 8 participants in the THC/CBD oromucosal spray group (44%). Moreover, analysis of the TTF indicated a significant difference in favor of Sativex - participants in the placebo group were three times more likely to withdraw from treatment, compared to those using THC/CBD oromucosal spray. It was concluded that Sativex remains effective in the relief of MS-related spasticity in the long-term. In case of treatment-related AEs, they were mild to moderate and included pain (experienced by 2 subjects in the active drug condition and 5 placebo patients), muscle spasticity (2 active, 3 placebo), muscle spasms (2 active, 2 placebo) and depressed mood (2 active, 2 placebo).

An investigation by Zajicek et al. (2012) examined the influence of Cannador (capsules containing 2.5 mg THC and around 1.25 mg CBD) on symptoms of muscle stiffness in 279 MS patients over the study period of 12 weeks, using a between-group design. Subjects self-titrated the total daily dosage up to 25 mg THC and the main variable of interest was muscle stiffness scored on an 11 point NRS (ranging 0-10). The results demonstrated that 29.4% of subjects treated with the cannabis extract experienced significant stiffness relief compared to 15.7% using placebo. Combining this with the beneficial effects of the active drug on body pain, spasms and sleep quality, the results were considered as an indication of the effectiveness of the cannabis extract in treating symptoms of muscle stiffness in MS patients. As for the AEs, more than 95% of these events in each condition were mild or moderate in severity and included mainly nervous system (71.3%) and gastrointestinal effects (41.3%). However, several AEs were observed at higher rates (more than 3% difference) only in the cannabis extract group: dizziness, attentional disturbance, balance disorder, somnolence, dry mouth, nausea, diarrhea, fatigue, asthenia, feeling abnormal, urinary tract infection,

disorientation, confusional state and falling. The AEs led to the exclusion of 30 participants from the active drug group (21.0%) and 9 from the placebo condition (6.7%).

2.2. Oral THC

A second between-group study by Zajicek et al. (2013) investigated the impact of oral capsulated THC on the progression of MS, instead of just symptom relief. A total of 493 progressive MS patients randomly received either oral THC (n=329; capsules containing 3.5 mg THC), or placebo (n=164) over a period of 36 months. The maximum allowed daily dosage of THC was 28 mg. There were two main variables of interest: 1) time to expanded disability status scale (EDSS) score progression of at least 1 point from a baseline EDSS score of 4.0, 4.5, or 5.0, or at least 0.5 points from a baseline EDSS score of 5.5 or more, established at the next scheduled 6 monthly visit; and 2) difference from baseline to end of trial in the physical impact subscale of the self-reported 29-item multiple sclerosis impact scale (MSIS-29-PHYS). The results did not show significant effects of oral THC on any of the scales. Consequently, it was concluded that THC has no impact on the progression of MS in a progressive phase. Treatment-related AEs were difficult to quantify, since patients also reported AEs that could have been the result of MS symptoms and the authors did not differentiate between drug- and disease-related AEs. Regarding SAEs, 114 subjects (35%) who were administered oral THC experienced at least one SAE in comparison with 46 (28%) who received placebo. The most frequent SAE were related to MS-associated events and infections. The number and type of SAEs observed did not significantly differ between conditions, suggesting that most of them were not treatment-related.

2.3. Inhaled cannabis

A single crossover study (Corey-Bloom et al. 2012) administered smoked cannabis in order to determine the efficacy of this drug on spasticity in MS patients. Thirty MS subjects completed the trial in which they received cannabis cigarettes containing 800 mg of 4% THC cannabis or placebo cigarettes with THC removed. Each treatment lasted 3 days and the two conditions were separated by a 11-day washout period. The primary measure was the change in spasticity scores on a modified 0-5 Ashworth scale. The results pointed to a significant decrease in ratings of spasticity in the cannabis group, in comparison to placebo. Additionally, pain ratings on a visual analogue scale (VAS; a 100mm scale) were significantly reduced as well (on average by 5.28 points more than placebo). The results suggested that inhaled cannabis is effective in reducing symptoms of spasticity and pain in MS patients resistant to treatment. AEs were mild and led to only 5 treatment-related withdrawals: two patients reported an intense "high", two reported dizziness and one reported fatigue.

3. Irritable bowel syndrome

3.1. Oral THC

Research by Wong et al. (2011) focused on the impact of oral THC (dronabinol) on colonic motility in patients with irritable bowel syndrome (IBS). Seventy-five participants included in this between-group study were administered a single dose of either placebo (n=27), 2.5 mg (n=24) or 5 mg of THC (n=24) in the form of capsules. The measurements included left colonic compliance, the motility index (MI; index of colonic phasic pressure activity), tone, and colonic sensation after a meal and during fasting. Each subject had a balloon-manometry assembly placed in their colon which assessed colonic functions first during fasting, then after a standard 1000kcal liquid meal. Moreover, genetic polymorphisms of CNR1, FAAH and MGLL genotypes were analyzed to see whether genetic variants modulate the impact of THC on the assessed symptoms. The results demonstrated that a single oral THC dose of 5 mg led to improved colonic compliance and decreased fasting colonic motility in specific subgroups of IBS patients, i.e.: those with diarrhea (IBS-D) and alternating IBS (IBS-A). In contrast, the 2.5 mg THC dose had no significant effect on any of the functions measured. It was suggested that these results point to the critical role of the dosage of THC in producing clinically significant effects in IBS patients and that CNR1 and FAAH genetic variations can modulate the effects of the drug on colonic motility. AEs included fatigue (23% of all subjects) , hot flashes (19%), headache (13%), dizziness (11%), foggy thinking (11%), increased heart rate (11%), dream-like state (9%), nausea (8%), dry mouth and eyes (7%) and were evenly observed in all of the conditions, except for foggy thinking, which was more pronounced in the THC groups.

Klooker et al. (2011) examined the effect of oral THC (dronabinol) on a different aspect of IBS, i.e. visceral sensitivity to rectal distension. This crossover study included 10 IBS patients and 12 healthy volunteers. The participants were given single doses of either placebo, 5 mg, or 10 mg oral THC on three separate days. All subjects underwent a procedure in which an electronic barostat and a rectal balloon were used in order to evoke rectal pressure, combined with noxious sigmoid stimulation in order to increase visceral perception. The main variable of interest was the self-reported (using a 6-point scale) threshold for discomfort and pain during rectal distension before and after sigmoid stimulation. The results were not promising, as THC did not decrease visceral perception to rectal distension in any of the subjects groups. It was concluded that THC may not be the best treatment for reducing visceral sensitivity in IBS patients. Observed AEs were mild and occurred mostly at the highest dose (10 mg THC). Participants reported increased awareness of their surroundings (80% in the IBS group, 58% in the volunteers group), light-headedness (60% IBS, 42% volunteers) and sleepiness (50% IBS, 67%

volunteers). AEs in the 5 mg THC condition could only be observed in the healthy volunteers group: sleepiness (50%), mildly increased awareness (25%), and light-headedness (7%).

Another between-group study by Wong et al. (2012) inquired into the effect of oral THC capsules on gut transit in IBS-D patients and genetic variations which may act as modulators of this process. Thirty-six patients were administered placebo (n=13), 2.5 mg (n=10) or 5 mg of THC (n=13) twice daily, for 2 days. Gastric, small bowel, and colonic transit was examined by radioscintigraphy, and FAAH and CNR1 genetic variants were genotyped. The results did not reveal significant effects of oral THC on any of the measures. However, the CNR1 rs806378 CT/TT polymorphism was suggested to be related to a moderate delay in colonic transit, as compared to the CC genetic variant. It was suggested that neither of the THC doses had impact on gut transit in IBS-D, however, a genotype effect was suggested to be a moderating factor that might allow to identify a IBS-D patient subgroup that may respond more positively to cannabinoid therapy. Although AEs were not reported in detail, it seemed that the groups did not significantly differ from each other in terms of observed AEs.

4. Crohn's disease

4.1. Inhaled cannabis

A single study by Naftali et al. (2013) looked into the impact of smoked cannabis on induction of remission in patients with Crohn's disease. A between-group design was used in which 21 treatment-resistant patients were administered cannabis cigarettes twice daily containing herbal cannabis with a total dose of 115 mg THC (n=11) or placebo (n=10) for a period of 8 weeks. The main variable of interest was the Crohn's Disease Activity Index (CDAI) which is an indicator of remission. Although the results demonstrated that 5 subjects in the cannabis condition and 1 subject in the placebo condition entered clinical remission, the groups did not significantly differ from each other. Nevertheless, the cannabis group was still associated with a significant decrease of 100 points in CDAI scores after 8 weeks of treatment. In spite of the relatively high THC dose, there were no significant differences between the occurrences of AEs between the two groups, with sleepiness, nausea and confusion being the main ones.

5. Appetite and chemosensory perception

5.1. Oral THC

Brisbois et al. (2011) inquired into whether oral THC can enhance taste and smell (chemosensory) perception, including appetite, caloric intake, and quality of life (QOL) in cancer patients with chemosensory alterations. Twenty-one cancer patients completed this between-group study and were administered either oral THC (2.5 mg THC capsules, n=24) or placebo (n=22) two times daily for a period of 18 days. Over the course of the study, subjects were allowed to increase their dose to a total of 20 mg THC per day. All the measures included self-report forms. The results showed that THC, in comparison with placebo, enhanced chemosensory perception, macronutrient preference, appeal of foods, appetite, relaxation, and sleep quality of the patients. The AEs were minor and did not differ significantly between the groups (nausea/vomiting being the main one). However, there was one possible THC treatment-related SAE (irregular heartbeat). Consequently, it was concluded that oral THC is a well-tolerated drug that may palliate chemosensory alterations and increase food satisfaction and enjoyment.

5.2. Inhaled cannabis

A study by Riggs et al. (2012) evaluated whether smoking cannabis leads to changes in appetite-related hormones among HIV-infected male patients. Seven patients were administered cannabis joints 4 times daily for a period of 5 days, each with an individualized dose which was optimized during an initial titration session (using joints with a concentration range between 1% to 8% THC). The drugs were given in a crossover manner, with a 2-week washout period in between. The variables of interest were the concentrations of the appetite hormones ghrelin, leptin, PYY and insulin, as determined by analysis of blood samples. The results indicated that cannabis administration led to significant increases in plasma concentrations of ghrelin and leptin, and reductions in PYY, as compared to placebo. There were no effects on insulin levels. The authors concluded that the findings point to the modulation of appetite hormones through the endocannabinoid system. No AEs were reported.

6. Chemotherapy-induced nausea and vomiting

6.1. Oral cannabis

A single between-group investigation evaluated the potential of Sativex for decreasing chemotherapy-induced nausea and vomiting (CINV) in treated cancer patients (Duran et al. 2010). Sixteen patients with CINV were administered THC/CBD oromucosal spray (n=7) or placebo (n=9) for a period of 4 days (following a chemotherapy cycle) during which they self-titrated their dosage (up to maximum 48 sprays per day). Structured interviews, subject diaries, self-report questionnaires and visual analog scales were used to assess symptoms in the patients. The results pointed to a significantly higher proportion of subjects in the active condition demonstrating a complete response to treatment (defined as no vomiting and a mean nausea VAS score of ≤10mm on a 100mm scale). The AEs were rather mild, with somnolence, fatigue and dry mouth being the most common ones. Nonetheless, there were 2 AEs that were considered somewhat severe: one participant in the Sativex group and one in the placebo group experienced severe fatigue and mild somnolence and dysgeusia with vomiting. It was concluded that THC/CBD oromucosal

spray may be a safe and promising treatment for CINV that needs further confirmation in future trials.

7. Pulmonary disease

7.1. Oral cannabis

Pickering et al. (2011) inquired into the effects of Sativex on pulmonary ventilation and breathlessness. Five healthy volunteers and four chronic obstructive pulmonary disease (COPD) patients were administered a single dose of THC/CBD oromucosal spray or placebo in a crossover manner (up to 4 sprays). Breathlessness was induced by inhalation of fixed carbon dioxide loads. The measurements included self-reported breathlessness indicators, mood and activation, end-tidal carbon dioxide tension and ventilatory parameters. The results did not show any differences between the two conditions in terms of breathlessness scores or any respiratory evaluations. However, COPD patients reported fewer descriptions of the unpleasantness of the breathlessness procedure (pre-defined phrases to describe their sensation of breathlessness). The authors concluded that the addition of respiratory descriptors might be useful in the evaluation of drug effects on breathlessness. In case of AEs, one healthy subject experienced drowsiness, one COPD patient reported confusion and another COPD patient experienced transient cardiac dysrhythmia.

8. Cannabis dependence

8.1. Oral cannabis

Research by Allsop et al. (2014) investigated the efficacy of Sativex on treating cannabis dependence and withdrawal using a between-group design. Fifty-one patients with DSM-IV-TR cannabis dependence were administered increasing doses of THC/CBD oromucosal spray (up to 32 sprays per day) for a period of 6 days. The Cannabis Withdrawal Scale (CWS) was used as the measure of severity of cannabis withdrawal and cravings. Retention in the withdrawal treatment and AEs were also included as main variables of interest. The results showed that THC/CBD oromucosal spray significantly decreased CWS scores (average 66% reduction from baseline), as compared to placebo (average 52% increase from baseline) during the treatment. Subjects in the active group reported lower withdrawal-related irritability, depression, and cannabis cravings. In addition, they were more likely to stay in treatment, in comparison to participants in the placebo condition. In contrast, there were no significant differences between the two conditions in terms of number of AEs. In sum, the results were considered as a promising basis for further evaluation of the effectiveness of THC/CBD oromucosal spray for treating cannabis dependence.

8.2. Oral THC

A between-group study by Levin et al. (2011) investigated the effect of oral THC on treating cannabis addiction in 156 patients with DSM-IV-TR cannabis dependence. Subjects received either placebo or 20 mg oral THC twice daily for the period of 12 weeks. They were then required to provide urine samples, complete self-report instruments and have their vital signs and AEs evaluated twice daily. Treatment retention was significantly higher at the end of the study for the oral THC condition (77%), compared to placebo (61%). Moreover, withdrawal symptoms were significantly decreased in the oral THC group, compared to placebo. Although both conditions displayed a decrease in cannabis use over time, there were no significant differences between the groups. As for treatment-related AEs, four instances of drowsiness were observed (2 in the THC group and 2 in the placebo group), four patients reported feeling overly intoxicated (3 THC, 1 placebo), two reported heightened blood pressure (both THC), two reported nightmares and sleep disturbances (1 THC, 1 placebo), and one reported light-headedness (THC). It was concluded that oral THC is a well-tolerated, promising treatment for cannabis dependence that can enhance treatment retention and decrease withdrawal symptoms.

9. Anxiety

9.1. Oral CBD

A crossover investigation by Crippa et al. (2011) was conducted to examine the effects of oral purified CBD on generalized social anxiety disorder (SA). Ten SA patients were administered 400 mg of CBD or placebo at two separate visits, at which their regional cerebral blood flow (rCBF) was measured using 99mTc-ethylcysteinate dimer (ECD) Single Photon Emission Computed Tomography (SPECT), combined with self-assessments of subjective effects. The results displayed that CBD was related to significantly reduced subjective anxiety, decreased ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and enhanced ECD uptake in the right posterior cingulate gyrus. The authors suggested that CBD may decrease anxiety in SA and that this may be associated with its' effects on activity in limbic and paralimbic brain areas. There were no reported AEs.

A between-group study examined the impact of oral CBD on anxiety induced by a simulated public speaking test in SA patients and healthy controls (Bergamaschi et al. 2011). Twenty-four patients with SA were given either a single dose of 600 mg of oral CBD (n=12), or placebo (n=12). Twelve healthy volunteers did not receive any treatment (untreated control). All the groups participated in a simulation public speaking test (SPST) during which they completed subjective ratings on the Visual Analogue Mood Scale (VAMS) and Negative Self-Statement scales (SSPS-N). Additionally, physiological data (blood pressure, heart rate, and skin conductance) was obtained. The placebo SA condition displayed significantly increased anxiety ratings and more

Table 2. Studies on chronic pain

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Issa et al. (2014)	United States	Subjective effects in pain management	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) and THC (oral) - single administration; 1.99% or 3.51% THC (smoked); 10 mg or 20 mg THC (oral)	30 chronic noncancer pain patients	Oral dronabinol had similar psychoactive effects to smoked marijuana
Lynch et al. (2014)	Canada	Neuropathic pain	Placebo-controlled, double-blind, crossover study	Sativex (sublingual) - 4 week treatment; maximum daily dosage: 12 sprays	16 patients with chemotherapy-induced neuropathic pain	Reduction in pain intensity
Serpell et al. (2014)	United Kingdom	Peripheral neuropathic pain associated with allodynia	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment; maximum daily dosage: 24 sprays	246 patients with peripheral neuropathic pain	Significant improvements in pain, sleep quality and subjective evaluations of patients.
Johnson et al. (2013)	United Kingdom	Chronic cancer pain	Follow-up, open-label study	Sativex and THC spray (sublingual) - long-term variable treatment; maximum daily dosage: 48 sprays	43 patients with chronic cancer pain	Long-term safety and effectiveness in pain reduction
Langford et al. (2013)	United Kingdom	Central neuropathic pain associated with MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment + 14 week open-label phase; maximum daily dosage: 12 sprays	339 patients with central neuropathic pain associated with MS	No significant difference between placebo and Sativex in Phase A; Phase B demonstrated an analgesic effect
Wilsey et al. (2013)	United States	Neuropathic pain	Placebo-controlled, double-blind, crossover study	Cannabis (vaporized) - single administration; 1.29% or 3.53% THC	39 patients with central and peripheral neuropathic pain	Reduction in pain. No difference in efficacy between the two doses
Portenoy et al. (2012)	United States	Chronic cancer pain	Placebo-controlled, double-blind, graded-dose, between-groups study	Sativex (sublingual) - 5 week treatment; maximum daily dosage: 16 sprays	263 patients with chronic cancer pain	Significant analgesic effects in secondary pain analyses when added to standard opioid therapy
Johnson et al. (2010)	United Kingdom	Chronic cancer pain	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) and THC spray (sublingual) - 2 week treatment; maximum daily dosage: 48 sprays	177 patients with chronic cancer pain	Significant reduction in pain severity when added to standard opioid therapy

Selvarajah et al. (2010)	United Kingdom	Painful diabetic peripheral neuropathy	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 12 week treatment; variable dosage	30 patients with painful DPN	No significant improvement over placebo. Depression suggested confounding factor
Rintala et al. (2010)	United States	Central neuropathic pain	Active-controlled, double-blind, crossover study	THC (oral) - 8 week treatment; maximum daily dosage: 20 mg THC	7 patients with neuropathic pain associated with spinal cord injury	Dronabinol not more effective than diphenhydramine for pain relief
Ware et al. (2010)	Canada	Chronic neuropathic pain	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 14 day treatment; variable daily dosage: 75 mg plant material	21 patients with neuropathic pain	Significant pain reduction. Improved sleep and reduced anxiety

Table 3. Studies on multiple sclerosis

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Zajicek et al. (2013)	United Kingdom	Progressive MS	Placebo-controlled, double-blind, between-groups study	THC (oral) - 36 month treatment; maximum daily dosage: 28 mg THC	493 patients with progressive MS	No overall treatment effect on clinical disease progression
Corey-Bloom et al. (2012)	United States	Spasticity in MS	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 3 day treatment; 4 % THC, 800 mg plant material	30 patients with MS and spasticity	Significant reduction in spasticity and pain
Zajicek et al. (2012)	United Kingdom	Stable MS	Placebo-controlled, double-blind, between-groups study	Cannabis extract (oral) - 12 week treatment; maximum daily dosage: 25 mg THC	279 patients with stable MS	Significant reduction in muscle stiffness
Notcutt et al. (2012)	United Kingdom	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 1 week baseline open-label treatment + 4 week double-blind treatment; variable dosage	36 patients with MS receiving benefits from using Sativex for spasticity for at least 12 weeks	Significant difference in time to treatment withdrawal in favor of Sativex
Novotna et al. (2011)	Czech Republic	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 4 week single-blind treatment + 12 week double-blind treatment; maximum daily dosage: 12 sprays	241 patients with MS and spasticity	Significant reduction in spasticity in patients showing adequate response to Sativex in initial study phase

Collin et al. (2010)	United Kingdom	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment; maximum daily dosage: 24 sprays	337 patients with MS and spasticity	Significant reduction in treatment-resistant spasticity
Kavia et al. (2010)	United Kingdom	Bladder dysfunction in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 8 week treatment; maximum daily dosage: 48 sprays	135 patients with MS and overactive bladder	No significant reduction in number of urinary incontinence episodes. Beneficial effects on other bladder symptoms

Table 4. Studies on irritable bowel syndrome

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Wong et al. (2012)	United States	Colonic transit in IBS	Placebo-controlled, double-blind, between-groups study	THC (oral) - 2 day treatment; daily dosage: 5 mg or 10 mg THC (twice daily)	36 patients with IBS	No significant effects on gut transit
Klooker et al. (2011)	The Netherlands	Rectal sensitivity in IBS	Placebo-controlled, double-blind, crossover study	THC (oral) - single administration; maximum dosage: 10 mg THC	10 patients with IBS; 12 healthy controls	No significant effects of THC on visceral hypersensitivity
Wong et al. (2011)	United States	Colonic motility and sensation in IBS	Placebo-controlled, double-blind, between-groups study	THC (oral) - single administration; 2.5 mg or 5 mg THC	75 patients with IBS	Reduction in fasting colonic motility in subgroup of patients

Table 5. Studies on Crohn's disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Naftali et al. (2013)	Israel	Pain in Crohn's disease	Placebo-controlled, double-blind, between-groups study	Cannabis (smoked) - 8 week treatment; daily dosage: 115 mg THC	21 patients with Crohn's disease	Cannabis produced significant clinical benefits to 10 of 11 patients with active Crohn's disease. Induction of remission was not achieved

Table 6. Studies on appetite and chemosensory perception

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Riggs et al. (2012)	United States	Appetite hormones in HIV-infected men	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 10 day treatment; maximum daily dosage: four 8% THC cigarettes	7 patients with HIV infection	Significant alterations in appetite hormones
Brisbois et al. (2011)	Canada	Reduced appetite and chemosensory alterations in cancer	Placebo-controlled, double-blind, between-groups study	THC (oral) - 18 day treatment; maximum daily dosage: 20 mg THC	21 cancer patients with chemosensory alterations	Significant improvement of chemosensory perception and appetite

Table 7. Studies on chemotherapy-induced nausea and vomiting

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Duran et al. (2010)	Spain	Chemotherapy-induced nausea and vomiting	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 4 day treatment; maximum daily dosage: 48 sprays	16 cancer patients with CINV	Significantly improved protection against delayed CINV when added to standard antiemetic therapy

Table 8. Studies on pulmonary disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Pickering et al. (2011)	United Kingdom	Breathlessness	Placebo-controlled, double-blind, crossover study	Sativex (sublingual) - single administration; maximum dosage: 4 sprays	4 patients with COPD; 5 healthy controls	No reduction in breathlessness, but reduction in unpleasantness of symptoms

Table 9. Studies on cannabis dependence

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Allsop et al. (2014)	Australia	Cannabis withdrawal symptoms	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 6 day treatment; maximum daily dosage: 86.4 mg THC, 80 mg CBD	51 patients with DSM-IV-TR cannabis dependence	Significant reduction in severity and time course of cannabis withdrawal symptoms

Levin et al. (2011)	United States	Cannabis withdrawal symptoms	Placebo-controlled, double-blind, between-groups study	THC (oral) - 12 week treatment; maximum daily dosage: 40 mg THC	156 patients with DSM-IV-TR cannabis dependence	Significant improvement in treatment retention and withdrawal symptoms

Table 10. Studies on anxiety

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Das et al. (2013)	United Kingdom	Fear extinction and consolidation	Placebo-controlled, double-blind, between-groups study	CBD (vaporized) - single administration; 32 mg CBD	48 healthy subjects	CBD administered post-extinction enhanced consolidation of extinction. No acute effects of CBD were found on extinction
Bergamaschi et al. (2011)	Brazil	Anxiety associated with public speaking	Placebo-controlled, double-blind, between-groups study	CBD (oral) - single administration; 600 mg CBD	24 patients with SAD; 12 healthy controls	Significant reduction in anxiety, discomfort and cognitive impairment
Crippa et al. (2011)	Brazil	rCBF in social anxiety	Placebo-controlled, double-blind, crossover study	CBD (oral) - single administration; 400 mg CBD	10 patients with SAD	Reduction in anxiety associated with altered activity in limbic and paralimbic brain areas

Table 11. Studies on psychosis

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Leweke et al. (2012)	Germany	Psychotic symptoms	Active-controlled, double-blind, between-groups study	CBD (oral) vs. amisulpride - 4 week treatment; maximum daily dosage: 800 mg CBD	42 patients with DSM-IV-TR schizophrenia	Significant antipsychotic effects of CBD

Table 12. Studies on Parkinson's disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Chagas et al. (2014)	Brazil	Parkinson's disease: motor functioning, neuroprotection and well-being	Placebo-controlled, double-blind, between-groups study	CBD (oral) - 6 week treatment; daily dosage: 75 mg or 300 mg CBD	21 patients with idiopathic PD	Significant improvement in well-being. No effects on motor functioning or neuroprotection

pronounced cognitive impairment, discomfort, and alertness, in comparison with the untreated control group. In contrast, CBD significantly decreased anxiety, cognitive impairment, and discomfort during speech performance in SA patients. Moreover, CBD led to a significant reduction in anticipatory speech alert. In general, similar effects were observed both in the CBD-SA group, as well as in the healthy volunteer condition. It was concluded that a single dose of CBD can decrease the anxiety induced by SPST in SA patients, suggesting a beneficial effect of the drug on fear of speaking in public. No AEs were observed, which is in line with other studies using higher doses of CBD.

9.2. Inhaled CBD

In an experiment with 48 healthy participants who underwent a fear-conditioning test CBD enhanced consolidation of subsequent fear extinction learning and thus may be helpful in anxiety disorders (Das et al. 2013). Participants received a single dose of 32 mg vaporized CBD either before or after extinction in a between-group design. Successful fear conditioning and extinction were found in both treatment groups. CBD given post-extinction enhanced memory consolidation of extinction learning. No acute effects of CBD were found on extinction. There were no adverse events reported.

10. Psychosis

10.1. Oral CBD

Leweke et al. (2012) conducted an active-controlled between-group study into the effects of oral CBD on symptoms of psychosis in DSM-IV-TR schizophrenia patients. A total of 42 subjects were administered daily doses of either 800 mg oral CBD or amisulpride (a dopamine receptor antagonist) for the period of 4 weeks (starting with a dose of 200 mg and titrating up in the first week). The main measures included the scores of the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptoms Scale (PANSS), which were administered at baseline, and at day 14 and day 28 of treatment. Both groups were found to display significant enhancements in clinical symptoms, while CBD was found not to produce side-effects typical of amisulpride. Moreover, the decrease in psychotic symptoms following CBD administration was associated with an increase in serum anandamide levels. In sum, the authors suggested that the inhibition of anandamide deactivation might play a role in the antipsychotic impact of CBD, potentially highlighting a new mechanism for treating schizophrenia.

11. Parkinson's disease

11.1. Oral CBD

One between-group investigation into the effectiveness of CBD for treating Parkinson's disease (PD) included 21 patients with PD without dementia or comorbid psychiatric disorders (Chagas et al. 2014). Three groups of 7 subjects each received either placebo, 75 mg, or 300 mg of oral CBD per day for a period of 6 weeks. Evaluations were done at baseline and in the last week of the dosage regimen. The main variables of interest were scores regarding motor and general symptoms (UPDRS), well-being and quality of life (PDQ-39), and potential neuroprotective effects (BDNF and H1-MRS). The 300 mg CBD group was found to differ significantly from placebo only in case of the PDQ-39. It was concluded that CBD has the potential to enhance the quality of life of PD patients without psychiatric comorbidities, however, no neuroprotective or motor effects of CBD were found. There were no observed AEs.

Discussion on the state of cannabis research in medicine

In recent years, the medical use of herbal cannabis has gained unprecedented attention worldwide. Despite the fact that limited clinical data is available for most medical indications, multiple countries have introduced legislation, and sometimes entire government supported programs, to provide patients access to cannabis-based medicine. The Netherlands, Canada and Israel have had such programs already for many years, while Australia, Uruguay, Chile, Jamaica, Czech Republic, Croatia, Italy and Germany are just a few of the more recent examples. In other countries such as Spain and Portugal patients may use the national laws, which allow possession of cannabis for personal use to enable self-medication.

Given the limited clinical research on cannabis and cannabinoids in many indications, patients, physicians, scientists and policy-makers in many countries alike struggle with the task to make responsible choices regarding administration forms, dosing regimen, cannabis botanical variety, and long-term effects. Further properly designed clinical trials are needed to provide more information on these questions.

What makes cannabinoids particularly fascinating is the wide range of possible therapeutic effects they are claimed to have. Currently, cannabis and cannabinoids are being used by patients for treatment of anything ranging from pain, cancer and epilepsy, to sleep, depression and anxiety, from attention deficit/hyperactivity disorder (ADHD), autism, cluster headaches and Crohn's disease to irritable bowel syndrome, restless legs syndrome and Tourette's syndrome, (Grotenhermen et al. 2015; Hazekamp et al. 2013). But despite the major promise these compounds seem to hold, in the period 2010-2014 (see Table 1) significant clinical data has only been added for multiple sclerosis (1515 patients in total) and chronic pain (1211 patients). Compared to

our previous review of the period 2005-2009 (Hazekamp and Grotenhermen 2010) an increase can be observed mainly in the number of patients included in pain trials. Consequently, it seems that the investigation of the effects of cannabinoids on different types of chronic pain (central and peripheral neuropathic pain, cancer pain, etc.) is currently of major interest to the cannabinoid research field. Indeed, all cannabinoid-based drugs covered in this review have been studied in at least one trial addressing some type of pain. Interestingly, surveys performed among medicinal cannabis users usually indicate pain as the main indication for which cannabis is used (Hazekamp and Pappas 2014).

It has recently been suggested that THC may target the affective quality of pain, instead of simply reducing pain intensity and hyperalgesia (de Vries et al. 2014). If such is the case, it would seem interesting to also explore the analgesic potential of CBD - a cannabinoid not commonly associated with pain reduction. After all, aside of the anxiolytic effects discussed in this review (Bergamaschi et al. 2011; Crippa et al. 2011; Das et al. 2013), CBD has been suggested to affect emotional processing through modulation of the activity of the anterior cingulate cortex (Kowal et al. 2013), and enhance emotional facial recognition (Hindocha et al. 2015). As a result, such emotion-regulating properties of CBD allow us to speculate whether this cannabinoid may also be beneficial in targeting the affective qualities of pain. Possibly, it may prove to modulate the effects of THC in this regard.

Potential interactions between THC and CBD is only one example to show the complexity of performing studies on cannabinoid-based drugs - especially those containing whole-plant cannabis extracts. Evidence indicates that the synergy of different compounds present in cannabis defines the final effect of the drug in various aspects (Russo 2011). Consequently, researchers, patients and physicians should keep in mind the complete composition of the cannabinoid-based drug that they are interested in - not only the amounts of specific cannabinoids such as THC or CBD. Possibly, subtle differences in composition may significantly affect the usefulness of the drug in treating specific medical conditions.

Conclusion

By providing a clear overview of the design, outcomes and side effects of clinical trials performed with cannabis and cannabinoids, this review hopes to inspire the development of more and better trials in the future. Currently, the clinical researchers' toolbox contains a wide range of cannabinoid-based drugs, including single cannabinoids (Marinol, Dronabinol, CBD), plant-based extracts (Sativex, Cannador), herbal cannabis (NIDA, Bedrocan), and synthetic analogues (Nabilone, various others not covered in this review). Taken together, clinical experiences with these compounds may provide us further knowledge on the indications for cannabinoid based medicines.

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Role of Cannabinoids in Pain Management

18

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Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

Introduction

Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

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The Endocannabinoid System

There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are "relax, eat, sleep, forget, and protect" [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

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Cannabis Reduces Opioid Dose in the Treatment of Chronic Non-Cancer Pain

To the Editor:

Cannabinoids block pain responses in virtually every laboratory pain model tested. In models of acute or physiological pain, cannabinoids are highly effective against thermal, mechanical, and chemical pain, and are comparable to opioids in potency and efficacy.[1] In models of chronic pain, cannabinoids exhibit efficacy in the modulation of both inflammatory[2] and neuropathic pain.[3] Recent reviews describe an endogenous cannabinoid system involved in pain modulation that produces analgesia through the same brainstem circuitry involved in opioid analgesia.[1,4,5,6] Although co-administration of Δ-9-tetrahydrocannabinol (THC) with μ opioid agonists can potentiate the antinociceptive effects of each agent, an opioid is not required for cannabinoid analgesia.[5,6] Co-administration of a cannabinoid may lead to a lower opioid requirement. In an N-of-1 trial, oral THC reduced the pain of familial Mediterranean fever such that the use of breakthrough opioid for pain relief decreased significantly.[7]

Recently, in Canada, the Medical Marijuana Access Program allows patients to apply to Health Canada for access to dried cannabis for medicinal purposes. Although smoked cannabis is not an ideal delivery system, it is efficient and results in plasma concentration curves parallel to those seen after intravenous administration.[8] We present three patients who used small doses of smoked marijuana in combination with an opioid.

Case 1

A 47-year-old woman with a ten-year history of chronic progressive multiple sclerosis (MS) had headache, multisite joint pain, bladder spasm, and leg spasticity. Ambulation was significantly compromised by the joint pain and leg spasticity. She was wheelchair dependent, and also suffered from severe insomnia and fatigue, which she attributed to the combination of pain, bladder spasm, and leg spasticity. Physical examination revealed paraparesis, weakness in the left upper extremity, tremor involving both hands, intranuclear ophthalmoplegia and L'Hermitte's sign. Previous treatment included steroids, physiotherapy, acupuncture, interdisciplinary pain management, intramuscular injections of botulinum toxin, amitriptyline, fluoxetine, amantadine, acetaminophen with codeine, oxycodone, nonsteroidal anti-inflammatory drugs (NSAIDs), and baclofen. The patient's medications prior to access to smoked marijuana consisted of long-acting morphine 75 mg per day, tizanidine 24 mg per day, and sertraline 150 mg at bedtime. In spite of these treatments, the patient did not obtain adequate control of her pain, spasticity, or sleep.

The patient received permission for access to smoked marijuana and began to use a dose of 2–4 puffs of smoked marijuana at bedtime on a regular basis. Over the next six months, the morphine was reduced to 45 mg per day, tizanidine to 6 mg once per day, and sertraline to between 100 mg and 150 mg at bedtime. The patient reported improvement in pain, spasticity, bladder spasm, and sleep. The patient denied any adverse side effects, other than she felt somewhat "high" if she smoked more than 4 puffs per dose. She was able to adjust the dose so that this did not occur. The patient received legal access in the autumn of 2000 and continues to use marijuana.

Case 2

A 35-year-old HIV-positive man was initially assessed in 1992 for four-month history of HIV-related painful peripheral neuropathy involving the lower limbs and hands. His pain had initially involved the plantar aspect of his feet and had spread proximally to involve the lower leg and thighs, and later his hands. The pain was described as severe "stinging, numb, tingling, and throbbing" pain that was unpredictable and poorly controlled. On physical examination, positive findings included patches of hypesthesia and hyperalgesia to pinprick testing in a stocking-glove distribution. Electromyography studies were reported as normal. Prior treatments had included trials of physiotherapy, acupuncture, psychological therapies, NSAIDs, tricyclic antidepressants, anticonvulsants, intravenous and oral local anesthetics, and opioids. His medication regimen consisted of long-acting morphine 360 mg per day with morphine

sulfate 75 mg 4 times daily for breakthrough pain, and gabapentin 2,400 mg per day. The patient continued to report moderate to severe levels of pain.

After receiving approval to use marijuana in 2000, the patient began using smoked marijuana in a dose of 3–4 puffs 3–4 times per day. Over four months, the patient's dose of morphine decreased to 180 mg per day and by 9 months he had discontinued the morphine. By September 2001, he discontinued gabapentin. The patient was able to manage without the use of an opioid or gabapentin until February 2002, at which time he developed an episode of herpes zoster involving thoracic dermatomes T7 to T9 on the left side. Morphine was temporarily re-introduced for 8 weeks during the acute episode in a dose of 15 mg three times daily. The patient reported that the smoked marijuana was helpful for both the HIV neuropathy and the herpes zoster pain, but he required the additional analgesia provided by the opioid during the acute phase of the herpes zoster infection. He has since discontinued the morphine and remains opioid-free as of August 2002. The patient denied side effects related to the use of smoked marijuana.

Case 3

A 44-year-old man presented with a 6-year history of low back and left leg pain, which had resulted from a work-related fall from a ten-foot high landing onto the edge of a metal tank, striking his lumbar spine. Physical examination revealed a decrease in lumbar lordosis, wasting of paravertebral musculature, decreased extension at the lumbar spine, decreased straight leg raising from the supine position to 60° on the right and to 45° on the left, tenderness to palpation over the L3-4 to L5-1 facet joints, normal deep tendon reflexes bilaterally and hypesthesia to pinprick testing over the lateral aspect of the left calf. Previous treatments had included physiotherapy, transcutaneous electrical nerve stimulation, acupuncture, lumbar facet joint injections, radiofrequency facet neurolysis, and trials of NSAIDs, tricyclic antidepressant analgesics, muscle relaxants, tramadol, and long-acting morphine. The patient's medications prior to the introduction of smoked marijuana consisted of long-acting morphine 150 mg per day and cyclobenzaprine 10 mg three times per day.

The patient reported poor pain control with this regimen and initiated a trial of smoked marijuana. He reported using several puffs to one joint 4–5 times per day. After using the smoked marijuana on a regular basis for 2 weeks, the patient was able to decrease his morphine to 90 mg per day; after two more weeks, he decreased the morphine to 60 mg per day and his cyclobenzaprine to 10 mg once daily. He reported good pain control and was able to continue in his wage earning work. The patient continues to report improved pain control using the cannabis along with the lower dose of morphine as of August 2002.

Comment

These cases are consistent with preclinical work demonstrating that cannabinoids exhibit analgesic effects and may potentiate the antinociceptive effects of opioids. These patients were able to decrease the dose of opioid by 60–100% as compared to before the regular use of smoked marijuana. With the introduction of smoked marijuana, each patient reported better pain control. Unfortunately, the source of smoked marijuana used by patients, and the percentage of THC in it, is unknown. All patients reported previous exposure to cannabis at some time in their lives before the onset of their pain, and the relevance of this experience also is unknown. Standardized measures of pain were not used, and the information presented was based on the patients' verbal report when they presented for follow-up appointments at the Pain Management Unit. Nonetheless, these cases suggest that further research regarding the role of cannabinoids as analgesics and the combination of cannabinoids with opioids in the control of pain is needed.

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Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain

M Iskedjian, B Bereza, A Gordon, C Piwko, and TR Einarson.

Review published: 2007.

CRD summary

The review concluded that cannabinoids, including the cannabidiol/delta-9-tetrahydrocannabinol buccal spray, are effective in treating neuropathic pain in patients with multiple sclerosis. However, given the limitations of the evidence presented, the reliability of the authors' conclusions is uncertain.

Authors' objectives

To evaluate the effectiveness and safety of cannabis-based drugs in pain management related to multiple sclerosis (MS) or comparable neuropathic pain syndromes.

Searching

MEDLINE, EMBASE, the Cochrane CENTRAL Register and HealthSTAR were searched from inception to the end of June 2006. The reference lists of retrieved studies and from reviews on the topic were handsearched. Additional unpublished data were sourced from a drug manufacturer (Bayer). Abstracts were not included. No language restrictions were applied.

Study selection

Study designs of evaluations included in the review

Randomised, double-blinded, placebo-controlled trials were eligible for inclusion.

Specific interventions included in the review

Studies of the use of cannabis-based drugs for the treatment of pain associated with MS or comparable neuropathic pain in adults were eligible for inclusion. To be included, trials needed to have assessed at least one active treatment against either itself (e.g. different doses, dosage forms or times of administration) or against another active drug, and/or against placebo. All durations of drug administration were eligible for inclusion. The included studies evaluated cannabidiol in conjunction with a delta-9-tetrahydrocannabinol (THC) buccal spray, cannabidiol alone, or dronabinol alone in comparison with placebo. The duration of treatment ranged from 1 to 6 weeks.

Participants included in the review

Studies of adult patients aged 18 years or older who were receiving treatments for MS-associated pain or comparable neuropathic pain were eligible for inclusion. At least two of the included studies assessed general neuropathic pain rather than pain associated with MS. The average age of participants in the included studies ranged from 39 to 54.6 years.

Outcomes assessed in the review

Studies assessing pain score obtained from a visual analogue scale (VAS) or equivalent such as the Box Scale (BS-11) were eligible for inclusion. The included studies assessed pain using the BS-11 scale, VAS scale, a 100-mm VAS scale, or an 11-point ordinal scale. Scores on an 11-point scale ranged from 0 (no pain) to 10 (worst pain imaginable).

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for relevance, with any disagreements adjudicated by a third reviewer.

Assessment of study quality

The quality of the studies was assessed using the Jadad scale, which has a maximum score of 5; studies scoring 0 to 2 are rated poor, while studies scoring 3 to 5 are rated good. Two reviewers independently assessed validity and resolved any disagreements through discussion.

Data extraction

Two reviewers independently extracted the data onto a pre-designed form and resolved any disagreements through consensus, with outcomes verified by a third reviewer where required. Data on the mean pain scores, and standard deviations, at baseline and at the end of the trial in each group were extracted and used to derive the standardised mean difference (SMD) and its standard error (SE) relative to baseline and to placebo.

Methods of synthesis

How were the studies combined?

The results of individual studies were combined using a random-effects model to produce a weighted SMD (effect size). Rates of adverse events were compared for each drug, all active drugs combined and for placebo between end point and baseline. Active drugs were compared against placebo at baseline and end point. Publication bias was assessed using funnel plots and the Begg-Mazumdar statistical test.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared and I-squared tests.

Results of the review

Seven RCTs (298 unique patients: 222 treated with cannabis preparations (many of whom also crossed over to placebo) and 76 treated with placebo alone) were included. Four of these were crossover trials.

The quality of all 7 included studies was rated as good. Five studies scored 5, one scored 4 and one scored 3. Both the chi-squared and I-squared statistical tests indicated that there was no significant statistical heterogeneity between the studies. The Begg-Mazumdar test showed no evidence of publication bias.

There were no statistical differences at baseline between pain scores of patients treated with cannabinoids and those receiving placebo.

Cannabis preparations were more effective in reducing pain scores than placebo for the treatment of MS-related or neuropathic pain, with a difference in effect size of 0.8 points; the difference was statistically significant (p=0.029). The difference from baseline was 1.7 (SE 0.7, p=0.018) for cannabidiol/THC buccal spray (6 studies, n=196), 1.5 (SE 0.7, p=0.044) for cannabidiol alone (5 studies, n=41), 1.5 (SE 0.6, p=0.013) for dronabinol (3 studies, n=91) and 1.6 (SE 0.4, p<0.001) for all cannabinoids (14 trial arms, n=328).

Data for placebo groups (10 studies, n=250) reported an average reduction in pain scores of 0.8 points, which was statistically significant (p=0.023). A post hoc analysis removing 2 studies that allowed free use of 'rescue' medications, including analgesics, lowered the placebo effect to 0.6 points, which was not statistically significant.

Dizziness was the most commonly reported adverse event for all cannabinoid treatments (32.5% +/- 16.4) and for placebo (10.1% +/- 3.8). In studies of cannabidiol/THC buccal spray, 39% (+/- 16.3) reported dizziness.

Withdrawals due to adverse events were similar between patients receiving cannabis (5.5%, 14 out of 255) and those treated with placebo (5.1%, 13 out of 253).

Authors' conclusions

Cannabinoids are associated with a clinically relevant and statistically significant lowering of pain scores. Some patients did not experience pain relief but others responded well.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to locate unpublished studies. No language restrictions were applied and abstracts were excluded. No evidence of publication bias was found. No search terms were reported so it is not possible to either evaluate or replicate the searches. Methods were used to minimise error and bias in the study selection, validity assessment and data extraction processes. The analysis comparing changes from baseline and effectiveness relative to placebo was not clearly established. In addition, the clinical significance of the observed effects was unclear. The authors also made assumptions about the generalisability between pain in MS and neuropathic pain in other conditions. The included studies had small sample sizes and were of short-term treatment (the longest lasted 6 weeks), and this also should be considered when interpreting the results. Given the limitations of the evidence presented, the reliability of the authors' conclusions is uncertain.

The review was funded by Bayer Inc., which markets the cannabidiol/THC buccal spray in Canada.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research evaluating longer term clinical outcomes of cannabinoid treatment for pain in MS is needed. In addition, economic implications should also be assessed.

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THE UNIVERSITY of York
Centre for Reviews and Dissemination

CRD has determined that this article meets the DARE scientific quality criteria for a systematic review.

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RANDOMISED CONTROLLED TRIAL OF CANNABIS BASED MEDICINE (CBM, SATIVEX®) TO TREAT DETRUSOR OVERACTIVITY IN MULTIPLE SCLEROSIS

Hypothesis / aims of study

The overactive bladder (OAB) is a common and difficult problem to manage in patients suffering from multiple sclerosis (MS). Treatment at present is limited to anticholinergics with or without intermittent self catheterisation and most recently, intradetrusor injections of botulinum toxins. However patients using 'street cannabis' reported up to a 64% improvement in one of the symptoms of OAB and an improvement was also seen in an open labelled study of patient with severe MS. More recently a subset analysis of a double blind RCT (CAMS) with oral cannabis reported improvement in urgency incontinence (1). The scientific rationale for the use of cannabis is the finding of CB1 cannabinoid receptor on the rodent bladder and immunohistochemical endocannabinoid production in the human detrusor.

This study aims to report the preliminary results of a randomised double blind parallel group placebo-controlled of the use of oromucosal cannabis based medicinal extract with constituents of tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 mixture (2.7mg of THC and 2.5mg CBD per spray)

Study design, materials and methods

135 patients were randomised to receive either CBM or placebo (PLO) in a double blind parallel group study for eight weeks, with a two week baseline period. The study was powered to detect a difference between treatments of 0.5 episodes of incontinence per 24 hours. Ethical approved and written informed consent was obtained for all patients. 37 Male and 98 females were recruited from 3 European countries (UK, Belgium and Romania). The primary end point for this study was the reduction in urgency incontinence episodes as evaluated by voiding diary. Secondary end points included urgency, day frequency, nocturia, bladder symptom severity score, quality of life and Patients Global Impression of Change. Intention to treat analysis and Per-Protocol analysis was utilised, as well as subgroup analysis using recognised statistical tests.

Results

The primary end point i.e. reduction in numbers of daily incontinence at the end of treatment, did not reach significance

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CBM was superior to placebo for nocturia (CBM -0.52 PLO – 0.24, p=0.01). This was present at all levels of severity of nocturia and the size of effect was greater for more severe disease. Substantial numbers of patients became nocturia free on the active treatment.

The patient's opinion of bladder symptom severity (0 – 10 NRS) showed a significant difference in favour of CBM at the end of treatment (CBM -2.21 PLO -1.05, p=0.001). Patients on CBM were three times more likely to report an improvement of more than 30% compared with those on placebo (P = 0.006).

The reduction in the number of daytime voids also reached significance (P = 0.044) and the total number of voids per 24 hours was also significantly reduced (P = 0.001). There was no difference in the volume of urine produced between the CBM and placebo groups.

Patient's global impression of change (i.e. how much better the patient felt on medication as compared to baseline) which was highly significant in favour of CBM (p = 0.001) There was a trend in favour of improvement in Quality of Life in the treated group but this did not reach statistical significance.

CBM was well tolerated. The most common adverse events were dizziness, UTI and headache and (18% vs 7%, 6% vs 10% and 8% vs 7% for CBM and placebo respectively).

Interpretation of results

This randomised placebo controlled trial demonstrates that CBM has a major impact on bladder symptoms in patients with MS and severe urinary symptoms particularly on the nocturia and frequency. The difference that patients reported in the PGIC and bladder symptom severity scores provides strong evidence of the positive impact of CBM on their condition for the patients. None of the difference in treatment effect was due to urine volumes, as these were comparable between the two groups.

Concluding message

Our results show a beneficial effect in a double blind randomised placebo controlled trial of (Sativex®) on the symptoms of overactive bladder in multiple sclerosis.

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CLINICAL TRIAL REGISTRATION: This clinical trial has not yet been registered in a public clinical trials registry.

HUMAN SUBJECTS: This study was approved by the Institute of Neurology and National Hospital for Neurology and Nerosurgery Joint REC No. 02/N053 and followed the Declaration of Helsinki Informed consent was obtained from the patients.

Therapeutic aspects of cannabis and cannabinoids

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Declaration of interest Funding from DOH. Between writing this paper and its acceptance for publication, P.R. was appointed Medical Director of GW Pharmaceuticals.

Abstract

Background Review commissioned in 1996 by the Department of Health (DOH).

Aims Assess therapeutic profile of cannabis and cannabinoids.

Method Medline search, references supplied by DOH and others, and personal communications.

Results and Conclusions Cannabis and some cannabinoids are effective anti-emetics and analgesics and reduce intra-ocular pressure. There is evidence of symptom relief and improved well-being in selected neurological conditions, AIDS and certain cancers. Cannabinoids may reduce anxiety and improve sleep. Anticonvulsant activity requires clarification. Other properties identified by basic research await evaluation. Standard treatments for many relevant disorders are unsatisfactory. Cannabis is safe in overdose but often produces unwanted effects, typically sedation, intoxication, clumsiness, dizziness, dry mouth, lowered blood pressure or increased heart rate. The discovery of specific receptors and natural ligands may lead to drug developments. Research is needed to optimise dose and route of administration, quantify therapeutic and adverse effects, and examine interactions.

In 1996 I was commissioned by the Department of Health (DOH) to review the scientific literature regarding the potential therapeutic utility of cannabis and its derivatives. The review was based upon primary sources (identified from a Medline literature search, reference lists supplied by the DOH and the Institute for the Study of Drug Dependence, and personal communications with relevant academics and clinicians). This paper is a greatly shortened version of the review. The 4 years which have elapsed have seen little in the way of new clinical results but considerable advances in cannabinoid basic science (**Institute of Medicine, 1999**). Government licences have recently been granted for several controlled trials of both synthetic and plant-derived cannabinoids in multiple sclerosis and chronic pain. In January 2000, I was appointed Medical Director of GW Pharmaceuticals, a company established to derive medicinal extracts from standardised cannabis plants.

HISTORY OF THERAPEUTIC USE

The first formal report of cannabis as a medicine appeared in China nearly 5000 years ago when it was recommended for malaria, constipation, rheumatic pains and childbirth and, mixed with wine, as a surgical analgesic (**Mechoulam, 1986**). There are subsequent records of its use throughout Asia, the Middle East, Southern Africa and South America. Accounts by Pliny, Dioscorides and Galen remained influential in European medicine for 16 centuries.

It was not until the 19th century that cannabis became a mainstream medicine in Britain. W. B. O'Shaughnessy, an Irish scientist and physician, observed its use in India as an analgesic, anticonvulsant, anti-spasmodic, anti-emetic and hypnotic. After toxicity experiments on goats and dogs, he gave it to patients and was impressed with its muscle-relaxant, anticonvulsant and analgesic properties, and recorded its use-fulness as an anti-emetic.

After these observations were published in 1842, medicinal use of cannabis expanded rapidly. It soon became available 'over the counter' in pharmacies and by 1854 it had found its way into the United States Dispensatory. The American market became flooded with dozens of cannabis-containing home remedies.

Queen Victoria's personal physician wrote (**Reynolds, 1890**), on the basis of more than 30 years' experience, that "Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess". He found it incomparable for "senile insomnia", " night restlessness" and "temper disease" in both children and adults, but not helpful in melancholia, "very uncertain" in alcoholic delirium, and "worse than useless" in mania. It was very effective in neuralgia, period pains, migraine, " lightning pain of the ataxic patient" and gout, but useless in sciatica and "hysteric pains". He found it impressive in clonic spasms and certain epileptiform convulsions related to brain damage, but no good at all in petit mal or "chronic epilepsy", tetanus, chorea or paralysis agitans. It effectively relieved nocturnal cramps, asthma and dysmenorrhoea.

Reynolds was writing at a time when the zenith of cannabis as prescribed medicine and home remedy was already past. Although Sir William Osler was still recommending it for migraine sufferers in 1913, it was by then in steep decline because of variable potency of herbal preparations, poor storage stability, unpredictable response to oral administration, increasing enthusiasm for parenteral medicines and availability of potent synthetic alternatives, commercial pressures and American concern about recreational use. Cannabis was outlawed in 1928 by ratification of the 1925 Geneva Convention on the manufacture, sale and movement of dangerous drugs. Prescription remained possible until final prohibition under the 1971 Misuse of Drugs Act, against the advice of the Advisory Committee on Drug Dependence.

In the USA, medical use was effectively ruled out by the Marijuana Tax Act 1937. This ruling has been under almost constant legal challenge and many special dispensations were made between 1976 and 1992 for individuals to receive 'compassionate reefers'. Although this loophole has been closed, a 1996 California state law permits cultivation or consumption of cannabis for medical purposes, if a doctor provides a written endorsement. Similar arrangements apply in Italy and Canberra, Australia.

CANNABINOID PHARMACOLOGY RELEVANT TO THERAPEUTICS

Cannabinol was isolated in 1895 and cannabidiol in 1934, but the most significant discovery was that of Δ^9-tetrahydrocannabinol (THC) in 1964. Chromatographic and spectroscopic methods subsequently uncovered many closely related compounds.

Capsules of synthetic THC (dronabinol) have been available for restricted medical use in the USA since 1985. Nabilone, a synthetic THC analogue, was marketed in 1983 and is the only cannabinoid licensed for prescription in the UK, restricted to treatment of nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional anti-emetics. Use in other indications is only possible on a 'named patient' basis if the drug is supplied by a hospital pharmacy.

In 1988, a specific protein receptor (known as CB_1) for THC was discovered in mouse nerve cells. This mediates most of the central nervous system (CNS) responses to cannabinoids, and is abundant in basal ganglia, hippocampus and cerebellum, globus pallidus, substantia nigra and cerebral cortex. An endogenous ligand was identified in 1992 and labelled anandamide (*ananda*: 'bliss' in Sanskrit). Anandamide has analgesic and tranquillising effects in animals, is involved in muscle coordination and affects the secretion and function of certain hormones. Other endogenous agonists almost certainly exist.

In 1993, a second receptor (CB_2) was identified in rat spleen macrophages, and this occurs only outside the CNS. There is scope for chemical manipulation of cannabinoids to maximise selectivity for CB_2 and so avoid psychoactive effects. It is thought this receptor has relevance for anti-inflammatory and immunosuppressive activity.

Pertwee (**1995**) has suggested that the anandamide system might be concerned with mood, memory and cognition, perception, movement, coordination, posture and skeletal muscle tone, sleep, thermo-regulation, appetite and immune response.

CLINICAL APPLICATIONS

Nausea and vomiting

Many cytotoxic drugs are powerful emetics, and this is the major limiting factor in patients' acceptance of cancer chemotherapy (see **Table 1** and Appendix).

Table 1 **Collapse inline**

Human randomised controlled trials (RCTs): anti-emetic effects

Study	Subjects	Study design	Results
Sallan *et al* (1975)	22 patients mainly resistant to	db, pc, r, x, sd; THC 10 mg/m^2	THC significantly superior to placebo. Sedation and euphoria occurred in the majority of patients in THC phase

	conventional anti-emetics		
Chang *et al* (1979)	15 patients on high-dose methotrexate	db, pc, r, x, md; THC; oral 10 mg/m^2, smoked approx. 17 mg	" Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo"
Einhorn *et al* (1981)	100 patients on cancer chemotherapy	db, r, x, md; nabilone 2 mg q.d.s.; prochlorperazine 10 mg q.d.s.	Nabilone was significantly superior in reducing nausea and vomiting frequency, but produced more lethargy and hypotension. Nabilone was preferred by 75% of patients
Orr & McKeman (1981)	55 patients on cancer chemotherapy	db, pc, r, x, md; THC 7 mg q.d.s.; prochlorperazine 7 mg q.d.s.	THC was significantly superior to prochlorperazine ($P < 0.005$). Side-effects were evenly distributed, except that THC produced a ' high' in 82% of patients
Jones *et al* (1982)	54 patients on various chemotherapy (24 evaluable)	db, pc, r, x, md; nabilone 2 mg	Nabilone reduced mean number of vomiting episodes ($P < 0.001$) and nausea ($P < 0.001$) in comparison with placebo. Side-effects common but "acceptable"
Ungerleider *et al* (1982)	214 patients on various chemotherapy	db, r, x, md; THC 7.5-12.5 mg prochlorperazine	No significant difference in anti-nausea and vomiting between the two drugs. More side-effects on THC, yet more patients preferred it
Niiranen & Mattson (1985)	24 patients on various chemotherapy	db, r, x, sd; nabilone 2 mg *v.* 15 mg prochlorperazine	Nabilone significantly superior in reducing vomiting. More side-effects yet majority of patients preferred it
Dalzell *et al* (1986)	23 children on various chemotherapy	db, r, x, md; nabilone *v.* domperidone	Significantly fewer vomiting episodes and less nausea on nabilone. More side-effects, but 2/3 children preferred it
Niederle *et al* (1986)	20 patients on cisplatin	db, r, x, md; nabilone 2 mg b.d., alizapride 150 mg t.d.s.	Nabilone reduced emesis and relieved nausea significantly better than alizapride but caused more adverse effects
Pomeroy *et al* (1986)	38 patients on various chemotherapy	db, r, md; nabilone 1 mg *v.* domperidone 20 mg	Mean number of vomiting episodes in two cycles of treatment was 4.53 for nabilone and 10.81 for domperidone ($P < 0.01$)
Chan *et al* (1987)	30 children with chemotherapy-induced emesis	db, r, x, md; nabilone *v.* prochlorperazine	Improvement of retching and emesis was 70% during nabilone and 30% during prochlorperazine (P=0.015)
Lane *et al* (1991)	62 patients on various chemotherapy	db, r, md; dronabinol 10 mg q.d.s.; prochlorperazine 10 mg q.d.s.; or both	Percentage of patients with any nausea or vomiting was 51% for dronabinol group and 83% for prochlorperazine. A combination of the two drugs was significantly better than either alone

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; q.d.s., four times daily; b.d., twice daily; THC, tetrahydrocannabinol.

Many recreational smokers receiving cancer chemotherapy have told their doctors that cannabis relieved their nausea (**Grinspoon & Bakalar, 1993**). Sallan *et al*'s (**1975**) randomised control trial (RCT) compared oral THC and placebo in 22 cancer patients who had proved resistant to conventional anti-emetics. Comparisons using patients' self-reports of nausea and vomiting demonstrated that THC was statistically superior to placebo. THC (10 mg/m^2) produced euphoria in the majority of patients, and one-third experienced sedation.

Subsequent RCTs (listed in **Table 1**) confirmed that natural and synthetic THC is invariably superior to placebo. Comparisons with anti-emetics available in the 1970s and 1980s suggest that THC is either equivalent in effect or better. A combination of prochlorperazine and THC was superior to either drug alone, and nabilone combined

with prochlorperazine was better than dexamethazone plus metoclopramide. Although THC and nabilone produced more unwanted effects than comparison drugs, patients generally preferred them.

Children seem to respond well to nabilone and are tolerant of side-effects, but larger studies are required. Δ^8-THC performed well in a pilot study (**Abrahamov *et al*, 1995**) involving eight children aged 3-13 years with various blood cancers receiving chemotherapy, 60% of whom had experienced distressing vomiting despite treatment with metoclopramide. Δ^8-THC was given orally 2 hours before cytotoxics and repeated 6-hourly. No vomiting was recorded during this treatment and over the following 2 days. Two children were "slightly irritable" and one also showed "slight euphoria".

In a review of 12 studies involving 600 patients (**Penta *et al*, 1981**), THC was "effective" in 8/9 and nabilone in 3/3. The most common side-effects were somnolence (33%), dry mouth (9%), ataxia (8%), dizziness (6%), dysphoria (6%), and orthostatic hypotension (4%). A further review (**Levitt, 1986**) incorporating 55 studies, of which 32 were RCTs, showed that low-dose preventive treatment gives better results than targeting established vomiting. Younger patients may respond better than older ones.

Meta-analysis (**Plasse *et al*, 1991**) suggested that an optimal balance of efficacy and unwanted effects was achieved with relatively modest doses (7 mg/m^2 or less). Sedation and psychotropic symptoms are commonly reported, but are usually mild to moderate in intensity and resolve rapidly on discontinuation. No "persistent or fatal" adverse effects have been reported. Many American oncologists encourage nauseous patients to try cannabis and would prescribe it if it were legal (**Doblin & Kleiman, 1991**). Mode of action remains uncertain.

Multiple sclerosis and other neurological conditions

Drug therapy of muscle spasticity is generally only moderately effective and is limited by adverse effects (see Appendix). Spasticity is a central feature of multiple sclerosis (MS), cerebral palsy and spinal cord injury. Tremor, ataxia and incontinence also contribute to the high incidence of anxiety and depression in these conditions. Cannabis was often used to treat pain, muscle spasm, cramps and ataxia in the 19th century, and many modern sufferers have reported benefits (**Grinspoon & Bakalar, 1993**).

Most respondents to a questionnaire sent to British and American MS patients reported problems with symptom control (**Consroe *et al*, 1997**). Those who smoked cannabis claimed improvements in night-time spasticity and muscle pain (91-98%); night leg pain, depression, tremor, anxiety, spasms on walking, paraesthesiae (80-89%); leg weakness, trunk numbness, facial pain (71-74%); impaired balance (57%); constipation (33%); memory loss (31%).

In a small single-blind comparison with placebo (**Clifford, 1983**), THC improved tremor and ataxia in most patients. All experienced a 'high' at the top dose (15 mg), and two reported dysphoria. Dose-related improvements in dystonia were noted in five patients given cannabidiol 100-600 mg daily for 6 weeks.

Hypotension, dry mouth, sedation and light-headedness occurred but were described as mild. Parkinsonian symptoms were aggravated in two subjects.

An RCT by Petro & Ellenberger (**1981**) compared the effects of placebo and THC in doses of 5 or 10 mg on muscle tone, reflexes and muscle power in nine MS patients. Both doses of THC reduced spasticity ($P < 0.005$). One patient receiving THC 10 mg and one patient receiving placebo felt 'high' but no other side-effects were recorded. In a small RCT (**Ungerleider *et al*, 1987**) with 5-day treatment periods, THC 7.5 mg significantly improved spasticity in comparison with placebo. Nabilone 1 mg on alternate days was compared with placebo in a double-blind randomised cross-over trial with 4-week treatment periods in a single MS patient. Nocturia, muscle spasm and general well-being showed striking improvement during each active treatment period. Mild sedation was noted on active medication.

Cannabidiol had no beneficial effects in 15 patients with Huntington's disease (**Consroe *et al*, 1991**). Posture and balance were impaired by a single dose of smoked THC in 10 MS patients and 10 non-MS volunteers (**Greenberg *et al*, 1994**), but there was no active control to determine the effects of standard anti-spastic medication in this model.

Possible sites of action of cannabinoids in dystonia include basal ganglia, cerebellum, spinal motor neurons, somatic nerves and neuromuscular junction.

Loss of appetite and weight in cancer and AIDS

Several studies have investigated effect on appetite and weight (**Table 2**). The appetite-stimulating effect of cannabis was confirmed in fasting and non-fasting volunteers in an RCT of oral THC with alcohol, amphetamine and placebo (**Hollister, 1971**). A standardised THC smoking regime over 25 days in a residential laboratory was associated with significant increases in calorie intake and frequency of eating occasions in comparison with placebo.

Table 2 **Collapse inline**

Human randomised controlled trials (RCTs): appetite and weight

Study	Subjects	Study design	Results
Hollister (1971)	i. 12 fasting volunteers	i. db, pc, r, x, sd; THC 0.5 mg/kg; 1 ml/kg 95% ethanol; 0.2 mg/kg dexamphetamine	There was large variation between subjects, but "those results confirm the notion that marijuana has a stimulating effect upon appetite and food consumption"
	ii. 12 non-fasting volunteers	ii. db, pc, r, x, sd; THC 0.35 mg/kg ethanol as in i	
Regelson *et al* (1976)	54 patients with cancer	db, pc, r, x, md; oral THC 0.1 mg/kg t.d.s.	"THC stimulates appetite and helps retard the chronic weight loss associated with cancer". "Limiting side-effects which restrict use in 25% patients are somnolence, dizziness, and disassociation"
Gross *et al* (1983)	11 patients with anorexia nervosa	db, pc, r, x, md; THC 7.5-10 mg daily; diazepam (active placebo) 3-15 mg/day	"THC is not efficacious, in short-term administration, in the treatment of primary anorexia nervosa and is associated with significant psychic disturbances in some PAN patients"
Foltin *et*	9 volunteers	sb, pc, r, x, md; marijuana	"Smoked marijuana can produce significant increases in food intake with

al (1986)		(1.84% THC)	small groups of subjects in a residential laboratory setting"
Beal *et al* (1995)	139 patients with AIDS-related anorexia and weight loss	db, pc, r, md; dronabinol 2.5 mg b.d.	In comparison with placebo, dronabinol improved appetite (P=0.015), mood (P=0.06) and decreased nausea (P=0.05). There was a trend toward weight stabilisation (P=0.1)

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; t.d.s., three times daily; b.d., twice daily; PAN, primary anorexia nervosa; THC, tetrahydrocannabinol.

Open studies in cancer patients also showed appetite improvements and slowing of weight loss. Regelson *et al*'s (**1976**) RCT explored the effect on appetite (and mood) of oral THC in 54 cancer patients over a 2-week period. There were nine with-drawals due to side-effects (six in THC period - dizziness, disassociation, confused thinking, panic, "feelings of disturbance"; three in the placebo period - anxiety, fits, dizziness, lethargy, weakness). Patients receiving THC in the first period gained weight (P<0.05), and those receiving placebo first showed reduced weight loss on transfer to THC (P<0.05). Depression, tranquillity and " forthrightness" scores all improved on THC. In a quarter of the patients, somnolence, dizziness and disassociation were severe enough to negate these effects.

Many people with AIDS have claimed that smoking marijuana inhibits nausea, improves appetite, reduces anxiety, relieves aches and pains, improves sleep and inhibits oral candidiasis. A small pilot study supported the hypothesis that dronabinol might reduce weight loss or even promote weight gain (**Plasse *et al*, 1991**).

Beal *et al* (**1995**) conducted an RCT over 42 days of treatment with dronabinol 5 mg daily in 139 AIDS patients who had lost at least 2.3 kg. Six receiving dronabinol and three receiving placebo withdrew because of "perceived drug toxicity". Dronabinol boosted appetite in comparison to placebo (P<0.015) and nausea was reduced (P=0.05). Improvement in mood was a strong trend (P=0.06) and there was a tendency toward weight gain (P=0.1). Dronabinol produced more adverse effects than placebo (P<0.001), but 75% of these were mild or moderate. Most frequent were euphoria (9), dizziness (5), thinking abnormalities (5) and sedation (4).

Further investigation is amply justified. Careful monitoring of possible effects upon the immune system is needed, although a prospective multi-centre study (**Kaslow *et al*, 1989**), which followed nearly 5000 HIV-positive men for 18 months, showed no link between use of psychoactive substances and mean T-cell counts or progression to AIDS.

Pain

Cannabinoids are effective analgesics in animal models with non-opiate mechanisms predominating. There are many anecdotal reports (**Grinspoon & Bakalar, 1993**) of benefits in bone and joint pain, migraine, cancer pain, menstrual cramps and labour.

Five small RCTs (**Table 3**) show that THC is significantly superior to placebo and produces dose-related analgesia peaking at around 5 hours, comparable to but out-lasting that of codeine. Side-effects were also dose-related, and consisted of slurred speech, sedation and mental clouding, blurred vision, dizziness and ataxia.

Levonantradol was also superior to placebo and notably long-acting, but almost half the patients reported sedation. Cannabinoids may have considerable potential in neuropathic pain (**Institute of Medicine, 1999**).

Table 3

Collapse inline

Human randomised controlled trials (RCTs): pain

Study	Subjects	Study design	Results
Noyes *et al* (1975*a*)	10 patients with cancer pain	db, pc, r, x, sd; THC 5, 10, 15 & 20 mg	" Pain relief significantly superior to placebo was demonstrated at high dose levels (15, 20 mg)"
Noyes *et al* (1975*b*)	36 patients with cancer pain	db, pc, r, x, md; THC 20 mg, codeine 120 mg	Codeine and THC were equally effective, but higher dose of THC sedated most patients and some found its psychoactive effects uncomfortable
Jain *et al* (1981)	56 patients with postoperative pain	db, pc, r, sd; levonantradol 1.5, 2, 2.5 or 3 mg i.m.	All doses significantly superior to placebo (at least $P<0.05$), but no dose—response effect; 57% patients reported at least one side-effect, but "general acceptability was good"
Maurer *et al* (1990)	1 patient with spinal cord injury	db, pc, r, x, md; THC 5 mg, codeine 50 mg	" Delta-9-THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant effect on spasticity"
Holdcroft *et al* (1997)	1 patient with GI tract pain (familial Mediterranean fever)	db, pc, x, md; THC 50 mg daily	Morphine requirement significantly reduced ($P<0.01$) during active treatment

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; i.m., intramuscularly; GI, gastrointestinal; THC, tetrahydrocannabinol.

Raised intra-ocular pressure

Glaucoma due to obstructed outflow of aqueous humour or anatomical eye defects is the most common cause of blindness in the Western world. Some RCTs investigating this area are given in **Table 4**.

Table 4

Collapse inline

Human randomised controlled trials (RCTs): raised intra-ocular pressure (IOP)

Study	Subjects	Study design	Results
Hepler *et al* (1976)	i. 429 normal volunteers	i. db, pc, r, sd; smoked THC 1, 2 & 4%; oral THC 15, 30 & 40 mg	i. "dose-related and statistically significant effect in reducing acutely the intraocular pressure"; "pressure drop was in the range of 30% for 2% THC"
	ii. 48 hospitalised subjects	ii. sb, pc, md; smoked THC 1 & 2%	ii. "consistent drop in IOP around 30% for 2% THC" and "no indications of cumulative effects upon IOP"
	iii. 11 patients with glaucoma	iii. o; smoked THC 1, 24% oral THC 15 mg	iii. 7 patients showed a similar response to the above, 4 patients had no demonstrable drug effect
Perez-Reyes *et al* (1976)	12 normal volunteers	sb, pc, r, x, sd; i.v. infusion of various cannabinoids	"Δ^{8}-THC, Δ^{9}-THC, and 11-hydroxy-THC produced significant reductions in IOP, whereas cannabinol, 8-β-OH-THC and cannabidiol were less effective"
Merritt *et al* (1980)	18 patients with glaucoma	db, pc, sd; smoked marijuana - THC=2%	Significant reductions in IOP, but hypotension, tachycardia, palpitations and psychotropic effects "mitigate against routine use in the general glaucoma population"

Merritt *et al* (1981)	8 patients with "hypertensive glaucoma"	db, pc, sd; THC eye drops; 0.01%, 0.05%, 1%	Dose-related reductions in IOP; 1% drops produced mild hypotension, no psychic effects at any dose. Effect in both eyes suggests systemic mechanism of action
Jones *et al* (1981)	13 normal volunteers	db, pc, x, md; 10-30 mg THC 4-hourly	Significant reductions in IOP tend to tolerate out after 10 days regular dosing. Abrupt withdrawal of THC produces rebound increase in pressure above baseline

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; i.v., intravenous; THC, tetrahydrocannabinol.

There have been many anecdotal reports that street marijuana can relieve glaucoma symptoms and individuals have successfully argued in the USA for legal access to the drug (**Grinspoon & Bakalar, 1993**). A pilot study of smoked marijuana and oral THC (15 mg) in 11 glaucoma patients found an average intra-ocular pressure (IOP) reduction of 30% in seven subjects and no response in four (**Hepler *et al*, 1976**).

Randomised controlled trials in volunteers confirmed that oral, injected or smoked cannabinoids produce dose-related reductions of IOP (**Hepler *et al*, 1976**; **Perez-Reyes *et al*, 1976**). Conjunctival engorgement and tear reduction were often noted. THC, Δ^8-THC and 11-hydroxy- THC are more effective than cannabinol, while cannabidiol was without effect. Tolerance may develop on multiple dosing.

An RCT in patients showed IOP reductions of similar magnitude following smoked THC along with "alterations in mental status" and tachycardia (**Merritt *et al*, 1980**). THC eyedrops produced dose-related IOP reduction with minimal side-effects though parallel reductions in the untreated eye (also seen in animal models) suggested a systemic rather than local mode of action.

Insomnia, anxiety and depression

Randomised controlled trials investigating insomnia, anxiety and depression are given in **Table 5**.

Table 5 **Collapse inline**

Human randomised controled trials (RCTs): insomnia, anxiety, depression

Study	Subjects	Study design	Results
Regelson *et al* (1976)	54 patients with cancer	db, pc, r, x, md; oral THC 0.1 mg/kg t.d.s.	" THC in cancer patients at acceptable dosage (0.1 mg/kg t.i.d. orally) had the effect of a tranquilliser and mild mood elevator, clearly without untoward effect on personality or emotional stability"
Carlini & Cunha (1981)	15 insomniac volunteers	db, pc, r, x, sd; cannabidiol 40, 80, 160 mg; nitrazepam 5 mg	Large placebo effect on sleep induction similar to that of active drugs. Cannabidiol significantly increased duration of sleep, and all three doses reduced dream recall
Fabre & McLendon (1981)	20 anxious patients	db, pc, r, md; nabilone 2-8 mg/day	A "dramatic improvement in anxiety in the nabilone group when compared with placebo ($P < 0.001$)" was reported. More dropouts from the placebo group ($P < 0.03$). Dry mouth and eyes and drowsiness were the most common adverse effects
Ilana *et al* (1981)	11 patients with anxiety	db, pc, r, x, md; nabilone 1-2.5 mg b.d.	Nabilone was superior to placebo ($P < 0.05$) in relieving anxiety scores on Hamilton Anxiety Scale and Global Improvement Scale

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; t.d.s., three times daily; b.d., twice daily; THC, tetrahydrocannabinol.

Nabilone (1 mg three times daily) produced "dramatic improvements" on the Hamilton Anxiety Scale in 20 anxious patients in comparison to placebo ($P<0.001$), which were mirrored by other measures (**Fabre & McLendon, 1981**). Seven days into the study, nabilone patients' anxiety scores were halved, and this persisted unchanged throughout treatment. Side-effects included dry mouth, dry eyes and drowsiness. The authors concluded that nabilone is a "very effective anxiolytic deserving of further study". In a cross-over comparison of nabilone (1-2.5 mg twice daily) and placebo in 11 anxious patients (**Ilaria *et al*, 1981**), significant improvements in anxiety scores ($P<0.05$) were again noted. The only clinically significant adverse effect was postural hypotension with related dizziness, light-headedness or weakness. This was dose-related, experienced by most patients, and tended to tolerate out over time.

Preliminary data suggest that cannabidiol (160 mg) may be an effective hypnotic, and that THC (0.1 mg/kg) may have antidepressant properties in cancer patients and others (**Grinspoon & Bakalar, 1993**).

Epilepsy

Epilepsy afflicts 1% of the world's population. Conventional anticonvulsants provide unsatisfactory control for up to 30% of patients, and all can produce disabling or even life-threatening adverse effects.

The effect of cannabinoids on seizure activity in laboratory animals is complicated. Cannabidiol is a powerful anticonvulsant free of tolerance, but its profile varies between species. THC can produce seizures in big doses or when genetically seizure-sensitive animals are used, yet it is also robustly anticonvulsant in certain seizure models. A lack of stereospecificity suggests that the mechanism may not be related to a single receptor interaction. Serotonin, γ-aminobutyric acid, acetylcholine or prostaglandin systems may be involved.

There are many anecdotal reports of beneficial effects in humans with epilepsy (**Grinspoon & Bakalar, 1993**) but research data are virtually non-existent. Two single-case reports (**Keeler & Reifler, 1967**; **Consroe *et al*, 1975**) give confounding information. A young man suffered seizures on his regular medication and began smoking several cannabis cigarettes nightly alongside this. No further seizures occurred while this combination was maintained. In contrast, a man with grand mal epilepsy stopped taking anticonvulsants and suffered no fits for 6 months. He then smoked cannabis on seven occasions over a 3-week period and suffered three fits during this time, although not coincident with actual intoxication.

Only one RCT (**Cunha *et al*, 1980**) exists. Fifteen poorly controlled patients with secondary generalised epilepsy continued with their regular therapy but were also given either cannabidiol or placebo daily for up to 4.5 months while under-going regular clinical and electroencephalogram evaluation. Half the patients on cannabidiol remained "almost free" of fits throughout the experiment, and all but one of the others showed "partial

improvement". All but one of the placebo patients remained entirely un-changed. Somnolence occurred in four patients receiving cannabidiol.

Asthma

Small-scale controlled studies in volunteers with asthma show that oral, smoked and aerosolised THC has comparable bronchodilatory activity to salbutamol, although onset is quicker with the latter. Dose-related tachycardia occurred in some individuals, and subjective intoxication with higher doses. A THC aerosol was free of systemic unwanted effects, but was irritant to the lungs (**Tashkin *et al*, 1977**). Nabilone does not produce bronchodilation. Since THC-induced bronchodilation is not mediated through the sympathetic nervous system, synergistic combinations with β_2-adrenoceptor stimulants might be possible.

Other possible therapeutic applications

Basic research indicates that THC and analogues inhibit opioid withdrawal (**Chesher & Jackson, 1985**). Anecdotal reports from patients also point to beneficial effects beyond those which could be accounted for by sedative or hypnotic activity. Cannabinoids inhibit primary tumour growth and increase survival in animal tumour models (**Harris *et al*, 1976**) by an unknown mechanism. They also show antipyretic and anti-inflammatory activity (**Formukong *et al*, 1989**). Mechoulam (**1986**) has drawn attention to the lack of modern research directed at possible antihelmintic, antimigraine and oxytocic applications.

DISCUSSION

Therapeutic profile on existing evidence

Tetrahydrocannabinol and nabilone are effective anti-emetics but there are no comparisons with 5-HT_3 antagonists, so a role in modern anti-emetic regimes remains to be determined. Currently, only nabilone is licensed in the UK and available for prescription and research. THC (as dronabinol) has recently been rescheduled to permit prescription but remains unlicensed and must be specially imported on a named-patient basis. Delta-8-THC looks worthy of further investigation, particularly in children, and is much simpler to synthesise than THC.

Many individuals with MS have claimed a benefit from cannabis and small controlled trials support this, although effect upon posture and balance requires clarification. THC is an effective analgesic at the expense of sedation with larger doses and may have special merit in neuropathic pain. No conclusions are possible as yet about anticonvulsant potential. Some cannabinoids reduce IOP, though side-effects of products currently available limit application and effects of tolerance are uncertain. The mechanism for bronchodilation probably differs from that of β_2-stimulants, so synergistic combinations may be possible.

Cannabis and THC are effective appetite stimulants. Alongside anti-emetic, analgesic, anxiolytic, hypnotic and anti-pyretic properties this suggests a unique role in alleviating symptoms in selected patients with cancer or

AIDS. This is a compelling area for future research, although possible effects upon immune function require careful monitoring.

Optimal doses and routes of delivery have not been established. Absorption by the oral route is unreliable. Smoking the drug is generally not a viable option since advantages such as rapid onset, accurate titration of effects and reliability in patients who are vomiting have to be set against the likelihood of lung irritation or damage, and it would in any case be unacceptable to most patients. However, pending availability of more satisfactory preparations, I believe that the existing profile of efficacy and toxicity justifies the provision of a legal supply of standardised herbal material ('compassionate reefers') to patients with terminal conditions who currently obtain relief with street cannabis. Sublingual sprays or tablets, nebulisers and aerosols look promising for the future, and THC is effective by the rectal route. Many potentially active cannabinoids have yet to be investigated and the recent identification of a peripheral receptor may lead to new drugs devoid of central nervous system effects.

Cannabis arouses passion in those who support or condemn it, and few people approach the clinical literature with dispassionate objectivity. Poorly controlled research produces ambiguous results which are then interpreted according to the prejudices of the reader. Anecdotes seem to be more readily accepted when they point to adverse rather than positive effects (**Hall *et al*, 1994**). Yet the known adverse effects of oral cannabinoids are rarely intolerable or life-threatening, in contrast to those associated with some standard therapies. A British Medical Association survey indicated that many UK doctors believe that cannabis should once again be available on prescription (**Meek, 1994**).

The way forward

A Select Committee of the House of Lords recently examined the scientific information concerning medical cannabis and took verbal and written evidence from a wide range of witnesses. Their conclusion (**House of Lords, 1998**) published in November 1998, was that, although cannabis should remain a controlled drug, the law should be changed to allow doctors to prescribe " an appropriate preparation of cannabis if they saw fit". The government rejected this recommendation on the day of publication.

Under the auspices of the Royal Pharmaceutical Society, large-scale multicentre trials are under way to explore further the efficacy of cannabinoids in relieving spasticity and postoperative pain. A pharmaceutical company has obtained a licence to cultivate medicinal cannabis on a large scale in the UK. By selecting a specific genotype then carefully controlling all other relevant variables such as soil conditions, temperature and humidity, it is possible to obtain levels of purity in plant extracts equal or superior to those of 'pure' synthetic cannabinoids. Most of the 60 or so naturally occurring cannabinoids are present in tiny amounts, and synthetic cannabinoids such as nabilone themselves contain up to 5% impurities, some of which are of unknown identity. Whether obtained by synthetic means or by plant extraction, it is essential that cannabinoids for prescription and research in the future should demonstrate excellent purity, stability and bioavailability.

The medicinal properties of cannabis are still mainly delineated by the anecdotal reports of those who believe their symptoms are relieved by its use, and these accounts are often dismissed as wishful thinking or even mischievous. Since the conventional treatments for many of these disorders are both toxic and relatively ineffectual, a more constructive response would be to expose such claims to careful scientific examination and, in the meantime, search for a way to avoid criminalising those who seek only to assuage their own suffering.

APPENDIX

Existing anti-emetics

Phenothiazzines and *butyrophenones* can cause sedation, movement disorders which may be irreversible, neuroleptic malignant syndrome, dry mouth, blurred vision, urinary retention, hypotension, allergic reactions, jaundice, hypothermia, hormonal disturbances, irreversible eye damage and, rarely, life-threatening anaemias. *Domperidone* has a more benign profile but is not recommended for long-term use. *Metoclopramide* produces movement disorders (1% of patients), dizziness and drowsiness. Selective 5-HT_3 antagonists (*ondansetron, granisetron*) are newer and more expensive. Side-effects include constipation, headache, flushing, liver enzyme changes, allergic reactions, visual disturbances, chest pain and dysrhythmias.

Existing neurological treatments

Baclofen alleviates spasticity, but may accentuate muscle weakness. It produces dose-related nausea and vomiting, drowsiness, vertigo, confusion, fatigue and hypotonia. Less commonly, fits, psychiatric disorder and hypotension occur. Sudden withdrawal can cause hallucinations. *Diazepam* is useful but can worsen weakness or incoordination and cause drowsiness, ataxia, depression, disinhibition and dependence. *Dantrolene* may cause weakness, hypotonia, drowsiness, dizziness, vertigo and anxiety. Rarely, it damages the liver, and is not recommended in those with co-existing heart or lung disease.

Existing glaucoma treatments

Eye-drops. *Miotics* can produce blurring of vision, headache, and parasympathetic effects including sweating, bradycardia, colic and bronchospasm. *Adrenaline* often causes local discomfort. *Dipivefrine* and *guanethidine* may cause conjunctival fibrosis on chronic use. *Beta-blockers* may cause bradycardia, heart block or bronchoconstriction.

Systemic drugs (*acetazolamide, dichlorphenamide*) can cause hypokalaemia, appetite suppression, paraesthesiae, drowsiness, depression, rashes and, rarely, bone marrow suppression.

Clinical Implications and Limitations

CLINICAL IMPLICATIONS

Cannabis and its derivatives show promise of beneficial effects in a number of medical conditions for which standard treatment is less than satisfactory, and further controlled research is fully justified.

Cannabis is very safe in overdose, but often produces unwanted effects which are better tolerated by patients with some conditions (e.g. multiple sclerosis, chronic pain, AIDS, cancer) than others (e.g. glaucoma).

Optimal formulations, doses and routes of delivery have not yet been established.

LIMITATIONS

Because of imposed time constraints, the review is not fully comprehensive, although all accessed sources were incorporated.

Much of the evidence is anecdotal, and many of the research studies cited have serious methodological shortcomings.

Few researchers (or reviewers) approach the subject of cannabinoid therapeutics in a spirit of dispassionate objectivity.

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Footnotes

- † See editorial, p. 98, this issue.

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Review

Review on clinical studies with cannabis and cannabinoids 2005-2009

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Abstract

To date, a large number of controlled clinical trials have been done evaluating the therapeutic applications of cannabis and cannabis-based preparations. In 2006, an excellent review was published, discussing the clinical trials performed in the period 1975 to June 2005 [Ben Amar 2006]. The current review reports on the more recent clinical data available. A systematic search was performed in the scientific database of PubMed, focused on clinical studies that were randomized, (double) blinded, and placebo-controlled. The period screened was from July 1, 2005 up to August 1, 2009.

The key words used were: cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador and Sativex. For the final selection, only properly controlled clinical trials were retained. Open-label studies were excluded, except if they were a direct continuation of a study discussed here.

Thirty-seven controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Based on the clinical results, cannabinoids present an interesting therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis.

Keywords: cannabinoids, cannabis, therapeutic potential, controlled clinical trial, efficacy, safety

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Introduction and Method

There is a growing number of clinical studies that indicate that cannabis or single cannabinoids may have medicinal value for certain diseases and under certain conditions. In the period from 1975 to current, at least 110 controlled clinical studies have been published, assessing well over 6100 patients suffering from a wide range of illnesses. Also the mechanisms of action are becoming increasingly clear since the discovery of the endocannabinoid system and its physiological functions.

In 2006, the Canadian researcher Ben Amar published a review discussing the results of clinical trials performed with cannabis and cannabinoids over the period 1975 to June 2005.The review presented here reports on the period following this, discussing the clinical trials published since then. Together, these two reviews can provide a convenient overview of clinical studies over the last 34 years.

The methodology of this review has been adopted from Ben Amar [2006]. In order to assess the current knowledge on the therapeutic potential of Cannabis, phyto-cannabinoids, and medicinal preparations directly based on phyto-cannabinoids, a systematic search was performed in the scientific database of *PubMed*. Hosted by the U.S. National Library of Medicine, this database contains about 20 million scientific publica-

tions from the field of life sciences and biomedical information.

The period screened was from July 1, 2005 up to August 1, 2009. Clinical data from the period up to July 2005 has been previously reviewed by Ben Amar [2006]. The search focused on clinical studies that were randomized, (double) blinded, and placebo-controlled. The key words used were: *cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador* and *Sativex*.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded, except when they were a direct continuation of a clinical trial discussed in this paper. The research included the works and data available in English, but also other languages (2x German, 1x Danish).

A range of different cannabis-based products are described in the studies presented in this review. For the ease of the less experienced reader, these preparations are briefly discussed below:

Cannabis refers to the dried flowertops of the female plant of Cannabis. This herbal product is also commonly known as marijuana or marihuana. The main way to administer cannabis is by smoking, which is also the way most medicinal users consume it. For clinical trials, most often these materials are standardized for their content (in % of dry weight) of THC.

THC, or delta-9-tetrahydrocannabinol, is the pharmacologically and toxicologically most relevant constituent found in the Cannabis plant, producing a myriad of effects in animals and humans. The most well-established palliative effect of THC is the inhibition of chemotherapy-induced nausea and vomiting, mainly in cancer patients. Pure THC can be derived from natural sources (extraction from cannabis plants) or produced synthetically. Chemically, THC belongs to a group of closely related compounds known as cannabinoids, and they are commonly considered the main bioactive components of Cannabis. Up to date, more than 100 different cannabinoids have been described, but only a few of the major ones have been characterized for biological activities, including cannabidiol (CBD, see below) and cannabinol (CBN).

Dronabinol is the INN (international non-proprietary name) of the isomer of delta-9-tetrahydrocannabinol that is present in the cannabis plant, the (-)-trans-isomer. This is the only naturally occurring of the four isomers. Oral capsules containing synthetically manufactured dronabinol are available under the name Marinol (see below).

CBD, or cannabidiol, is the major non-psychotropic cannabinoid found in Cannabis. It has shown anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and anti-psychotic activity and reduces the psychoactive effects of THC [Russo 2006]. The mode of action of cannabidiol is not fully understood and several mechanisms have been proposed: (1) CBD acts as antagonist at the central CB_1 receptor and was able to inhibit several CB_1 mediated THC effects [Zuardi et al. 1982]. In a study by Petitet et al. (1998), CBD considerably reduced the receptor activation by the potent classical CB_1 receptor agonist CP55940. (2) CBD stimulates the vanilloid receptor type 1 (VR_1) with a maximum effect similar in efficacy to that of capsaicin [Bisogno et al. 2001]. (3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration [Bisogno et al. 2001, Mechoulam & Hanus 2002]. (4) Finally, CBD may also increase the plasma THC level [Bornheim et al. 1995] by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system [Bornheim et al. 1998, Jaeger et al. 1996]. However, there was no or minimal effect of CBD on plasma levels of THC in man [Agurell et al. 1981, Hunt et al. 1981]. Further mechanisms have been described.

Marinol® (Solvay Pharmaceuticals, Belgium) is a synthetic version of dronabinol. It is formulated as a capsule containing synthetic dronabinol in sesame oil. In the US it is indicated for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. The patent on Marinol will expire in 2011, opening the way for the development of generic preparations of synthetic, as well as naturally-derived, THC.

Nabilone (Valeant Pharmaceuticals International, USA) is a synthetic analogue of THC which binds to the cannabinoid CB1 receptor. In Canada, the United States, the United Kingdom and Mexico, nabilone is marketed as Cesamet®. It is registered for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. It is also used for other medical conditions.

Sativex® (GW Pharmaceuticals, UK) is a cannabis-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, delivered in an oromucosal (into the mouth) spray. Because of the use of whole extracts, non-standardized amounts of ballast components are also present, such as minor cannabinoids and terpenoids. Sativex has been approved in Canada as adjunctive treatment for neuropathic pain in adults with multiple sclerosis (MS) and in cancer pain. Registration is pending in several European countries.

Cannador® (Society for Clinical Research, Germany) is an oral capsule containing a whole plant extract, with standardized THC content and a CBD amount controlled to lie within a fixed narrow range with a THC:CBD ratio of about 2:1. It has been used in several clinical trials. It has been clinically tested for reduction of muscle stiffness, spasms and associated pain in Multiple Sclerosis, for cachexia in cancer patients and for post-operative pain management.

Table 1: Number of studies and patients reviewed

Pathology	# of studies found	Total # of patients included
1. Neuropathic or chronic pain:	11	631
2. Experimental pain:	4	63
3. Multiple sclerosis and spasticity:	9	1300
4. HIV/AIDS:	4	118
5. Glaucoma:	1	6
6. Intestinal dysfunction:	2	82
7. Nausea/vomiting/appetite:	2	228
8. Schizophrenia:	2	55
Other indications:	2	80
Total	**37**	**2563**

Results

The review identified 8 main pathologies in which controlled studies on cannabinoids have been published: they are listed below. A number of other illnesses have been grouped under 'other indications'. Although experimentally induced pain is obviously not a pathological condition, it has been included in this review because it may add to our understanding of the use of cannabis for pain control.

In total, 37 controlled studies evaluating the therapeutic effects of cannabis or cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed the type of study and comparisons done, the products and the dosages used, and their efficacy are described. Noteworthy adverse and side effects for each study are discussed in the text.

Summary of the clinical trials

Neuropathic, chronic and acute pain

A range of studies has been done to determine the effect of nabilone on different types of pain. Based on the analgesic effects of cannabinoids in animal studies, it was hypothesized that nabilone would decrease morphine consumption, pain scores, nausea and vomiting following major surgery. **[Beaulieu 2006]** tested this hypothesis in a double-blind, randomized, placebo-controlled, parallel-group pilot trial with three doses of 1 or 2 mg of nabilone in the 24 hours after different types of major surgery. Surprisingly, and contrary to the main hypothesis, pain scores at rest and on movement were actually significantly higher in the 2 mg nabilone group compared to the other groups. Also, nabilone administration was not associated with a decrease in morphine consumption in patients. The most common adverse effects of nabilone were dry mouth, nausea and vomiting, respiratory depression, sedation and pruritus. No serious adverse events were observed.

It is concluded from animal experiments that cannabinoid receptor and mu-opioid receptor agonists act synergistically with respect to antinociception. In order to demonstrate this effect under clinical conditions, a study was performed with oral THC on patients after radical prostatectomy **[Seeling 2006]**. It was expected that patients receiving THC required significantly less of the synthetic opioid analgesic piritramide to control their pain compared to patients on placebo. From the evening before the operation until the morning of the second postoperative day, patients received eight oral doses of either placebo or 5 mg THC, which is a significant amount of THC for any clinical trial. However, neither synergistic effect nor even an additive antinociceptive interaction with the combination of THC and piritramide was found, even though plasma concentrations of THC were measurable in all patients in the verum group.

In another study on postoperative pain, **Holdcroft et al. [2006]** aimed to investigate whether a single oral dose of Cannador could provide pain relief with minimal side effects. Sixty-five patients received a single dose of 5, 10, or 15 mg Cannador when they had at least moderate pain after stopping patient-controlled analgesia. Pain relief, pain intensity, and side effects were recorded over 6h after administration. Rescue analgesia was requested by all 11 patients (100%) receiving 5 mg, 15 of 30 patients (50%) receiving 10 mg, and 6 of 24 patients (25%) receiving 15 mg Cannador. There was a significant dose-response effect for decreasing pain intensity at rest, and increasing sedation. The number needed to treat (NNT) to prevent one rescue analgesia request for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 and 1.3, respectively, which is equivalent to many routinely used analgesics. The majority of adverse events affected the central nervous (14 of 26) or cardiovascular (6 of 26) systems, but none persisted after the study. The study was terminated because of a serious vasovagal adverse event in one patient receiving 15 mg.

In a study with nabilone, focusing on chronic pain, results were more promising. [Pinsger 2006] investigated the effect of an add-on treatment with nabilone on patients with chronic therapy-resistant pain in causal relationship with a pathologic status of the skeletal and locomotor system. From the results, it was obvious that the nabilone treatment (up to 1 mg per day) was superior, resulting in a decrease in several different

Table 2: Studies on neuropathic or chronic pain

Study	Country	Indication	Type of study	Product	Patients assessed	Efficacy
Skrabek et al. (2008)	Canada	Fibromyalgia	Randomized, double-blind, placebo-controlled trial	Nabilone (oral)	40 fibromyalgia patients having continued pain despite the use of other oral medications.	Nabilone improved symptoms and was well-tolerated.
Wilsey et al. (2008)	United States	Neuropathic pain	Double-blind, placebo-controlled, crossover study	Cannabis (smoked)	38 patients with complex regional pain syndrome (CRPS type I), spinal cord injury, peripheral neuropathy, or nerve injury.	Significant improvement of neuropathic pain.
Narang et al. (2008)	United States	Chronic pain	Phase I: randomized, single-dose, double-blind, placebo-controlled, crossover trial; Phase II: extended open-label titrated trial.	Dronabinol (oral)	30 patients with severe chronic noncancer pain, taking stable doses of opioid analgesics for longer than 6 months.	THC (in combination with opioids) reduced pain & pain bothersomeness, and increased satisfaction. No difference was observed between 10-20mg THC.
Frank et al. (2008)	Great Britain	Chronic neuropathic pain	Randomised, double blind, crossover trial	Nabilone (oral)	96 patients with chronic neuropathic pain.	Dihydrocodeine provided better pain relief than Nabilone.
Nurmikko et al. (2007)	Great Britain	Neuropathic pain, allodynia	Randomised, double-blind, placebo-controlled, parallel-group trial	Sativex (sublingual)	125 patients with a current history of unilateral peripheral neuropathic pain and allodynia.	Significant improvement in pain by Sativex.
Holdcroft et al. (2006)	Great Britain	Postoperative pain	Multicenter dose-escalation study	Cannador (oral)	65 Postoperative patients experiencing at least moderate pain, after stopping patient controlled analgesia.	The optimal dose was 10 mg Cannador, effectively reducing postoperative pain without serious side effects.
Pinsger et al. (2006)	Austria	Chronic pain	Placebo-controlled, double-blind pilot study	Nabilone (oral)	30 patients with chronic therapy-resistant pain in causal relationship with a pathologic status of the skeletal and locomotor system.	Nabilone caused a significant reduction in pain and improvement of quality of life.
Blake et al. (2006)	Great Britain	Pain in rheumatoid arthritis	Placebo-controlled, randomized, double-blind, parallel group study	Sativex (sublingual)	58 patients with active arthritis not adequately controlled by standard medication.	Sativex produced improvements in pain and sleep.
Ware et al. (2006)	Canada	Chronic pain	Randomized, controlled, crossover trial	Cannabis (smoked)	8 experienced and authorized (Canada) cannabis users with chronic pain.	Medical cannabis users can appreciate differences in herbal cannabis products.
Seeling et al. (2006)	Germany	Postoperative pain	Randomized, double blind trial	THC (oral)	100 patients after radical prostatectomy.	No synergistic or additive interaction between THC and piritramide.
Beaulieu et al. (2006)	Canada	Postoperative pain	Double-blind, randomized, placebo-controlled, parallel-group pilot trial	Nabilone (oral)	41 patients undergoing gynecologic, orthopedic or other surgery.	Nabilone did not reduce 24h morphine consumption or improve effects of morphine. Nabilone did increase pain scores.

Table 3: Studies on experimental pain

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Kraft et al. (2008)	Austria	Acute inflammatory pain and hyperalgesia	Double-blind, placebo-controlled, crossover study	Cannador (oral)	18 healthy female volunteers without a history of cannabis use.	No analgesic or antihyperalgesic activity observed for the cannabis extract. However, Cannador did lead to hyperalgesic effect.
Redmond et al. (2008)	Canada	Experimental heat pain	Double-blind, placebo controlled, crossover study	Nabilone (Oral)	17 healthy volunteers.	Nabilone failed to produce analgesic effect, and it did not interact with descending pain inhibitory systems. Significant difference was observed in effects between men and women.
Wallace et al. (2007)	United States	Pain: capsaicin-induced and hyperalgesia	Randomized, double-blind, placebo-controlled, crossover trial	Cannabis (smoked)	15 healthy volunteers.	A medium dose of cannabis reduced pain, while a high dose increased pain induced by capsaicin.
Roberts et al. (2006)	United States	Analgesia, synergy with morphine	Double-blind, four treatment, four period, four sequence, crossover trial	THC (oral)	13 healthy volunteers.	There was a synergistic effect between THC and morphine on the affective component of pain but not on the sensory component.

Table 4: Studies on multiple sclerosis and spasticity

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Aragona et al. (2009)	Italy	MS: psycho-pathological and cognitive effects	Double-Blind, placebo-controlled, crossover trial	Sativex (sublingual)	17 cannabis-naïve MS patients	Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patients
Conte et al. (2009)	Italy	MS: pain	Randomized, double-blind, placebo-controlled, cross-over study	Sativex (sublingual)	18 patients with secondary progressive MS	Results provide objective neurophysiological evidence that cannabinoids modulate the nociceptive system in patients with MS
Collin et al. (2007)	Great Britain	MS: spasticity	Randomized, placebo-controlled trial	Sativex (sublingual)	189 MS patients with spasticity.	Significantly reduction in spasticity.
Rog et al. (2007)	Great Britain	MS: neuropathic pain (Open label extension of Rog 2005)	Uncontrolled, open-label trial	Sativex (sublingual)	63 MS patients with central neuropathic pain.	Sativex was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced side effects, the most common of which were dizziness and nausea.
Kavia et al. (2006)	Great Britain	MS-associated detrusor overactivity	Double blind, randomized, placebo controlled parallel group trial	Sativex (sublingual)	135 MS patients with an overactive bladder.	Sativex has a beneficial effect on the symptoms of overactive bladder.
Freeman et al. (2006)	Great Britain	MS: urge incontinence	Multicentre, randomised placebo-controlled trial	Cannador (oral); dronabinol (oral)	630 MS patients with muscle spasticity.	Cannabis and THC caused a significant reduction in incontinence.
Wissel et al. (2006)	Austria	Spasticity related pain	Double-blind placebo-controlled cross-over trial.	Nabilone (oral)	11 patients with chronic upper motor neuron syndrome (UMNS).	Significant reduction of pain, but not of spasticity, motor function, or activities of daily living.
Wade et al. (2006)	Great Britain	MS: spasticity (Open label extension of Wade 2004)	Open label continuation after placebo-controlled study	Sativex (sublingual)	137 MS patients with symptoms not controlled satisfactorily using standard drugs.	Long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit. The precise nature and rate of risks with long-term use, especially epilepsy, will require larger and longer-term studies.
Katona et al. (2005)	Great Britain	MS: cytokine profile	Randomised, placebo-controlled trial at 33 UK centers	Sativex (sublingual)	100 MS patients with muscle spasticity.	No evidence for cannabinoid influence on serum levels of cytokines.

Table 5: Studies on HIV/AIDS

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Ellis et al. (2009)	United States	Neuropathic pain	Phase II, double-blind, placebo-controlled, crossover trial	Cannabis (smoked)	28 patients with documented HIV infection and neuropathic pain refractory to a least two previous analgesics.	Significant pain relief with cannabis.
Haney et al. (2007)	United States	HIV: caloric intake, mood, sleep	Placebo-controlled within-subjects study	Dronabinol (oral); Cannabis (smoked)	10 patients taking at least 2 antiretroviral medications, currently under the care of a physician for HIV management, and smoking marijuana at least twice weekly for the past 4 weeks.	THC and cannabis caused an increase in caloric intake and weight.
Abrams et al. (2007)	United States	HIV: sensory neuropathy	Prospective randomized placebo-controlled trial	Cannabis (smoked)	50 patients with HIV infection and symptomatic HIV-associated sensory neuropathy.	Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy.
Haney et al. (2005)	United States	HIV: caloric intake, mood	Randomized, within-subject, staggered, double-dummy design	Dronabinol (oral); Cannabis (smoked)	30 HIV-positive patients smoking marijuana.	THC and cannabis cause increased caloric intake.

Table 6: Studies on glaucoma

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Tomida et al. (2006)	Great Britain	Glaucoma: intraocular pressure	Randomized, double-blind, placebo-controlled, 4 way crossover study	2 cannabis extracts rich in THC or CBD (sublingual)	6 patients with ocular hypertension or early primary open angle glaucoma.	Significant reduction of intraocular pressure.

Table 7: Studies on Intestinal dysfunction

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Esfandyari et al. (2007)	United States	Colonic motor and sensory functions	Randomized, placebo-controlled study	Dronabinol (oral)	52 healthy volunteers.	THC relaxes the colon and reduces postprandial colonic motility.
Esfandyari et al. (2006)	United States	Gastrointestinal transit and postprandial satiation	Double-blind, randomized, placebo-controlled, parallel group study	Dronabinol (oral)	30 healthy volunteers.	Dronabinol retards gastric emptying in humans; effects are gender-related. Dronabinol also increases fasting gastric volumes in males.

Table 8: Studies on nausea/vomiting/appetite

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Meiri et al. (2007)	United States	Chemotherapy-induced nausea and vomiting	Double-blind, placebo-controlled study	Dronabinol (oral)	64 patients receiving moderately to highly emetogenic chemotherapy.	Dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. Active treatments were well tolerated.
Strasser et al. (2006)	Switzerland	Cancer: anorexia-cachexia	Multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial	Cannador (oral); THC (oral)	164 patients with advanced cancer, Cancer-Related Anorexia-Cachexia Syndrome, and severe weight loss.	Insufficient difference between Cannador, THC and placebo on appetite or quality of life.

Table 9: Studies on schizophrenia

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Leweke et al. (2007)	Germany	Schizophrenia	Double-blind, controlled clinical trial	CBD (oral), amisulpride (oral)	42 patients suffering from acute paranoid schizophrenia and schizophreniform psychosis.	CBD significantly reduced psychopathological symptoms of acute psychosis. CBD was as effective as amisulpride, a standard antipsychotic.
D'Souza et al. (2005)	United States	Schizophrenia	Double-blind, randomized, placebo-controlled study	THC (intravenous)	13 stable, antipsychotic-treated schizophrenia patients.	THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. These data do not provide a reason to explain why schizophrenia patients use cannabis in self-treatment.

Table 10: Studies on other indictaions

Study	Country	Indication	Type of study	Product	Patients affected	Efficacy
Guzmán et al. (2006)	Spain	Cancer: recurrent glioblastoma multiforme	pilot phase I trial	THC (intra-tumoral)	9 patients with recurrent glioblastoma multiforme	THC inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients
Sylvestre et al. (2006)	United States	Hepatitis C	prospective observational study	Cannabis (smoked)	71 patients, being recovering substance users	Modest cannabis use may offer symptomatic and virological benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen

pain-parameters (VAS), and an increase in quality of life (ΔQOL score). Although typical side effects of nabilone were commonly observed, such as dizziness, fatigue, dry mouth and sleepiness, the study concluded that a majority of patients classified nabilone intake in addition to the standard treatment as a positive measure. Thus, this kind of treatment may be an interesting and attractive enrichment of analgesic therapy.

Also **Frank *et al.* [2008]** focused on the potential analgesic effects of nabilone in neuropathic pain. Objective of this study was to compare the analgesic efficacy and side effects of this synthetic cannabinoid with those of the weak opioid dihydrocodeine for chronic neuropathic pain in 96 patients aged 23-84 years. It was found that the opioid was a better analgesic than nabilone. However, the clinical significance of the difference was small, and in fact the majority of patients had no clinically relevant drop in their pain score on either treatment. Nabilone was associated with more sickness than dihydrocodeine, while dihydrocodeine was associated with more tiredness and nightmares. No major adverse events occurred with either drug and both drugs were equally well tolerated. Although a dose of only 2 mg of nabilone was used in this study, the observed side effect profile argues against giving higher doses of the drug.

In patients with fibromyalgia, the first randomized, controlled trial to assess the benefit of nabilone on pain reduction and quality of life improvement was done only recently **[Skrabek 2008]**. It has been suggested that a clinical endocannabinoid deficiency may be involved in the etiology of fibromyalgia. As no treatment has been specifically approved for management of this condition, further research into treatment strategies is important. Nabilone (up to 1 mg BID) appeared to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement. The most common side effects reported by subjects in the nabilone group included drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events occurred during the study. There was a significant, but transient, increase in the weight of subjects treated with nabilone over the 8 weeks of the trial (mean 1.13 kg). Nabilone did not appear to have any lasting benefit in subjects when treatment was discontinued. During the study, subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications. Future studies could be done using nabilone as a single agent to determine its effect on pain and quality of life alone.

The efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy was assessed by **[Narang 2008]** in a study combining a phase I (double-blind, single dose) and phase II (Open-label, multi-dose) trial. Results of the phase I study showed that patients who received dronabinol (10 or 20 mg) experienced decreased pain intensity and increased satisfaction compared with placebo. No differences in pain relief were found between the active treatments. According to the authors, a lack of an active placebo may have contributed to unblinding. Phase II was an extended open-label titrated trial of dronabinol as add-on medication to patients on stable doses of opioids. In this phase, titrated dronabinol contributed to significant relief of pain, reduced pain bothersomeness, and increased satisfaction compared with baseline. Overall, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic noncancer pain. Subjects also showed improvements in quality of sleep. The most frequently reported side effects, compared to placebo, were dry mouth, tiredness, sleepiness, and drowsiness. Despite these side effects, subjects' overall satisfaction with treatment was significantly higher (54%) on active doses than placebo. The results imply that dronabinol may be a useful adjuvant analgesic for patients with persistent pain in spite of taking stable doses of opioids. Future studies need to examine whether the benefits and the side effects of THC among chronic pain patients change with prolonged use.

The majority of patients using cannabis for self-medication administer it by smoking, but there is currently no significant experience within the pharmaceutical world with the preparation and composition of cannabis cigarettes. As a result, it may be difficult to evaluate the experience of self-medicating patients, and to prove or disprove the medicinal effects of smoked cannabis. A unique study by **[Ware 2006]** addressed this issue by testing a range of different cannabis cigarettes in a randomized controlled crossover trial. Four different herbal cannabis preparations were tested among 8 experienced and authorized cannabis users with chronic pain. Preparations were varied with respect to grind size, THC content and humidity. The product with highest THC content (12%), highest humidity (14%) and largest grind size (10 mm) was rated highest overall. Significant differences were noted between preparations on overall appearance and color. While the small size of the study precludes broad conclusions, the study shows that medical cannabis users can appreciate differences in herbal product. A more acceptable cannabis product may increase recruitment and retention in clinical studies of medical cannabis.

[Wilsey 2008] studied the effects of smoked cannabis on patients with central and peripheral neuropathic pain. A standardized procedure was used for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis. The amount of THC consumed was estimated to be 19 mg during the low-dose sessions and 34 mg during the high-dose sessions. Results indicated that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. There was no apparent correlation of cannabinoid serum levels with analgesia. It was concluded that, as with opioids, cannabis does not rely on a relaxing or tranquilizing effect (e.g., anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree.

Undesirable consequences of smoking cannabis were clearly identifiable, but no participant dropped out because of an adverse event related to an experimental intervention.

In a first ever controlled trial of a cannabis preparation in rheumatoid arthritis, a significant analgesic effect was observed and disease activity was significantly suppressed following Sativex treatment **[Blake 2006].** In comparison with placebo, a significant analgesic effect was observed and disease activity was significantly suppressed. Sativex produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and inflammation (DAS28). The suppression of pain on movement, the primary endpoint, suggests a peripheral analgesic action, while the suppression of pain at rest may suggest a more central effect. The modest suppression of the present gold standard inflammation activity measure, the DAS28, might indicate an influence on the immune effector system. Importantly, the trial did not demonstrate significant toxicity and Sativex was generally well tolerated. The large majority of adverse effects were mild or moderate, and there were no adverse effect-related withdrawals or serious adverse effects in the active treatment group. About a quarter of patients receiving Sativex experienced transient dizziness at some point, though in all cases this was rated as mild.

A study by **[Nurmikko 2007]** demonstrated that Sativex is effective in the relief of peripheral neuropathic pain when given in addition to existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Greater than 30% improvement in pain intensity, generally considered as clinically meaningful [Farrar 2000], was reported by 26% of subjects receiving Sativex, compared with 15% of patients taking placebo. A self-titration regimen permitted individual patients to optimize their dose on the basis of their own efficacy and tolerability response. Both experimental and human volunteer studies suggest that tolerance to some of the side effects of cannabis occurs within days of its repeated administration [Guy 2003, Jones 2002]. A self-titration regimen allows for this to occur, further optimizing the therapeutic response. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks. The majority of patients took far less than the highest allowable dosage. Fifty-seven (91%) patients in the Sativex group experienced at least one adverse event (AE) during the course of the study compared with 48 (77%) patients in the placebo group. The AEs reported by the patients were mostly gastrointestinal, central nervous system related or topical. While reported gastrointestinal AEs were more common in the Sativex group, central nervous system AEs were not. Most were observed at onset of treatment, and in the majority described as mild. Intoxication scores remained low throughout the study. At recruitment, all patients were either non-responders to several conventional neuropathic analgesics, or were in severe pain despite taking appropriate therapy. Considering the refractory nature of their pain, and that patients remained on their existing analgesia, the improvement of the ongoing pain in those on the active drug is encouraging.

Experimental pain

Co-administration of various cannabinoids with morphine has been found to produce a greater-than-additive effect with respect to antinociception in mice [Smith 1998], and crosstalk between the endocannabinoid- and endorphin-systems has been shown [Corchero 2004]. Therefore, the synergistic affective analgesic interaction between THC and morphine was determined in a double-blind, four treatment, crossover design **[Roberts 2006]**. Subjects received THC (5 mg orally) or placebo and 90 min later morphine (0.02 mg/kg) intravenously, or placebo. Fifteen minutes later subjects rated the pain associated with the application of thermal stimuli to skin. Neither morphine nor THC had a significant effect at the doses used, and there was no significant interaction between the two. A small, but non-significant synergy was found only for the affective component of pain. Subjects described a variety of mild euphoric or dysphoric effects, but no serious or unexpected toxicities occurred. The study concluded that future studies of THC or other cannabinoids in combination with opiates should focus upon clinical rather than experimental pain.

Based on the results of preclinical studies, another study **[Wallace 2007]** hypothesized that inhaled cannabis would reduce capsaicin-induced pain and hyperalgesia, and change the affective quality of pain in a dose-dependent manner. In 19 healthy volunteers, the concentration-response effects were evaluated of low-, medium-, and high-dose smoked cannabis (respectively 2%, 4%, and 8% THC by weight). Only the medium dose cannabis significantly decreased capsaicin-induced pain. Interestingly, as has been observed in other studies [e.g. Kraft 2008], a significant *increase* in capsaicin-induced pain occurred with the high dose. The authors suggested that there is a window of modest analgesia for smoked cannabis, with lower doses decreasing pain and higher doses increasing it. There was a significant correlation between plasma levels of THC and metabolites with decrease in pain, but no correlation between the high-dose plasma levels and increase in pain. This suggests that there may be another compound within the cannabis used that was not measured but that was responsible for the increased pain at the high dose. Mild to moderate side effects were experienced by 7 of 19 subjects, primarily at the highest dose of cannabis, but no serious AEs occurred.

The double-blind, placebo-controlled, crossover study performed by **Kraft *et al.* [2008]** was designed to detect a potential analgesic activity of Cannador by two different and well-established human models of acute inflammatory pain and hyperalgesia. Only female volunteers were included, because animal studies using the same models have suggested a more pronounced effect of cannabinoids in females compared with males

[Tseng 2004, Craft 2005]. The dose of THC in each cannabis administration was standardized to 20 mg. Also a significant amount of CBD was present (about 10 mg per administration). No analgesic or antihyperalgesic activity of this cannabis extract was found, even though the high levels of THC and its metabolites detected in the plasma of study subjects, and the occurrence of psychotropic side effects, argue for a sufficient bioavailability. In contrast, the results actually seem to support the impression that high doses of cannabinoids may cause hyperalgesia in certain acute pain conditions. One subject experienced acute psychotic symptoms after Cannador, but all symptoms spontaneously disappeared after 4 hours. Despite the standardized conditions, a broad variability in peak plasma levels for all measured cannabinoids was observed, possibly indicating the difficulties of standardizing the administration of orally used cannabis products.

One way cannabinoids may act to dampen the intensity of nociceptive signals in prolonged pain models is through their potentiating actions on descending inhibitory systems, which at least partly depends on the release of endogenous opioids. Descending inhibitory systems originate in the brainstem and are dynamically triggered following prolonged noxious insult [Millan 2002]. A double-blind, placebo-controlled, crossover study explored the analgesic and antihyperalgesic properties of the synthetic cannabinoid nabilone on long-lasting experimental heat pain, as well as its effects on descending pain inhibitory systems **[Redmond 2008]**. Single doses of 0.5 and 1 mg nabilone were administered to 10 men and 10 women. Primary outcome measures included average heat pain, temporal summation of heat pain, and drug-induced changes in the strength of descending analgesia. Administration of low-dose Nabilone did not act as an analgesic agent. However, a significant antihyperalgesic effect was observed in women only. No important AEs were observed during testing, and the most commonly observed side effects were dry mouth, red eyes, mild sedation, and euphoria.

Multiple sclerosis and spasticity

Although cannabinoids have been used mainly to alleviate symptoms of multiple sclerosis, there is also experimental evidence to suggest that they may be immunomodulatory. Cannabinoids are believed to be anti-inflammatory, mainly through activation of the CB2 receptor, which is principally located peripherally, especially on leucocytes. CB2 activation may be associated with a Th1 to Th2 shift. Consequently, there is some evidence that cannabinoids may be therapeutically useful in treating multiple sclerosis, which is generally believed to be an autoimmune condition. A clinical study **[Katona 2005]** investigated the nature of potential cannabinoid immunomodulation on serum samples obtained from patients with MS taking part in the CAMS study [Zajicek 2003, 2005]. Cannador and THC were used as study medication. With 657 patients recruited, this is to date the largest clinical trial performed with any cannabis-based medicine. Serum samples of 100 subjects were available for analysis. Results did not demonstrate any significant effects of cannabinoids on the cytokine profiles examined, which included interferon-gamma (IFN-γ), interleukin (IL)-10, IL-12 and C-reactive protein. However, the standard deviations were large, so that relatively small but possibly clinically useful effects cannot be excluded from these results.

In **2004, Wade *et al.*** performed a 10-week placebo-controlled study with 160 MS patients, administering Sativex using a self-titration dosing regimen. The study suggested that Sativex is an effective treatment for spasticity associated with MS, but the supporting data was not very strong. Therefore, the investigation was continued as an open label trial to monitor the safety and efficacy of long-term use of Sativex. A total of 137 MS patients who perceived to benefit from treatment entered the extension trial **[Wade 2006]**. Patients were assessed every eight weeks and were followed for an average of 434 days. This study concluded that patients with MS who derive symptom relief from Sativex in the first 10 weeks, generally maintain that relief over an extended period of treatment without any increase in dose. Patients tended to stabilize at a dose of approximately 11 sprays daily (equivalent to 30 mg THC and 28 mg CBD). Unwanted effects were common but rarely troublesome, and the majority was found to be unrelated to the treatment. Four patients experienced seizures, but all four were also taking other potentially epileptogenic drugs. Nevertheless, the relationship between Sativex (or other cannabis based medicines) and seizures warrants further investigation. Although only 67% of the initial number of subjects could be followed for at least one year on the medication, the obtained data nevertheless provides a large body of safety and tolerability data. A number of subjects who had received Sativex for at least one year were asked to participate in a planned abrupt interruption of the study medication for up to 14 days, in order to explore the possibility of a withdrawal syndrome and to determine whether MS-related symptoms would reappear. Of 25 patients participating, five resumed Sativex before the end of 14 days because of reemergence of marked MS symptoms. There was no consistent withdrawal syndrome on abrupt cessation, although just under half the patients experienced new symptoms that may have been related to withdrawal.

A study by **Rog *et al.* [2005]** compared the efficacy, safety, and tolerability of Sativex with placebo in relieving central neuropathic pain in 64 patients with MS. Patients could gradually self-titrate and the median dose used by subjects was equal to 25 mg of THC. The study concluded that Sativex is effective in reducing pain and sleep disturbance in the population studied. Patients in this study were taking, on average, two other medications, with limited efficacy given their baseline pain scores. Therefore, as adjunctive analgesic treatment, Sativex had a significant treatment effect. The numbers needed to treat (NNT) to achieve a 50%

reduction in central pain in at least one patient was 3.7, similar to the value of 3.5 obtained in a previous dronabinol trial [Svendsen 2004]. The same group **[Rog 2007]** continued their study with a long-term extension, treating MS patients for neuropathic pain with Sativex in an uncontrolled, open-label trial. Patients remained on a self-titration scheme, while maintaining their existing analgesia as required. Of 64 patients completing the original trial, 28 patients completed the extension with a mean duration of treatment of 839 days. In this group a relatively small but sustained reduction in pain was observed. Seventeen patients withdrew due to AEs; the most common of which were nausea, dizziness, weakness, and fatigue. Only two serious AEs were judged to be treatment-related. The mean dose of Sativex, and number of patients experiencing intoxication remained stable throughout the follow-up trial.

Lower urinary tract symptoms (LUTS) are very common symptoms of MS and are mainly due to neurogenic detrusor overactivity [Goldstein 1982], and often lead to bladder dysfunction. Anecdotal reports from MS patients have suggested that cannabis might have a beneficial effect on LUTS [Brady 2002]. Therefore, the effect of Cannador and pure THC on urge incontinence in patients with multiple sclerosis was determined in a multicentre, randomised placebo-controlled trial **[Freeman 2006]**. The data for this substudy was collected from the patient population of the CAMS study [Zajicek 2003], by asking subjects to complete incontinence diaries. Finally, 255 patients could be fully evaluated. Both Cannador and THC treatments showed significant effects over placebo in urge incontinence episodes. The authors hypothesized that cannabinoids relax the detrusor smooth muscle during filling, thereby improving neurogenic detrusor overactivity. Further support for a positive treatment effect comes from the measurement of lower volumes of involuntary urine loss in the active treatment groups. Because this was an "add-on" study to the CAMS study, which was assessing spasticity, patients were selected on this symptom rather than on incontinence. A proper trial set up specifically to test for incontinence may therefore yield more robust results. Nevertheless, it has been shown that even a modest 25% reduction in urge incontinence might be clinically significant [Coyne 2005].

Another, smaller, study was performed to determine the effects of Sativex treatment on the overactive bladder in MS **[Kavia 2006]**. Patients were treated over a period of 8 weeks, in order to detect an improvement in urgency incontinence. Although the study failed to show a reduction in *daily* incontinence at the end of the study, Sativex was superior to placebo for nocturia. This effect was greater for more severe disease, and a substantial number of patients became nocturia free on the active treatment. Patients on Sativex were three times more likely to report an improvement of >30% compared to placebo. Active treatment was well tolerated, and the most common adverse effects were dizziness, urinary tract infection, and headache.

Because THC was reported to add benefit in the treatment of pain in patients with MS, the question arose whether synthetic cannabinoids with lower potential for psychotropic side effects could be effective as well. A double-blind, placebo-controlled, cross-over trial was performed to evaluate the safety and efficacy of low dose treatment with nabilone (1 mg per day) on spasticity-related pain **[Wissel 2006]**. Patients all suffered from chronic upper motor neuron syndrome (UMNS) not sufficiently correctable by conventional treatment. Results showed a significant decrease of pain under nabilone after 4 weeks of treatment, while spasticity, motor function and activities of daily living did not change. Although one patient dropped out because of weakness of lower limbs which could be attributed to nabilone, the other side effects observed in the present study were stated as mild and easily tolerable, or not related to the treatment. The study also assessed neuropsychological parameters relevant for driving ability in a subset of patients [Kurtzhaler 2005], but no cognitive side effects were found in domains of attentional performance, psychomotor speed, and mental flexibility.

In a randomized, placebo-controlled trial on the efficacy and tolerability of Sativex, 189 subjects with definite MS and spasticity were treated over a 6 week period. Subjects were allowed to self-titrate their daily dose, which resulted in a mean dose of ca. 25 mg of THC and of CBD (9.4 sprays) per day. Results rated Sativex significantly more effective than placebo in relieving spasticity **[Collin 2007].** Of the Intention to Treat (ITT) population, 40% of the subjects achieved >30% improvement from baseline. The secondary outcomes did not achieve statistical significance but were all in favour of Sativex. The low rate of subject withdrawal due to AEs in this study may seem surprising given that the dose of THC, present in the cannabis extract, was being taken in mean daily doses in excess of 25 mg, considerably more than was given in most other published studies. However, this may reflect the presence of CBD, which is known to modify some of the psychoactive effects of THC, so that THC as part of a cannabis extract may become better tolerated than THC as a single molecule [Zuardi 1982].

In a group of 18 patients with secondary progressive MS, a study was performed to identify the neurotransmitter system involved in the pain control by cannabinoids in MS **[Conte 2009].** The flexion reflex method was used, an objective tool for assessing pain threshold, pain pathways and the neurotransmitter system involved in pain control [Sandrini 1993]. After administration of Sativex, at a mean dose of 8 sprays daily (ca. 20 mg THC and CBD), a significant effect was observed on the parameters recorded. Also the patients' VAS pain scores decreased, although not significantly. It was concluded that cannabinoids modulate human pain perception mainly by acting at the pre-motorneuronal level in the spinal cord. Cannabinoids, like opioids, could act by decreasing neurotransmitter release.

Although no significant cognitive deficits were reported in frequent but moderate users of cannabis [Jager 2006] the persistent effects of cannabis on cognition remain uncertain [Verdejo-Garcia 2004]. Therefore, the primary aim of a double-blind, placebo controlled, crossover study performed by **Aragona *et al.* [2009]** was to explore the onset of psychopathological symptoms and cognitive deficits in cannabis-naïve patients with MS treated with Sativex for relieving their spasticity. The mean daily dose used by self-titration corresponded to ca. 22 mg of THC. The effects on psychopathology were evaluated after 3 weeks of treatment. During the study, plasma levels of THC and CBD were monitored. Cannabinoid treatment did not induce psychopathology and did not impair cognition in subjects. Also the effects of cannabinoids on quality of life, fatigue, and motor function of MS patients were non-significant; however, the positive correlation between plasma levels of THC and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoiac features might arise. All subjects finished the study. Safety and tolerability were generally good, drug tolerance and dose increasing were not reported during the trial, and desire for Sativex or abuse was not present at follow-up.

HIV/AIDS

In two studies, Haney *et al.* demonstrated that smoked cannabis, and oral dronabinol, stimulates appetite in already experienced cannabis smokers. In the first study **[Haney 2005]**, using only acute doses, it was found that for experienced cannabis smokers with clinically significant wasting, both dronabinol (at acute doses at least four to eight times the current recommendation) and cannabis produced substantial and comparable increases in food intake without causing major adverse effects. Caloric intake was only increased in the group with significant wasting, but not in a control group of HIV patients without signs of wasting. Only the highest dose of dronabinol (30 mg) was poorly tolerated, producing at least one adverse effect (e.g., headache, nausea, overintoxication) in 20% of the participants, suggesting that this (oral) dose may be too high, even among regular cannabis smokers.

The second study **[Haney 2007]** showed that also repeated long-term doses of both dronabinol (up to 10 mg daily) and smoked cannabis (up to 3.9% THC) were well tolerated and produced substantial and comparable increases in food intake. Both drugs dose-dependently increased daily caloric intake and body weight, without causing disruptions in psychomotor functioning. For the high-dose dronabinol and cannabis conditions, this resulted in a significant increase in body weight within 4 days (>1 kg). Both active treatments increased daily food intake by increasing the number of times participants ate throughout the day, without altering the number of calories consumed during each eating occasion. Increased food intake paralleled increased ratings of intoxication (generally rated as positive by patients) for all cannabinoid conditions, except for the low dose of dronabinol (5 mg).

HIV-associated sensory neuropathy is the most common peripheral nerve disorder complicating HIV-1 infection, most often defined by hyperalgesia and allodynia. **Abrams *et al.* [2007]** determined the effect of smoked cannabis on this condition. Patients were randomly assigned to smoke either cannabis or identical placebo cigarettes three times daily for 5 days. It was found that smoked cannabis reduced daily pain significantly compared to placebo; the number needed to treat (NNT) in order to achieve a >30% pain reduction (commonly seen as a clinically relevant improvement) among all completing patients was 3.6. These findings are comparable to oral drugs routinely used for chronic neuropathic pain, such as Gabapentin [Backonja 1998]. Cannabis also reduced some types of experimentally induced hyperalgesia in the same patients. Although the active treatment was well tolerated, side effects ratings were higher in patients in the cannabis group for anxiety, sedation, disorientation, confusion, and dizziness. No serious AEs were reported, and no patient withdrew from the study because of AEs.

Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. In a randomized cross-over trial, smoked cannabis at maximum tolerable dose (1-8% THC), significantly reduced neuropathic pain intensity in HIV-associated distal sensory predominant polyneuropathy (DSPN) compared to placebo when added to stable concomitant analgesics **[Ellis 2009]**, Among the completers, pain relief was greater with cannabis than placebo. Using verbal descriptors of pain magnitude from the Descriptor Differential Scale (DDS), cannabis was associated with an average reduction of pain intensity from 'strong' to 'mild to moderate'. Also, cannabis was associated with a sizeable (46%) and compared to placebo (18%) significantly greater proportion of patients who achieved a >30% reduction in pain. Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in these patients. The frequency of some non-treatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities.

Glaucoma

There is increasing evidence suggesting that cannabinoids may lower IOP primarily by influencing aqueous humor production and outflow, through activation of the CB1 receptor. In glaucoma, the final pathway leading to visual loss is the selective death of retinal ganglion cells through apoptosis. Recent studies have documented the neuroprotective properties of cannabinoids independently of their effect on IOP [listed in Tomida 2006]. But despite these promising results, in

recent years only a single clinical trial has been added to the scientific literature.

Tomida *et al.* [2006] performed a pilot study to assess the effect on IOP, and the safety and tolerability of a low dose of THC and CBD. Although topical administration (eye drops) of cannabinoids would be ideal for glaucoma, this type of application has been associated with irritation and corneal damage [Jay 1983]. Therefore, an oromucosal spray was used because it has been shown to have a satisfactory pharmacokinetic profile and has been well tolerated in clinical studies [Guy 2003]. Patients with ocular hypertension or early primary open angle glaucoma received single dose standardized cannabis extracts, containing either 5 mg THC, 20 mg CBD, 40 mg CBD, or placebo. Two hours after administration of THC, the IOP was significantly lower than after placebo, returning to baseline level after 4 hours. CBD administration did not reduce the IOP at any time with either of the two doses studied. Instead, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration. One patient experienced mild psychotropic side effects, but there were no serious AEs.

Intestinal dysfunction

Two controlled clinical trials have been performed in the period covered by this review. The first study **[Esfandyari 2006]** evaluated the effects of dronabinol on gastrointestinal transit, gastric volume and satiation in healthy volunteers, who were randomly assigned to receive three doses of THC (5 mg) or placebo over a period of 24h. The results suggested that THC administration was associated with a significant delay in gastric emptying of a standard solid and liquid meal, and there was a suggestion of a gender effect: THC significantly slowed gastric emptying in females, but not in males, which is consistent with earlier findings [Bateman 1983]. In contrast, THC increased fasting gastric volumes specifically in males. The data obtained suggested that the antiemetic effect of cannabinoids may not be due to a direct effect on gastric accommodation or sensation, but rather to a central modulation of perception.

A second study by the same group **[Esfandyari 2007]** aimed to compare the acute effects of single dose dronabinol (7.5 mg) versus placebo on colonic sensory and motor functions in healthy adults. The study demonstrated that THC was associated with relaxation of the colon and inhibition of the increase in tone after the meal. It was concluded that the potential for CB agonists to modulate colonic motor function in diarrheal disease such as irritable bowel syndrome deserves further study. As in the previous trial [Esfandyari 2006], the study observed greater effect of THC on gastric emptying prolongation in female volunteers than in males. The significance of the observed gender-related differences is unclear.

Nausea-vomiting-appetite

The purpose of the placebo-controlled study by **Strasser *et al.* [2006]** was to compare the effects of Cannador and THC on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome (CACS). Adult patients with significant weight loss were treated with Cannador (standardized for 2.5 mg THC and 1 mg CBD) or THC (2.5 mg) twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily. Cannador at the oral dose administered was well tolerated by the study subjects. Results showed no significant differences between the three arms for appetite, quality of life, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving Cannador, THC, or placebo, respectively. Finally, an independent data review board recommended termination of recruitment because of insufficient differences between study arms. A large number of adverse effects were observed, but there were no differences between treatment arms, and only a minority of adverse effects was found to be linked to study medication. Authors assumed that the study medications were underdosed.

Delayed chemotherapy-induced nausea and vomiting (CINV), defined as nausea and vomiting occurring more than 24 hours after chemotherapy and lasting for up to 1 week, is common, with at least 50% of patients experiencing it following moderately emetogenic chemotherapy. The impaired quality of life imparted by CINV can affect treatment outcomes when patients refuse chemotherapy because of severe AEs. A recent study **[Meiri 2007]** evaluated the efficacy of dronabinol versus ondansetron in delayed CINV. Over the course of 2-5 days after receiving chemotherapy, subjects received an increasing dose of up to 20 mg dronabinol daily, either alone, or in combination with ondansetron. Efficacy of dronabinol alone was comparable with ondansetron, and combination therapy did not provide benefit beyond that observed with either agent alone. Nevertheless, specifically on day 1 after chemotherapy, significantly greater efficacy on intensity of nausea was demonstrated in the combined active treatment group versus placebo. Active treatments were well tolerated. The highest rate of CNS-related AEs (dizziness and fatigue) was found in patients receiving combination therapy, while the incidence of these events in the THC group was low. Also, it was found that quality of life was most improved in patients receiving dronabinol compared with patients in the other treatment groups.

Schizophrenia

An explorative, 4-week, double-blind, controlled clinical trial was performed by **Leweke [2007]** on the antipsychotic properties of CBD in acute schizophrenia compared to the standard antipsychotic amisulpride. Furthermore, side-effects and anxiolytic capabilities of both treatments were investigated. Forty-two patients fulfilling DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis participated in the study. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4

weeks. However, there was no statistical difference between both treatment groups. In contrast, cannabidiol induced significantly less side effects (EPS, increase in prolactin, weight gain) when compared to amisulpride. It was concluded that CBD proved substantial antipsychotic properties in acute schizophrenia.

In another clinical study **[D'Souza 2005]**, the behavioral, cognitive, motor, and endocrine effects of up to 5 mg intravenous THC were characterized in stable, antipsychotic-treated schizophrenia patients. These data were compared with effects in healthy subjects reported elsewhere. It was found that THC transiently exacerbated a range of positive and negative symptoms, perceptual alterations, cognitive deficits, and medication side effects associated with schizophrenia without producing any obvious "beneficial" effects. The data do not provide a reason to explain why schizophrenia patients use or misuse cannabis. Furthermore, schizophrenia patients were more vulnerable to THC effects on learning and memory than healthy subjects. The enhanced sensitivity to the cognitive effects of THC warrants further study into whether brain cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia.

Other indications

The effects of intratumoral THC **[Guzmán 2006]** were studied on 9 patients with recurrent glioblastoma multiforme. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. The treatment was found to inhibit tumour-cell proliferation *in vitro* and to decrease tumour-cell Ki67 immunostaining in two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

[Sylvestre 2006] performed a study on 71 patients suffering from hepatitis C, all being recovering heroin users consuming cannabis on their own account. It was found that modest use of smoked cannabis may offer symptomatic and virological benefit to some patients undergoing viral treatment by helping them maintain adherence to the challenging medication regimen. The lack of dose response in this study argues against specific receptor- or metabolism-related effects, and suggests instead that cannabis exerted its benefit by non-specific improvements in symptom management. It must be noted that the authors point out a number of limitations that warrant caution in the interpretation of this study.

Discussion

This review is intended to support the discussion on the question whether there is currently enough clinical data to accept cannabis and cannabinoids as drugs in certain indications. In the review by Ben Amar [2006], a therapeutic potential of cannabinoids was concluded for a range of disorders. Based on the data presented here, covering the period 2005-2009, it is possible to confirm that cannabinoids exhibit a strong therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis. For each of the 8 main indications discussed in this review, the general conclusions are discussed below.

It may be interesting to note that in the last few years, some well-designed studies on the effects of smoked cannabis have been released, mainly on HIV/AIDS. This is of specific interest because most patients administer their medicinal cannabis by smoking. The studies particularly show a benefit on neuropathic pain and appetite. Obviously, the noxious pyrolytic byproducts released through combustion remain a public health deterrent to the use of smoked cannabis. However, specific herbal vaporizers have been devised to provide a safer and more efficient delivery system for inhaling cannabis. It is reasonable to assume that future clinical trials will utilize this alternative delivery method.

Pain

Although cannabinoid-induced analgesia is now well-recognized in animal models, evidence of its analgesic properties in humans is less conclusive. Interestingly, trials involving pain patients with neuropathic-like features (e.g. multiple sclerosis, neuropathic pain and fibromyalgia) have produced mostly positive results, whereas studies measuring the efficacy of cannabinoids for acute pain (e.g. postoperative pain) have generated mostly negative results. For that reason, experimental pain and chronic (neuropathic) pain are discussed in separate sections. It has been demonstrated that endocannabinoids produced in the spinal cord can enhance pain by dampening the synapses of inhibitory interneurons that usually prevent the perception of innocuous stimuli as painful [Christie and Mallet 2009]. The pain-promoting action of endocannabinoids wanes during the development of chronic pain that is induced by inflammation or nerve injury. This can explain the differences observed in clinical studies with cannabinoids on acute and chronic pain.

The results of the clinical trials on chronic and neuropathic pain conditions are equivocal. A wide range of cannabis-based medicines exhibit analgesic effects on different forms of pain. THC, nabilone, Sativex, Cannador and even smoked cannabis have been used in these studies, either alone or in addition to existing analgesia. The large majority of adverse effects were mild or moderate. Chronic neuropathic pain is a common and difficult to treat condition that has limited treatment options. As a consequence, even modest clinical effects may be relevant. Studies with cannabinoids should therefore be regarded as highly significant for the intended patient population. Clearly, the optimal type of cannabinoids and administration route may

differ for each indication.

Acute types of pain did not respond as well to cannabinoids. For postoperative pain management, the use of THC or nabilone did not reveal a positive effect on pain scores and a higher dose of nabilone (2 mg) actually increased pain scores. The use of Cannador, a standardized extract containing both THC and CBD, was more successful, and dose-dependently decreased postoperative pain. The presence of CBD may modulate the effects of THC (e.g. by changing the pharmacokinetic profile of THC and its metabolites), and it may also be possible that CBD has an effect on pain by itself as shown in an animal model of neuropathic pain [Costa et al. 2007].

A crucial caveat in the study of cannabis or cannabinoids in experimental pain models is that the data is mainly collected with healthy, regular marijuana users who smoke acute doses in a controlled laboratory situation and are exposed to artificial pain stimuli. Obviously, it is not possible to predict whether chronically ill patients taking cannabinoids for pain relief would respond similarly. The respective mechanisms underlying the whole variety of chronic pain syndromes may considerably differ from acute nociception. It has previously been reported that in rats, cannabinoid CB1 receptors are upregulated in chronic neuropathic pain and therefore could lead to an increased analgesic effect of THC in chronic pain [Siegling 2001]. It is interesting to note that a selective effect on women was observed in some pain studies. This may be an indication that certain cannabinoids may help alleviate chronic pain conditions which predominantly affect women, such as fibromyalgia.

Experimental pain studies often show that THC-induced analgesia is accompanied (and outlasted) by side-effects such as sedation. At doses producing substantial biological exposure, the antinociceptive effects of cannabis - although statistically significant - are often rather weak compared with motor-impairing and subjective effects. Nevertheless, in certain groups of chronically ill patients with severe enough symptoms, and without further options for treatment, even this weak effect on pain may be significant enough.

In previous animal and human studies, it has been shown that cannabinoids and opioids have synergistic actions on pain control [Iversen 2003; Lynch and Clark 2003; Maldonado and Valverde 2003], but for chronic pain this could not be firmly confirmed in the clinical trials reported here. More study is needed to evaluate the combined analgesic effects of both types of drugs.

Multiple sclerosis and spasticity

In clinical trials, more patients have been treated with cannabinoids for MS then for any other indication. Symptomatic therapy for MS often provides inadequate relief and can be limited by toxicity. As a consequence, people with multiple sclerosis have experimented with many alternative therapies, including cannabis, to ease their physical problems. There is much anecdotal suggestion that cannabis and cannabinoids, have beneficial effects on disease-related pain, bladder symptoms, tremor, and particularly spasticity, but until recently, little scientific evidence existed for their efficacy. In the period covered by this review, nine studies have been released on the effect of cannabinoids on MS symptoms. Most studies were done with Sativex, which is currently approved only in Canada, and the largest studies have been conducted with Cannador and dronabinol.

MS is one of the few conditions where long-term extension studies have been performed with cannabis-based medicines. When assessing clinical results, it should be acknowledged that the degree of evidence for many of the commonly used drugs to combat MS symptoms is weak. A Cochrane review [Shakespeare 2003] of antispasticity agents for multiple sclerosis concluded that the paucity of evidence meant no recommendations could be made to guide prescribing, and that better outcome measures need to be developed. It may therefore not be surprising that it has proven hard to collect evidence for the efficacy of cannabis in the treatment of MS.

The current studies presented in this review provide us with cautious optimism that Sativex, but also Cannador, THC and nabilone, can improve the symptoms of spasticity in MS sufferers, specifically for the treatment of spasticity, pain and incontinence. Often the improvements were gained over and above the concomitant anti-spasticity medication being taken by the subjects during the study. In those patients perceiving initial benefit from their medication, the positive effects often persisted in longer term extension trials without tolerance. This is representative of clinical practice, where only patients who consider a treatment beneficial will continue taking it. Cannador or THC did not show any detectable effects on a range of cytokines that influence inflammation in serum samples of MS patients.

HIV/AIDS

The primary constituent of cannabis, THC, is approved by the Food and Drug Administration (FDA) for oral administration as appetite stimulant in the case of anorexia associated with weight loss in patients with HIV/AIDS. Studies on the effects of cannabinoids in patients with HIV are particularly important given that they constitute one of the largest groups using dronabinol and cannabis for medicinal reasons [Institute of Medicine 1999], and a considerable proportion of those with HIV currently smoke cannabis. Reasons for smoking cannabis cited by patients include countering the nausea, anorexia, stomach upset, and anxiety associated with the disease and with antiretroviral therapy.

The four studies presented here all used smoked cannabis, but also THC, and clearly showed the beneficial effects on pain, appetite and weight gain. Although cannabinoids tend to increase fat rather than the more wanted lean muscle mass [Abrams 2003], HIV patients who are able to maintain stable weight often report improved quality of life [Beal 1995]. Overdosing ef-

fects were relatively common, because the exact dose of cannabinoids is relatively difficult to control in smoked studies, compared to oral administration.

Glaucoma

Glaucoma is one of the leading causes of blindness in the world, affecting about 70 million people worldwide. As glaucoma is a chronic disease lacking a cure, the quest for new ocular hypotensive agents is important for its treatment, and these agents are likely to remain frontline therapy for the foreseeable future. Since the early 1970s, it was reported that smoking cannabis cigarettes could lower intraocular pressure (IOP) by up to 45% [Hepler & Frank 1971]; later works showed that THC lowered IOP when given intravenously, orally or by inhalation [Ben Amar 2006]. Since these early observations, numerous studies have been conducted confirming that different cannabinoids, including THC, CBD, cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, can reduce IOP when administered systemically and topically [listed in Tomida 2006]. In addition to the reduction of IOP THC may increase blood circulation in the retina, which was demonstrated in an open study [Plange et al. 2007], and is known to be neuroprotective, which both may increase survival of the optical nerve. Only one single controlled clinical study was added to the literature in the past years. The modest reduction of IOP observed after oromucosal administration of THC was not deemed to be clinically relevant. An important goal of further research may be to determine the additive effects of cannabinoids with the anti-glaucoma agents available.

Intestinal dysfunction

Cannabinoid receptor (CB) stimulation inhibits colon motility and increases food intake in rodents. However, effects of CB stimulation in human gastrointestinal (GI) tract are largely unclear. *In vitro* studies have suggested that cannabinoids delay transit in human colon and ileum [Manara 2002]. In general, reports of effects of cannabinoids on GI transit and sensation in humans *in vivo* are sparse, and the role of stomach function in the appetite-stimulating and anti-emetic effects of cannabinoid agonists is unclear. The two studies discussed here indicate that THC administration was associated with a significant delay in gastric emptying, relaxation of the colon and inhibition of the increase in tone after the meal. The obtained data may help to better understand the effects of cannabinoids in nausea, vomiting and appetite. In both studies, a greater effect of THC was observed on gastric emptying prolongation in female volunteers than in males. The significance of the observed gender-related differences is yet unclear.

Nausea, vomiting and appetite

Besides the use as an appetite stimulant for AIDS patients, THC is FDA approved in the USA as an antiemetic for cancer patients undergoing chemotherapy. One study showed no significant effect of either Cannador (containing THC and CBD) or THC on appetite and nausea in cancer patients, but study medications were obviously underdosed since there was no difference of side-effects compared to placebo. A second study demonstrated an effect in delayed chemotherapy-induced nausea and vomiting (CINV), and this effect was comparable to the standard drug ondansetron. The data suggest that the addition of THC directly before and after chemotherapy may offer more benefit than the standard regimen alone taken before chemotherapy.

Schizophrenia

The human endocannabinoid system interacts with various neurotransmitter systems and the endocannabinoid anandamide was found significantly elevated in CSF and inversely correlated topsychopathology in patients with schizophrenia [Giuffrida 2004] providing a link to the neurobiology of the disease. The major herbal cannabinoid compound CBD was suggested recently to be a re-uptake inhibitor of anandamide. In a study using purified CBD, it was found that this non-psychoactive compound shows substantial antipsychotic properties in acute schizophrenia, with an efficacy comparable to amisulpride. This is in line with the suggestion of an adaptive role of the endocannabinoid system in paranoid schizophrenia, and raises further evidence that endocannabinoid system may represent a valuable target for antipsychotic treatment strategies. Another study using high doses of intravenous THC caused schizophrenia-like symptoms.

Other indications

Most of the experiments performed so far in animal models of cancer have evidenced a tumour growth-inhibiting action of cannabinoids (Guzmán, 2003). The study by Guzmán *et al.* described in this review was the first clinical study aimed at evaluating cannabinoid antitumoral action. Owing to obvious ethical and legal reasons, this pilot study was conducted in a cohort of terminal patients harbouring actively growing recurrent tumours. In view of the fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies (Guzmán, 2003), it would be desirable that additional trials – on various types of tumours – were run to determine whether cannabinoids – as single drugs or in combination with established antitumoral drugs – could be used, other than for their palliative effects, to inhibit tumour growth.

Another indication that was clinically studied for the first time in recent years was hepatitis C. Although hepatitis C virus (HCV) treatment outcomes have improved dramatically over the past decade, the intolerability of interferon/ribavirin combination therapy remains a barrier to treatment success. Faced with severe treatment-related side-effects that respond inadequately to conventional medications, some patients turn to cannabis for symptom relief. Although widespread restrictions limit the ease with which medicinal

cannabis use can be formally studied, the pervasive use of cannabis by patients during HCV treatment provided a means for an observational study of its potential risks and benefits. Despite its shortcomings, the study by Sylvestre *et al.* [2006] begins to answer some of the key questions that arise about the use of cannabis during HCV treatment. The results of this observational study suggest that at least moderate use of cannabis during HCV treatment can improve adherence by increasing the duration of time that patients remain on therapy. However, because the benefits of heavy cannabis use were less apparent, the authors could not rule out the possibility that detrimental biological or immunological mechanisms may be relevant at higher levels of consumption.

A series of studies have previously [Ben Amar 2006] shown promising effects of THC on tics associated with Tourette's syndrome as well as its associated behavioral problems such as obsessive-compulsive behavior, providing a reason for careful optimism in the treatment of this poorly understood condition. However, no new data has been published in recent years. Also no new clinical studies were released in recent years on the use of cannabinoids for epilepsy.

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Therapeutic aspects of cannabis and cannabinoids†

PHILIP ROBSON

Background Review commissioned in 1996 by the Department of Health (DOH).

Aims Assess therapeutic profile of cannabis and cannabinoids.

Method Medline search, references supplied by DOH and others, and personal communications.

Results and Conclusions Cannabis and some cannabinoids are effective anti-emetics and analgesics and reduce intra-ocular pressure. There is evidence of symptom relief and improved well-being in selected neurological conditions, AIDS and certain cancers. Cannabinoids may reduce anxiety and improve sleep. Anticonvulsant activity requires clarification. Other properties identified by basic research await evaluation. Standard treatments for many relevant disorders are unsatisfactory. Cannabis is safe in overdose but often produces unwanted effects, typically sedation, intoxication, clumsiness, dizziness, dry mouth, lowered blood pressure or increased heart rate. The discovery of specific receptors and natural ligands may lead to drug developments. Research is needed to optimise dose and route of administration, quantify therapeutic and adverse effects, and examine interactions.

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†See editorial, p. 98, this issue.

In 1996 I was commissioned by the Department of Health (DOH) to review the scientific literature regarding the potential therapeutic utility of cannabis and its derivatives. The review was based upon primary sources (identified from a Medline literature search, reference lists supplied by the DOH and the Institute for the Study of Drug Dependence, and personal communications with relevant academics and clinicians). This paper is a greatly shortened version of the review. The 4 years which have elapsed have seen little in the way of new clinical results but considerable advances in cannabinoid basic science (Institute of Medicine, 1999). Government licences have recently been granted for several controlled trials of both synthetic and plant-derived cannabinoids in multiple sclerosis and chronic pain. In January 2000, I was appointed Medical Director of GW Pharmaceuticals, a company established to derive medicinal extracts from standardised cannabis plants.

HISTORY OF THERAPEUTIC USE

The first formal report of cannabis as a medicine appeared in China nearly 5000 years ago when it was recommended for malaria, constipation, rheumatic pains and childbirth and, mixed with wine, as a surgical analgesic (Mechoulam, 1986). There are subsequent records of its use throughout Asia, the Middle East, Southern Africa and South America. Accounts by Pliny, Dioscorides and Galen remained influential in European medicine for 16 centuries.

It was not until the 19th century that cannabis became a mainstream medicine in Britain. W. B. O'Shaughnessy, an Irish scientist and physician, observed its use in India as an analgesic, anticonvulsant, anti-spasmodic, anti-emetic and hypnotic. After toxicity experiments on goats and dogs, he gave it to patients and was impressed with its muscle-relaxant, anticonvulsant and analgesic properties, and recorded its usefulness as an anti-emetic.

After these observations were published in 1842, medicinal use of cannabis expanded rapidly. It soon became available 'over the counter' in pharmacies and by 1854 it had found its way into the United States Dispensatory. The American market became flooded with dozens of cannabis-containing home remedies.

Queen Victoria's personal physician wrote (Reynolds, 1890), on the basis of more than 30 years' experience, that "Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess". He found it incomparable for "senile insomnia", "night restlessness" and "temper disease" in both children and adults, but not helpful in melancholia, "very uncertain" in alcoholic delirium, and "worse than useless" in mania. It was very effective in neuralgia, period pains, migraine, "lightning pain of the ataxic patient" and gout, but useless in sciatica and "hysteric pains". He found it impressive in clonic spasms and certain epileptiform convulsions related to brain damage, but no good at all in petit mal or "chronic epilepsy", tetanus, chorea or paralysis agitans. It effectively relieved nocturnal cramps, asthma and dysmenorrhoea.

Reynolds was writing at a time when the zenith of cannabis as prescribed medicine and home remedy was already past. Although Sir William Osler was still recommending it for migraine sufferers in 1913, it was by then in steep decline because of variable potency of herbal preparations, poor storage stability, unpredictable response to oral administration, increasing enthusiasm for parenteral medicines and availability of potent synthetic alternatives, commercial pressures and American concern about recreational use. Cannabis was outlawed in 1928 by ratification of the 1925 Geneva Convention on the manufacture, sale and movement of dangerous drugs. Prescription remained possible until final prohibition under the 1971 Misuse of Drugs Act, against the advice of the Advisory Committee on Drug Dependence.

In the USA, medical use was effectively ruled out by the Marijuana Tax Act 1937. This ruling has been under almost constant legal challenge and many special dispensations were made between 1976 and 1992 for individuals to receive 'compassionate

reefers'. Although this loophole has been closed, a 1996 California state law permits cultivation or consumption of cannabis for medical purposes, if a doctor provides a written endorsement. Similar arrangements apply in Italy and Canberra, Australia.

CANNABINOID PHARMACOLOGY RELEVANT TO THERAPEUTICS

Cannabinol was isolated in 1895 and cannabidiol in 1934, but the most significant discovery was that of Δ^9-tetrahydrocannabinol (THC) in 1964. Chromatographic and spectroscopic methods subsequently uncovered many closely related compounds.

Capsules of synthetic THC (dronabinol) have been available for restricted medical use in the USA since 1985. Nabilone, a synthetic THC analogue, was marketed in 1983 and is the only cannabinoid licensed for prescription in the UK, restricted to treatment of nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional anti-emetics. Use in other indications is only possible on a 'named patient' basis if the drug is supplied by a hospital pharmacy.

In 1988, a specific protein receptor (known as CB_1) for THC was discovered in mouse nerve cells. This mediates most of the central nervous system (CNS) responses to cannabinoids, and is abundant in basal ganglia, hippocampus and cerebellum, globus pallidus, substantia nigra and cerebral cortex. An endogenous ligand was identified in 1992 and labelled anandamide (*ananda*: 'bliss' in Sanskrit). Anandamide has analgesic and tranquillising effects in animals, is involved in muscle coordination and affects the secretion and function of certain hormones. Other endogenous agonists almost certainly exist.

In 1993, a second receptor (CB_2) was identified in rat spleen macrophages, and this occurs only outside the CNS. There is scope for chemical manipulation of cannabinoids to maximise selectivity for CB_2 and so avoid psychoactive effects. It is thought this receptor has relevance for anti-inflammatory and immunosuppressive activity.

Pertwee (1995) has suggested that the anandamide system might be concerned with mood, memory and cognition, perception, movement, coordination, posture and skeletal muscle tone, sleep, thermoregulation, appetite and immune response.

CLINICAL APPLICATIONS

Nausea and vomiting

Many cytotoxic drugs are powerful emetics, and this is the major limiting factor in patients' acceptance of cancer chemotherapy (see Table 1 and Appendix).

Many recreational smokers receiving cancer chemotherapy have told their doctors that cannabis relieved their nausea (Grinspoon & Bakalar, 1993). Sallan *et al*'s (1975) randomised control trial (RCT) compared oral THC and placebo in 22 cancer patients who had proved resistant to conventional anti-emetics. Comparisons using patients' self-reports of nausea and vomiting demonstrated that THC was statistically superior to placebo. THC (10 mg/m^2) produced euphoria in the majority of patients, and one-third experienced sedation.

Subsequent RCTs (listed in Table 1) confirmed that natural and synthetic THC is invariably superior to placebo. Comparisons with anti-emetics available in the 1970s and 1980s suggest that THC is either equivalent in effect or better. A combination of prochlorperazine and THC was superior to either drug alone, and nabilone combined with prochlorperazine was better than dexamethazone plus metoclopramide. Although THC and nabilone produced more unwanted effects than comparison drugs, patients generally preferred them.

Children seem to respond well to nabilone and are tolerant of side-effects, but larger studies are required. Δ^8-THC performed well in a pilot study (Abrahamov *et al*, 1995) involving eight children aged 3–13 years with various blood cancers receiving chemotherapy, 60% of whom had experienced distressing vomiting despite treatment with metoclopramide. Δ^8-THC was given orally 2 hours before cytotoxics and repeated 6-hourly. No vomiting was recorded during this treatment and over the following 2 days. Two children were "slightly irritable" and one also showed "slight euphoria".

In a review of 12 studies involving 600 patients (Penta *et al*, 1981), THC was "effective" in 8/9 and nabilone in 3/3. The most common side-effects were somnolence (33%), dry mouth (9%), ataxia (8%), dizziness (6%), dysphoria (6%), and orthostatic hypotension (4%). A further review (Levitt, 1986) incorporating 55 studies, of which 32 were RCTs, showed that low-dose preventive treatment gives better results than targeting established vomiting. Younger patients may respond better than older ones.

Meta-analysis (Plasse *et al*, 1991) suggested that an optimal balance of efficacy and unwanted effects was achieved with relatively modest doses (7 mg/m^2 or less). Sedation and psychotropic symptoms are commonly reported, but are usually mild to moderate in intensity and resolve rapidly on discontinuation. No "persistent or fatal" adverse effects have been reported. Many American oncologists encourage nauseous patients to try cannabis and would prescribe it if it were legal (Doblin & Kleiman, 1991). Mode of action remains uncertain.

Multiple sclerosis and other neurological conditions

Drug therapy of muscle spasticity is generally only moderately effective and is limited by adverse effects (see Appendix). Spasticity is a central feature of multiple sclerosis (MS), cerebral palsy and spinal cord injury. Tremor, ataxia and incontinence also contribute to the high incidence of anxiety and depression in these conditions. Cannabis was often used to treat pain, muscle spasm, cramps and ataxia in the 19th century, and many modern sufferers have reported benefits (Grinspoon & Bakalar, 1993).

Most respondents to a questionnaire sent to British and American MS patients reported problems with symptom control (Consroe *et al*, 1997). Those who smoked cannabis claimed improvements in nighttime spasticity and muscle pain (91–98%); night leg pain, depression, tremor, anxiety, spasms on walking, paraesthesiae (80–89%); leg weakness, trunk numbness, facial pain (71–74%); impaired balance (57%); constipation (33%); memory loss (31%).

In a small single-blind comparison with placebo (Clifford, 1983), THC improved tremor and ataxia in most patients. All experienced a 'high' at the top dose (15 mg), and two reported dysphoria. Dose-related improvements in dystonia were noted in five patients given cannabidiol 100–600 mg daily for 6 weeks. Hypotension, dry mouth, sedation and light-headedness occurred but were described as mild. Parkinsonian symptoms were aggravated in two subjects.

An RCT by Petro & Ellenberger (1981) compared the effects of placebo and THC in doses of 5 or 10 mg on muscle tone, reflexes and muscle power in nine MS patients. Both doses of THC reduced

Table 1 Human randomised controlled trials (RCTs): anti-emetic effects

Study	Subjects	Study design	Results
Sallan *et al* (1975)	22 patients mainly resistant to conventional anti-emetics	db, pc, r, x, sd; THC 10 mg/m^2	THC significantly superior to placebo. Sedation and euphoria occurred in the majority of patients in THC phase
Chang *et al* (1979)	15 patients on high-dose methotrexate	db, pc, r, x, md; THC; oral 10 mg/m^2, smoked approx. 17 mg	"Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo"
Einhorn *et al* (1981)	100 patients on cancer chemotherapy	db, r, x, md; nabilone 2 mg q.d.s.; prochlorperazine 10 mg q.d.s.	Nabilone was significantly superior in reducing nausea and vomiting frequency, but produced more lethargy and hypotension. Nabilone was preferred by 75% of patients
Orr & McKernan (1981)	55 patients on cancer chemotherapy	db, pc, r, x, md; THC 7 mg q.d.s.: prochlorperazine 7 mg q.d.s.	THC was significantly superior to prochlorperazine ($P<0.005$). Side-effects were evenly distributed, except that THC produced a 'high' in 82% of patients
Jones *et al* (1982)	54 patients on various chemotherapy (24 evaluable)	db, pc, r, x, md; nabilone 2 mg	Nabilone reduced mean number of vomiting episodes ($P<0.001$) and nausea ($P<0.001$) in comparison with placebo. Side-effects common but "acceptable"
Ungerleider *et al* (1982)	214 patients on various chemotherapy	db, r, x, md; THC 7.5–12.5 mg prochlorperazine	No significant difference in anti-nausea and vomiting between the two drugs. More side-effects on THC, yet more patients preferred it
Niiranen & Mattson (1985)	24 patients on various chemotherapy	db, r, x, sd; nabilone 2 mg *v.* 15 mg prochlorperazine	Nabilone significantly superior in reducing vomiting. More side-effects yet majority of patients preferred it
Dalzell *et al* (1986)	23 children on various chemotherapy	db, r, x, md; nabilone *v.* domperidone	Significantly fewer vomiting episodes and less nausea on nabilone. More side-effects, but 2/3 children preferred it
Niederle *et al* (1986)	20 patients on cisplatin	db, r, x, md; nabilone 2 mg b.d., alizapride 150 mg t.d.s.	Nabilone reduced emesis and relieved nausea significantly better than alizapride but caused more adverse effects
Pomeroy *et al* (1986)	38 patients on various chemotherapy	db, r, md; nabilone 1 mg *v.* domperidone 20 mg	Mean number of vomiting episodes in two cycles of treatment was 4.53 for nabilone and 10.81 for domperidone ($P<0.01$)
Chan *et al* (1987)	30 children with chemotherapy-induced emesis	db, r, x, md; nabilone *v.* prochlorperazine	Improvement of retching and emesis was 70% during nabilone and 30% during prochlorperazine ($P=0.015$)
Lane *et al* (1991)	62 patients on various chemotherapy	db, r, md; dronabinol 10 mg q.d.s.; prochlorperazine 10 mg q.d.s.; or both	Percentage of patients with any nausea or vomiting was 51% for dronabinol group and 83% for prochlorperazine. A combination of the two drugs was significantly better than either alone

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; q.d.s., four times daily; b.d., twice daily; THC, tetrahydrocannabinol.

spasticity ($P<0.005$). One patient receiving THC 10 mg and one patient receiving placebo felt 'high' but no other side-effects were recorded. In a small RCT (Ungerleider *et al*, 1987) with 5-day treatment periods, THC 7.5 mg significantly improved spasticity in comparison with placebo. Nabilone 1 mg on alternate days was compared with placebo in a double-blind randomised cross-over trial with 4-week treatment periods in a single MS patient. Nocturia, muscle spasm and general well-being showed striking improvement during each active treatment period. Mild sedation was noted on active medication.

Cannabidiol had no beneficial effects in 15 patients with Huntington's disease (Consroe *et al*, 1991). Posture and balance were impaired by a single dose of smoked THC in 10 MS patients and 10 non-MS volunteers (Greenberg *et al*, 1994), but there was no active control to determine the effects of standard anti-spastic medication in this model.

Possible sites of action of cannabinoids in dystonia include basal ganglia, cerebellum, spinal motor neurons, somatic nerves and neuromuscular junction.

Loss of appetite and weight in cancer and AIDS

Several studies have investigated effect on appetite and weight (Table 2). The appetite-stimulating effect of cannabis was confirmed in fasting and non-fasting volunteers in an RCT of oral THC with alcohol, amphetamine and placebo (Hollister, 1971). A standardised THC smoking regime over 25 days in a residential laboratory was

associated with significant increases in calorie intake and frequency of eating occasions in comparison with placebo.

Open studies in cancer patients also showed appetite improvements and slowing of weight loss. Regelson *et al*'s (1976) RCT explored the effect on appetite (and mood) of oral THC in 54 cancer patients over a 2-week period. There were nine withdrawals due to side-effects (six in THC period – dizziness, disassociation, confused thinking, panic, "feelings of disturbance"; three in the placebo period – anxiety, fits, dizziness, lethargy, weakness). Patients receiving THC in the first period gained weight ($P<0.05$), and those receiving placebo first showed reduced weight loss on transfer to THC ($P<0.05$). Depression, tranquillity and "forthrightness" scores all improved on THC. In a quarter of the patients, somnolence, dizziness and disassociation were severe enough to negate these effects.

Many people with AIDS have claimed that smoking marijuana inhibits nausea, improves appetite, reduces anxiety, relieves aches and pains, improves sleep and inhibits oral candidiasis. A small pilot study supported the hypothesis that dronabinol might reduce weight loss or even promote weight gain (Plasse *et al*, 1991).

Beal *et al* (1995) conducted an RCT over 42 days of treatment with dronabinol 5 mg daily in 139 AIDS patients who had lost at least 2.3 kg. Six receiving dronabinol and three receiving placebo withdrew because of "perceived drug toxicity". Dronabinol boosted appetite in comparison to placebo ($P<0.015$) and nausea was reduced ($P=0.05$). Improvement in mood was a strong trend ($P=0.06$) and there was a tendency toward weight gain ($P=0.1$). Dronabinol produced more adverse effects than placebo ($P<0.001$), but 75% of these were mild or moderate. Most frequent were euphoria (9), dizziness (5), thinking abnormalities (5) and sedation (4).

Further investigation is amply justified. Careful monitoring of possible effects upon the immune system is needed, although a prospective multi-centre study (Kaslow *et al*, 1989), which followed nearly 5000 HIV-positive men for 18 months, showed no link between use of psychoactive substances and mean T-cell counts or progression to AIDS.

Pain

Cannabinoids are effective analgesics in animal models with non-opiate mechanisms predominating. There are many anecdotal reports (Grinspoon & Bakalar, 1993) of benefits in bone and joint pain, migraine, cancer pain, menstrual cramps and labour.

Five small RCTs (Table 3) show that THC is significantly superior to placebo and produces dose-related analgesia peaking at around 5 hours, comparable to but out-lasting that of codeine. Side-effects were also dose-related, and consisted of slurred speech, sedation and mental clouding, blurred vision, dizziness and ataxia. Levonantradol was also superior to placebo and notably long-acting, but almost half the patients reported sedation. Cannabinoids may have considerable potential in neuropathic pain (Institute of Medicine, 1999).

Raised intra-ocular pressure

Glaucoma due to obstructed outflow of aqueous humour or anatomical eye defects is the most common cause of blindness in the Western world. Some RCTs investigating this area are given in Table 4.

There have been many anecdotal reports that street marijuana can relieve glaucoma symptoms and individuals have successfully argued in the USA for legal access to the drug (Grinspoon & Bakalar, 1993). A pilot study of smoked marijuana

Table 2 Human randomised controlled trials (RCTs): appetite and weight

Study	Subjects	Study design	Results
Hollister (1971)	i. 12 fasting volunteers ii. 12 non-fasting volunteers	i. db, pc, r, x, sd; THC 0.5 mg/kg; 1 ml/kg 95% ethanol; 0.2 mg/kg dexamphetamine ii. db, pc, r, x, sd; THC 0.35 mg/kg ethanol as in i	There was large variation between subjects, but "those results confirm the notion that marijuana has a stimulating effect upon appetite and food consumption"
Regelson *et al* (1976)	54 patients with cancer	db, pc, r, x, md; oral THC 0.1 mg/kg t.d.s.	"THC stimulates appetite and helps retard the chronic weight loss associated with cancer". "Limiting side-effects which restrict use in 25% patients are somnolence, dizziness, and disassociation"
Gross *et al* (1983)	11 patients with anorexia nervosa	db, pc, r, x, md; THC 7.5–10 mg daily; diazepam (active placebo) 3–15 mg/day	"THC is not efficacious, in short-term administration, in the treatment of primary anorexia nervosa and is associated with significant psychic disturbances in some PAN patients"
Foltin *et al* (1986)	9 volunteers	sb, pc, r, x, md; marijuana (1.84% THC)	"Smoked marijuana can produce significant increases in food intake with small groups of subjects in a residential laboratory setting"
Beal *et al* (1995)	139 patients with AIDS-related anorexia and weight loss	db, pc, r, md; dronabinol 2.5 mg b.d.	In comparison with placebo, dronabinol improved appetite ($P=0.015$), mood ($P=0.06$) and decreased nausea ($P=0.05$). There was a trend toward weight stabilisation ($P=0.1$)

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; t.d.s., three times daily; b.d., twice daily; PAN, primary anorexia nervosa; THC, tetrahydrocannabinol.

and oral THC (15 mg) in 11 glaucoma patients found an average intra-ocular pressure (IOP) reduction of 30% in seven subjects and no response in four (Hepler *et al*, 1976).

Randomised controlled trials in volunteers confirmed that oral, injected or smoked cannabinoids produce dose-related reductions of IOP (Hepler *et al*, 1976; Perez-Reyes *et al*, 1976). Conjunctival engorgement and tear reduction were often noted. THC, Δ^8-THC and 11-hydroxy- THC are more effective than cannabinol, while cannabidiol was without effect. Tolerance may develop on multiple dosing.

An RCT in patients showed IOP reductions of similar magnitude following smoked THC along with "alterations in mental status" and tachycardia (Merritt *et al*, 1980). THC eyedrops produced dose-related IOP reduction with minimal side-effects though parallel reductions in the untreated eye (also seen in animal models) suggested a systemic rather than local mode of action.

Insomnia, anxiety and depression

Randomised controlled trials investigating insomnia, anxiety and depression are given in Table 5.

Nabilone (1 mg three times daily) produced "dramatic improvements" on the Hamilton Anxiety Scale in 20 anxious patients in comparison to placebo ($P < 0.001$), which were mirrored by other measures (Fabre & McLendon, 1981). Seven days into the study, nabilone patients' anxiety scores were halved, and this persisted unchanged throughout treatment. Side-effects included dry mouth, dry eyes and drowsiness. The authors concluded that nabilone is a "very effective anxiolytic deserving of further study". In a cross-over comparison of nabilone (1–2.5 mg twice daily) and placebo in 11 anxious patients (Ilaria *et al*, 1981), significant improvements in anxiety scores ($P < 0.05$) were again noted. The only clinically significant adverse effect was postural hypotension with related dizziness, lightheadedness or weakness. This was dose-related, experienced by most patients, and tended to tolerate out over time.

Preliminary data suggest that cannabidiol (160 mg) may be an effective hypnotic, and that THC (0.1 mg/kg) may have antidepressant properties in cancer patients and others (Grinspoon & Bakalar, 1993).

Epilepsy

Epilepsy afflicts 1% of the world's population. Conventional anticonvulsants provide unsatisfactory control for up to 30% of patients, and all can produce disabling or even life-threatening adverse effects.

The effect of cannabinoids on seizure activity in laboratory animals is complicated. Cannabidiol is a powerful anticonvulsant free of tolerance, but its profile varies between species. THC can produce seizures in big doses or when genetically seizure-sensitive animals are used, yet it is also robustly anticonvulsant in certain seizure models. A lack of stereospecificity suggests that the mechanism may not be related to a single receptor interaction. Serotonin, γ-aminobutyric acid, acetylcholine or prostaglandin systems may be involved.

There are many anecdotal reports of beneficial effects in humans with epilepsy (Grinspoon & Bakalar, 1993) but research data are virtually non-existent. Two single-case reports (Keeler & Reifler, 1967; Consroe *et al*, 1975) give confounding information. A young man suffered seizures on his regular medication and began smoking several cannabis cigarettes nightly alongside this. No further seizures occurred while this combination was maintained. In contrast, a man with grand mal epilepsy stopped taking anticonvulsants and suffered no fits for 6 months. He then smoked cannabis on seven occasions over a 3-week period and suffered three fits during this time, although not coincident with actual intoxication.

Only one RCT (Cunha *et al*, 1980) exists. Fifteen poorly controlled patients

Table 3 Human randomised controlled trials (RCTs): pain

Study	Subjects	Study design	Results
Noyes *et al* (1975*a*)	10 patients with cancer pain	db, pc, r, x, sd; THC 5, 10, 15 & 20 mg	"Pain relief significantly superior to placebo was demonstrated at high dose levels (15, 20 mg)"
Noyes *et al* (1975*b*)	36 patients with cancer pain	db, pc, r, x, md; THC 20 mg, codeine 120 mg	Codeine and THC were equally effective, but higher dose of THC sedated most patients and some found its psychoactive effects uncomfortable
Jain *et al* (1981)	56 patients with postoperative pain	db, pc, r, sd; levonantradol 1.5, 2, 2.5 or 3 mg i.m.	All doses significantly superior to placebo (at least $P < 0.05$), but no dose–response effect; 57% patients reported at least one side-effect, but "general acceptability was good"
Maurer *et al* (1990)	1 patient with spinal cord injury	db, pc, r, x, md; THC 5 mg, codeine 50 mg	"Delta-9-THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant effect on spasticity"
Holdcroft *et al* (1997)	1 patient with GI tract pain (familial Mediterranean fever)	db, pc, x, md; THC 50 mg daily	Morphine requirement significantly reduced ($P < 0.01$) during active treatment

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; i.m., intramuscularly; GI, gastrointestinal; THC, tetrahydrocannabinol.

Table 4 Human randomised controlled trials (RCTs): raised intra-ocular pressure (IOP)

Study	Subjects	Study design	Results
Hepler *et al* (1976)	i. 429 normal volunteers ii. 48 hospitalised subjects iii. 11 patients with glaucoma	i. db, pc, r, sd; smoked THC 1, 2 & 4%; oral THC 15, 30 & 40 mg ii. sb, pc, md; smoked THC 1 & 2% iii. o; smoked THC 1, 2 4% oral THC 15 mg	i. "dose-related and statistically significant effect in reducing acutely the intraocular pressure"; "pressure drop was in the range of 30% for 2% THC" ii. "consistent drop in IOP around 30% for 2% THC" and "no indications of cumulative effects upon IOP" iii. 7 patients showed a similar response to the above, 4 patients had no demonstrable drug effect
Perez-Reyes *et al* (1976)	12 normal volunteers	sb, pc, r, x, sd; i.v. infusion of various cannabinoids	"Δ^8-THC, Δ^9-THC, and 11-hydroxy-THC produced significant reductions in IOP, whereas cannabinol, 8-β-OH-THC and cannabidiol were less effective"
Merritt *et al* (1980)	18 patients with glaucoma	db, pc, sd; smoked marijuana – THC=2%	Significant reductions in IOP, but hypotension, tachycardia, palpitations and psychotropic effects "mitigate against routine use in the general glaucoma population"
Merritt *et al* (1981)	8 patients with "hypertensive glaucoma"	db, pc, sd; THC eye drops; 0.01%, 0.05%, 1%	Dose-related reductions in IOP; 1% drops produced mild hypotension, no psychic effects at any dose. Effect in both eyes suggests systemic mechanism of action
Jones *et al* (1981)	13 normal volunteers	db, pc, x, md; 10–30 mg THC 4-hourly	Significant reductions in IOP tend to tolerate out after 10 days regular dosing. Abrupt withdrawal of THC produces rebound increase in pressure above baseline

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; i.v., intravenous; THC, tetrahydrocannabinol.

Table 5 Human randomised controled trials (RCTs): insomnia, anxiety, depression

Study	Subjects	Study design	Results
Regelson *et al* (1976)	54 patients with cancer	db, pc, r, x, md; oral THC 0.1 mg/kg t.d.s.	"THC in cancer patients at acceptable dosage (0.1 mg/kg t.i.d. orally) had the effect of a tranquilliser and mild mood elevator, clearly without untoward effect on personality or emotional stability"
Carlini & Cunha (1981)	15 insomniac volunteers	db, pc, r, x, sd; cannabidiol 40, 80, 160 mg; nitrazepam 5 mg	Large placebo effect on sleep induction similar to that of active drugs. Cannabidiol significantly increased duration of sleep, and all three doses reduced dream recall
Fabre & McLendon (1981)	20 anxious patients	db, pc, r, md; nabilone 2–8 mg/day	A "dramatic improvement in anxiety in the nabilone group when compared with placebo ($P < 0.001$)" was reported. More dropouts from the placebo group ($P < 0.03$). Dry mouth and eyes and drowsiness were the most common adverse effects
Ilaria *et al* (1981)	11 patients with anxiety	db, pc, r, x, md; nabilone 1–2.5 mg b.d.	Nabilone was superior to placebo ($P < 0.05$) in relieving anxiety scores on Hamilton Anxiety Scale and Global Improvement Scale

o, open; sb, single-blind; db, double-blind; pc, placebo-controlled; r, randomised; x, cross-over design; sd, single-dose; md, multiple-dose; t.d.s., three times daily; b.d., twice daily; THC, tetrahydrocannabinol.

with secondary generalised epilepsy continued with their regular therapy but were also given either cannabidiol or placebo daily for up to 4.5 months while undergoing regular clinical and electroencephalogram evaluation. Half the patients on cannabidiol remained "almost free" of fits throughout the experiment, and all but one of the others showed "partial improvement". All but one of the placebo patients remained entirely unchanged. Somnolence occurred in four patients receiving cannabidiol.

Asthma

Small-scale controlled studies in volunteers with asthma show that oral, smoked and aerosolised THC has comparable bronchodilatory activity to salbutamol, although onset is quicker with the latter. Dose-related tachycardia occurred in some individuals, and subjective intoxication with higher doses. A THC aerosol was free of systemic unwanted effects, but was irritant to the lungs (Tashkin *et al*, 1977). Nabilone does not produce bronchodilation. Since THC-induced bronchodilation is not mediated through the sympathetic nervous system, synergistic combinations with β_2-adrenoceptor stimulants might be possible.

Other possible therapeutic applications

Basic research indicates that THC and analogues inhibit opioid withdrawal (Chesher & Jackson, 1985). Anecdotal reports from patients also point to beneficial effects beyond those which could be accounted for by sedative or hypnotic activity. Cannabinoids inhibit primary tumour growth and increase survival in animal tumour models (Harris *et al*, 1976) by an unknown mechanism. They also show antipyretic and anti-inflammatory activity (Formukong *et al*, 1989). Mechoulam (1986) has drawn attention to the lack of modern research directed at possible antihelmintic, antimigraine and oxytocic applications.

DISCUSSION

Therapeutic profile on existing evidence

Tetrahydrocannabinol and nabilone are effective anti-emetics but there are no comparisons with 5-HT_3 antagonists, so a role in modern anti-emetic regimes remains to be determined. Currently, only nabilone is licensed in the UK and available for prescription and research. THC (as dronabinol) has recently been rescheduled to permit prescription but remains unlicensed and must be specially imported on a named-patient basis. Delta-8-THC looks worthy of further investigation, particularly in children, and is much simpler to synthesise than THC.

Many individuals with MS have claimed a benefit from cannabis and small controlled trials support this, although effect upon posture and balance requires clarification. THC is an effective analgesic at the expense of sedation with larger doses and may have special merit in neuropathic pain. No conclusions are possible as yet about anticonvulsant potential. Some cannabinoids reduce IOP, though side-effects of products currently available limit application and effects of tolerance are uncertain. The mechanism for bronchodilation probably differs from that of β_2-stimulants, so synergistic combinations may be possible.

Cannabis and THC are effective appetite stimulants. Alongside anti-emetic, analgesic, anxiolytic, hypnotic and antipyretic properties this suggests a unique role in alleviating symptoms in selected patients with cancer or AIDS. This is a compelling area for future research, although possible effects upon immune function require careful monitoring.

Optimal doses and routes of delivery have not been established. Absorption by the oral route is unreliable. Smoking the drug is generally not a viable option since advantages such as rapid onset, accurate titration of effects and reliability in patients who are vomiting have to be set against the likelihood of lung irritation or damage, and it would in any case be unacceptable to most patients. However, pending availability of more satisfactory preparations, I believe that the existing profile of efficacy and toxicity justifies the provision of a legal supply of standardised herbal material ('compassionate reefers') to patients with terminal conditions who currently obtain relief with street cannabis. Sublingual sprays or tablets, nebulisers and aerosols look promising for the future, and THC is effective by the rectal route. Many potentially active cannabinoids have yet to be investigated and the recent identification of a peripheral receptor may lead to new drugs devoid of central nervous system effects.

Cannabis arouses passion in those who support or condemn it, and few people approach the clinical literature with dispassionate objectivity. Poorly controlled research produces ambiguous results which are then interpreted according to the prejudices of the reader. Anecdotes seem to be more readily accepted when they point to adverse rather than positive effects (Hall *et al*, 1994). Yet the known adverse effects of oral cannabinoids are rarely intolerable or life-threatening, in contrast to those associated with some standard therapies. A British Medical Association survey indicated that many UK doctors believe that cannabis should once again be available on prescription (Meek, 1994).

The way forward

A Select Committee of the House of Lords recently examined the scientific information concerning medical cannabis and took verbal and written evidence from a wide range of witnesses. Their conclusion (House of Lords, 1998) published in November 1998, was that, although cannabis should remain a controlled drug, the law should be changed to allow doctors to prescribe "an appropriate preparation of cannabis if they saw fit". The government rejected this recommendation on the day of publication.

Under the auspices of the Royal Pharmaceutical Society, large-scale multicentre trials are under way to explore further the efficacy of cannabinoids in relieving spasticity and postoperative pain. A pharmaceutical company has obtained a licence to cultivate medicinal cannabis on a large scale in the UK. By selecting a specific genotype then carefully controlling all other relevant variables such as soil conditions, temperature and humidity, it is possible to obtain levels of purity in plant extracts equal or superior to those of 'pure' synthetic cannabinoids. Most of the 60 or so naturally occurring cannabinoids are present in tiny amounts, and synthetic cannabinoids such as nabilone themselves contain up to 5% impurities, some of which are of unknown identity. Whether obtained by synthetic means or by plant extraction, it is essential that cannabinoids for prescription and research in the future should demonstrate excellent purity, stability and bioavailability.

The medicinal properties of cannabis are still mainly delineated by the anecdotal reports of those who believe their symptoms

are relieved by its use, and these accounts are often dismissed as wishful thinking or even mischievous. Since the conventional treatments for many of these disorders are both toxic and relatively ineffectual, a more constructive response would be to expose such claims to careful scientific examination and, in the meantime, search for a way to avoid criminalising those who seek only to assuage their own suffering.

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APPENDIX

Existing anti-emetics

Phenothiazzines and *butyrophenones* can cause sedation, movement disorders which may be irreversible, neuroleptic malignant syndrome, dry mouth, blurred vision, urinary retention, hypotension, allergic reactions, jaundice, hypothermia, hormonal disturbances, irreversible eye damage and, rarely, life-threatening anaemias. *Domperidone* has a more benign profile but is not recommended for long-term use. *Metoclopramide* produces movement disorders (1% of patients), dizziness and drowsiness. Selective 5-HT_3 antagonists (*ondansetron, granisetron*) are newer and more expensive. Side-effects include constipation, headache, flushing, liver enzyme changes, allergic reactions, visual disturbances, chest pain and dysrhythmias.

Existing neurological treatments

Baclofen alleviates spasticity, but may accentuate muscle weakness. It produces dose-related nausea and vomiting, drowsiness, vertigo, confusion, fatigue and hypotonia. Less commonly, fits, psychiatric disorder and hypotension occur. Sudden withdrawal can cause hallucinations. *Diazepam* is useful but can worsen weakness or incoordination and cause drowsiness, ataxia, depression, disinhibition and dependence. *Dantrolene* may cause weakness, hypotonia, drowsiness, dizziness, vertigo and anxiety. Rarely, it damages the liver, and is not recommended in those with co-existing heart or lung disease.

Existing glaucoma treatments

Eye-drops. *Miotics* can produce blurring of vision, headache, and parasympathetic effects including sweating, bradycardia, colic and bronchospasm. *Adrenaline* often causes local discomfort. *Dipivefrine* and *guanethidine* may cause conjunctival fibrosis on chronic use. *Beta-blockers* may cause bradycardia, heart block or bronchoconstriction.

Systemic drugs (*acetazolamide, dichlorphenamide*) can cause hypokalaemia, appetite suppression, paraesthesiae, drowsiness, depression, rashes and, rarely, bone marrow suppression.

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CLINICAL IMPLICATIONS

- Cannabis and its derivatives show promise of beneficial effects in a number of medical conditions for which standard treatment is less than satisfactory, and further controlled research is fully justified.
- Cannabis is very safe in overdose, but often produces unwanted effects which are better tolerated by patients with some conditions (e.g. multiple sclerosis, chronic pain, AIDS, cancer) than others (e.g. glaucoma).
- Optimal formulations, doses and routes of delivery have not yet been established.

LIMITATIONS

- Because of imposed time constraints, the review is not fully comprehensive, although all accessed sources were incorporated.
- Much of the evidence is anecdotal, and many of the research studies cited have serious methodological shortcomings.
- Few researchers (or reviewers) approach the subject of cannabinoid therapeutics in a spirit of dispassionate objectivity.

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Therapeutic aspects of cannabis and cannabinoids

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An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis

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The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of Cannabis sativa *in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ($P < 0.05$, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ($P < 0.05$, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.*
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Key words: *cannabidiol; cannabis; delta-9-tetrahydrocannabinol; multiple sclerosis; neurogenic detrusor overactivity; neuropathic pain; sleep disorder; spasticity; urinary incontinence*

Introduction

Ninety per cent of patients with multiple sclerosis (MS) develop lower urinary tract symptoms (LUTS) after 10 years of disease activity.[1] Urinary urgency and urge incontinence may affect quality of life and are often compounded by immobility. Standard treatment with anti-cholinergics and clean intermittent self-catheterization may be highly effective in the early stages, but with increasing disability indwelling catheterization, an intervention with significant morbidity, is often required. Additional therapies for refractory urinary symptoms in patients with advanced MS are required to prevent or postpone the need for long-term indwelling catheterization.

Some patients with MS use cannabis to alleviate urinary and other symptoms. In a survey of 112 patients who used 'street' cannabis as a medicine, 64%, 55% and 59% reported improvements in urgency, urge incontinence and hesitancy, respectively.[2] In addition, Wade has recently reported that medicinal cannabis extracts produced improvements in bladder symptoms in some patients recruited for neurogenic symptoms in MS.[3] Such effects are consistent with reports of the existence of cannabinoid receptors in rodent bladder, the activation of which reduces bladder motility,[4–7] as well as in regions of the central nervous system associated with bladder control.[8] Statistically significant improvements in MS-related neuropathic pain and improvements in spasticity in some patients have also been reported by Wade and Notcutt.[3,9]

Because cannabis has not yet been licensed for medicinal use in the UK, patients have to use 'street' cannabis that has not been subjected to rigorous quality control, with obvious implications for safety. Cannabis medicinal extracts (CME) are whole-plant extracts of *Cannabis sativa* that are derived from plants bred selectively to contain fixed proportions of the abundant cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in particular. In addition to THC or CBD, the remainder (<5%) of the cannabinoid fraction of the extract contains other 'minor' cannabinoids that occur naturally in smaller quantities. The cannabinoid fraction of CME accounts for 50% of the extract, the balance being comprised of noncannabinoid substances such as flavinoids and terpenoids. Ethanol (50%) and propylene glycol (50%) dissolve the highly lipophilic extract and facilitate sublingual

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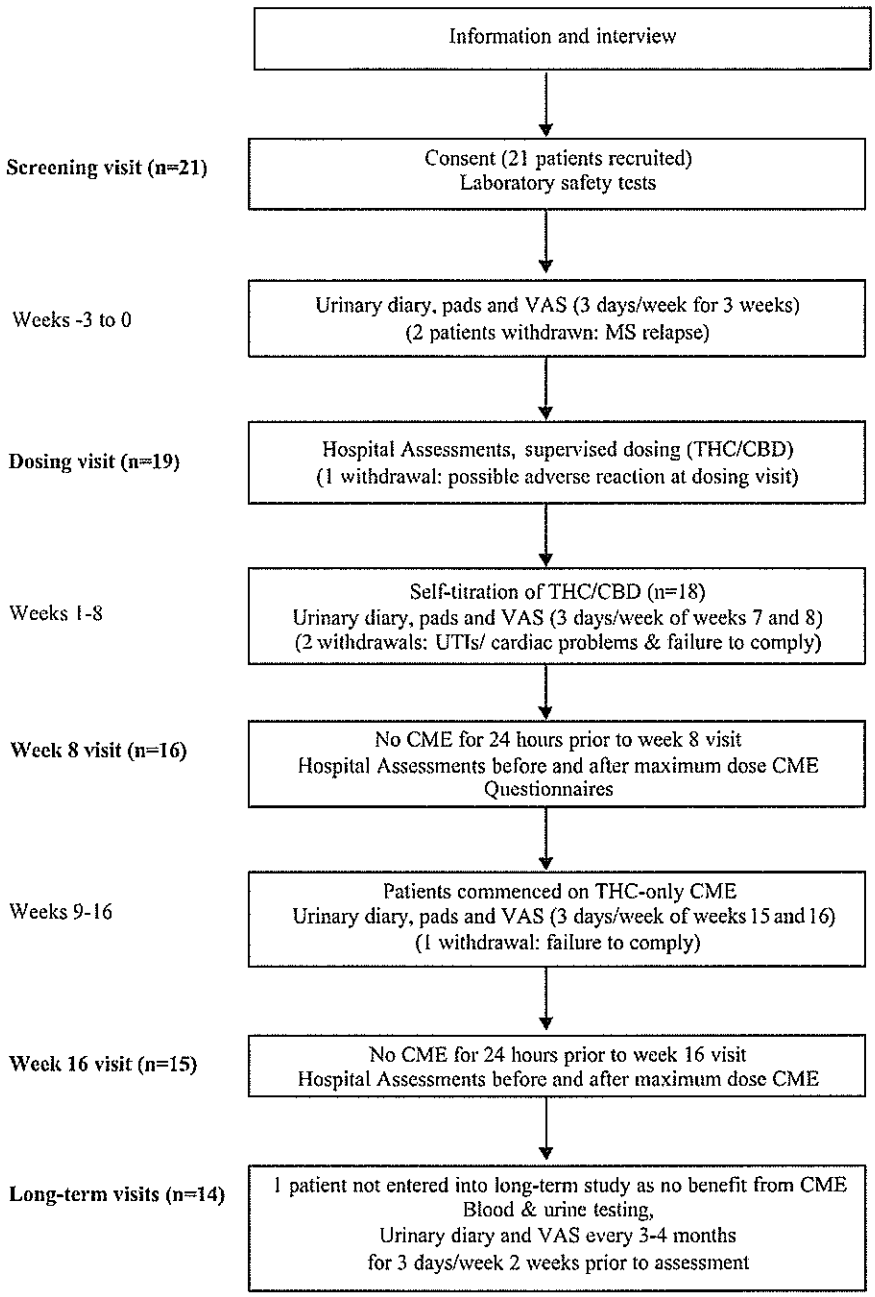

absorption.[10] The rate of absorption of CME following sublingual administration is more rapid and predictable than by the oral route, and enables patients to self-titrate the dose of CME, balancing symptom control against side effects, such as intoxication.[11]

The aim of this open-label, pilot study was to evaluate the safety, tolerability, dose range and efficacy of two preparations of CME on lower urinary tract and other troublesome symptoms in patients with advanced MS.

Patients and methods

Patient selection

Patients aged 18–65 with advanced MS (Kurtzke ≥ 6.5) and troublesome LUTS refractory to maximum conventional treatment were eligible for recruitment. Other inclusion criteria included detrusor overactivity proven on cystometry and a Mini-Mental State Examination[12] score >27. All patients continued on maximum tolerated dose of anti-cholinergic medications and clean intermittent self-catheterization when applicable throughout the trial. Patients using street cannabis were required to stop four weeks prior to and during the study and urine tests for cannabis were carried out prior to recruitment. Exclusion criteria included detrusor failure, an indwelling catheter or inability to fulfil the requirements of the study protocol.

Study procedures

The study protocol, summarized in Figure 1, had local ethics committee approval. The trial was conducted under

a 'DDX' (Doctor's and Dentist's exemptions) license issued by the Medicines Control Agency, with several restrictions on protocol design. Initial approval was given for eight weeks' treatment with CBD/THC, followed by THC-only in the long-term. Following informed consent and physical examination, suitable patients were asked to perform baseline home assessments (Table 1) for three consecutive days per week for three weeks, to confirm eligibility. Patients at risk of recurrent urinary tract infections were advised to increase their fluid intake, as UTI is a potential confounding factor. We considered that precise measurement of fluid intake would be too difficult for these significantly disabled patients to undertake in addition to their many other daily outpatient assessments.

Urinary diary and VAS scores were repeated for three days per week during the last fortnight of each eight-week treatment period on CME (see below) and during the long-term safety and efficacy extension (Figure 1). Outpatient hospital assessments (Table 1) were also performed at baseline and at the end of each treatment period. The patients did not take CME for 24 hours prior to the outpatient hospital visit. Cystometry was performed to calculate maximum bladder capacity. The patients then took their maximum tolerated dose of CME and cystometry was repeated. Thus 'chronic' and 'acute' effects of CME on cystometric capacity were evaluated. In a similar manner, at the same outpatient visit the chronic and acute effects of CME on spasticity were monitored using the Ashworth score, carried out by the same trained observer.

Table 1 Assessments performed at home and during outpatient hospital visits

Home assessments
Frequency and volume chart, noting time and nature of each micturition event, whether voluntary void or incontinence episode and sensation (planned void, normal, strong or urgent desire to void)
Incontinence pad weights
Daily Visual Analogue Scale for each neurogenic symptom (identified at tape-recorded interview)
Hospital (outpatient) assessments
Laboratory safety tests
Full blood count
Renal profile
Liver profile
Urinalysis and urine culture, urinary HCG, urine screen for cannabis at screening visit
Questionnaires
Mini Mental State Examination[12]
Medical Outcomes Study Short Form 36 (generic quality of life)[25]
Hospital Anxiety and Depression score[26]
Multiple Sclerosis Impact score[27]
Barthel Activities of Daily Living Index[28]
International Continence Society BPH[29]
Bristol Female Lower Urinary Tract Symptoms[30]
Urological
Filling and voiding cystometry (baseline visit and before and after maximum tolerated dose)
Post void residual
Neurological
Tape-recorded interview to identify neurogenic symptoms and effect of CME
Ashworth scale for spasticity[31]
Global patient comfort score

Drug administration

At the initial supervised dosing visit, patients were instructed on how to recognize symptoms of intoxication. Under close observation and cardiomonitoring, they took up to four sprays of THC/CBD (2.5 mg of THC and 2.5 mg CBD per spray) as tolerated over 2 hours. The patients were monitored for 4 hours after the start of dosing. At home, patients took THC/CBD at night-time only for the first two weeks of treatment and were monitored by daily telephone contact to check on their ability to use the spray, and to advise on dose escalation and side effects. Thereafter, divided daytime dosing was introduced, with a maximum permitted daily dose of 120 mg each of THC and CBD (48 sprays). However, a conservative dosing regimen was followed over the first four weeks of treatment, with gradual dose escalation such that patients titrated symptom relief against the acute side effects of CME (intoxication). After four weeks patients were actively encouraged to experiment with their dosing regimen and to take the maximum tolerated dose of CME. After eight weeks' treatment on THC/CBD the patients were switched to the THC-only extract (2.5 mg THC per spray) for a further eight weeks. Adverse events and CME consumption were recorded daily throughout the study. At the conclusion of the trial, with ethics committee approval, patients were permitted to continue treatment with CME and were allowed to choose either extract in a long-term safety and efficacy study. Assessments including urinary diary and VAS were completed every 3–4 months.

Data analysis

Data from the first six weeks of each treatment period were not analysed because this period had been used for self-titration to arrive at a stable dose. Statistical calculations were performed using Wilcoxon's signed rank test (Graphpad Prism version 3.02).

Results

Previous use of cannabis

Ten patients had used cannabis as a medicine previously and four of these were considered 'regular' users (cannabis used as a medicine >15 times) with smoking or ingestion of the drug within three months of recruitment. Urine testing for cannabis was negative prior to recruitment in all patients.

Recruitment and withdrawals

Twenty-one patients (4M:17F; mean age 48 years, range 31–64) were recruited. Mean (median) time from the date of formal diagnosis of MS was 11 (10) years and the mean duration from first onset of symptoms to diagnosis was 6 (3) years. Fourteen had primary or secondary progressive MS and the remainder had relapsing–remitting disease

that was considered stable. Mean Kurtzke score at entry to the trial was 7.0 (range 6.5–8.0).

All patients reported troublesome LUTS for >5 years. Eleven patients took Oxybutynin and seven took Tolterodine regularly. Five patients took Desmopressin in addition to an anti-cholinergic on an 'as required' basis. Two patients had found anti-cholinergics to be ineffective and one was unable to tolerate the side effects. The patients had varying degrees of detrusor dysfunction and detrusor sphincter dyssynergia with 11 requiring regular clean intermittent self-catheterization. Fifteen patients completed 16 weeks of treatment; the timing and reasons for withdrawal of the other six patients are detailed in Figure 1.

Duration of treatment and follow-up

Patients took THC/CBD for a mean (median) of 11 (10) weeks and THC-only for 10 (9) weeks during each treatment period. Fourteen patients were entered into the long-term safety and efficacy extension and all opted to take the THC-only extract. Mean (median) long-term follow-up with voiding diary and VAS scores was 31 (35) weeks. Eleven of these 14 patients continue to take CME in the long-term extension for a mean (median) of 27 (30) months (22.2 patient years) and 3 discontinued CME after physical deterioration necessitated an indwelling catheter.

Dose of CME

Although the range of doses in use by the end of the initial self-titration treatment periods for THC/CBD or THC was quite wide across the group, the doses after the titration periods remained stable for each patient individually. Patients took 1–39 sprays/24 hours of THC/CBD (2.5–97.5 mg each/24 hours), with a daily mean of 33.7 mg (median 30.5) each. The number of sprays of THC-only extract was 1–30.2 sprays/24 hours (2.5–75 mg/24 hours) with a daily mean of 31.2 mg (median 29.4), significantly less than on THC/CBD ($P < 0.05$, Wilcoxon's signed rank test). The four patients who were previous regular users of cannabis as a medicine took a mean (median) of 52 mg (49) each of THC and CBD and 50 mg (55) of THC during the last two weeks of each eight week treatment period.

Patients took a mean (median) of 23.4 mg (16.3) of THC-only/24 hours during the long-term extension, which was significantly less than during the first eight weeks of treatment on THC/CBD. However, long-term dosing data from one patient with above average consumption were not available. There was no correlation between the dosage of CME in individual patients and the effect on bladder symptoms or VAS scores. Tolerance to CME (increasing doses required to achieve the same therapeutic benefit) did not occur in the long-term.

The body mass index (BMI) was available for 12 of the 15 patients who completed 16 weeks of treatment; mean (median, range) BMI was 24 (24, 17–30). The doses of CME taken by each patient were not related to their BMI.

Laboratory safety tests

There were no clinically significant changes in haematological, renal or hepatic indices throughout the study.

Side effects

As a result of the study design, most patients experienced symptoms of intoxication such as mild drowsiness, disorientation and altered time perception during the dose titration period. However three patients had single short-lived hallucinations (two visual and one auditory) that did not recur when they lowered their dose. Two patients appeared to be exquisitely sensitive to the psychoactive effects of CME and could tolerate no more than one spray of either extract daily, but still reported beneficial effects. One of these patients had improvement in spasms but neither tremor nor urinary symptoms improved. This patient continues to take CME with beneficial effects on spasms. The other patient had improvements in frequency and incontinence, but not in episodes of urgency or nocturia or VAS scores of pain, tremor or spasms. It is likely that these improvements were related to the placebo effect as this patient later discontinued CME without significant deterioration in symptoms.

All patients complained of a worsening of dry mouth (already present due to anti-cholinergic treatment) and two complained of mouth soreness at the site of drug administration.

Diary data

Functional bladder capacity and bladder emptying efficiency Voided (plus catheterized where applicable) urine volumes provide a measure of 'functional' bladder capacity. This measure did not increase significantly from baseline after eight weeks' treatment with either THC/CBD or THC-only or in the long-term study. Bladder emptying efficiency [volume voided × 100/(volume voided + post void residual)] is a measure of detrusor function, but is affected by bladder outlet obstruction. For the eight patients who voided and catheterized throughout the study, mean (median) bladder emptying efficiency was 44% (45) at baseline and did not change significantly following eight weeks of treatment with either extract (44% (47), THC/CBD and 42% (48), THC-only) or in the long-term study (40% (41), THC-only).

Urinary incontinence, frequency, and total voided volumes The number of daily incontinence episodes, the volume of incontinence, nocturia and daytime urinary frequency all decreased significantly on both extracts after eight weeks of treatment ($P < 0.05$, Wilcoxon's signed rank test; Figure 2). Both extracts were comparable in terms of efficacy. In the long-term study, the number of incontinence episodes and daytime frequency also decreased significantly (Figure 2). The total daily volume of urine produced (assessed by adding voided, catheterized and incontinence pad weights) also decreased significantly from baseline after using THC/CBD for eight weeks (median 1800 versus 1464 mL, $P < 0.05$, Wilcoxon's signed rank test) and after eight weeks of THC-only (median 1334 mL, $P < 0.05$). The mean combined voided and catheterized volumes were similar across the treatment periods (1953, 1631, 1636 and 1589 mL for baseline, weeks 7 and 8, weeks 15 and 16 and the long-term respectively,

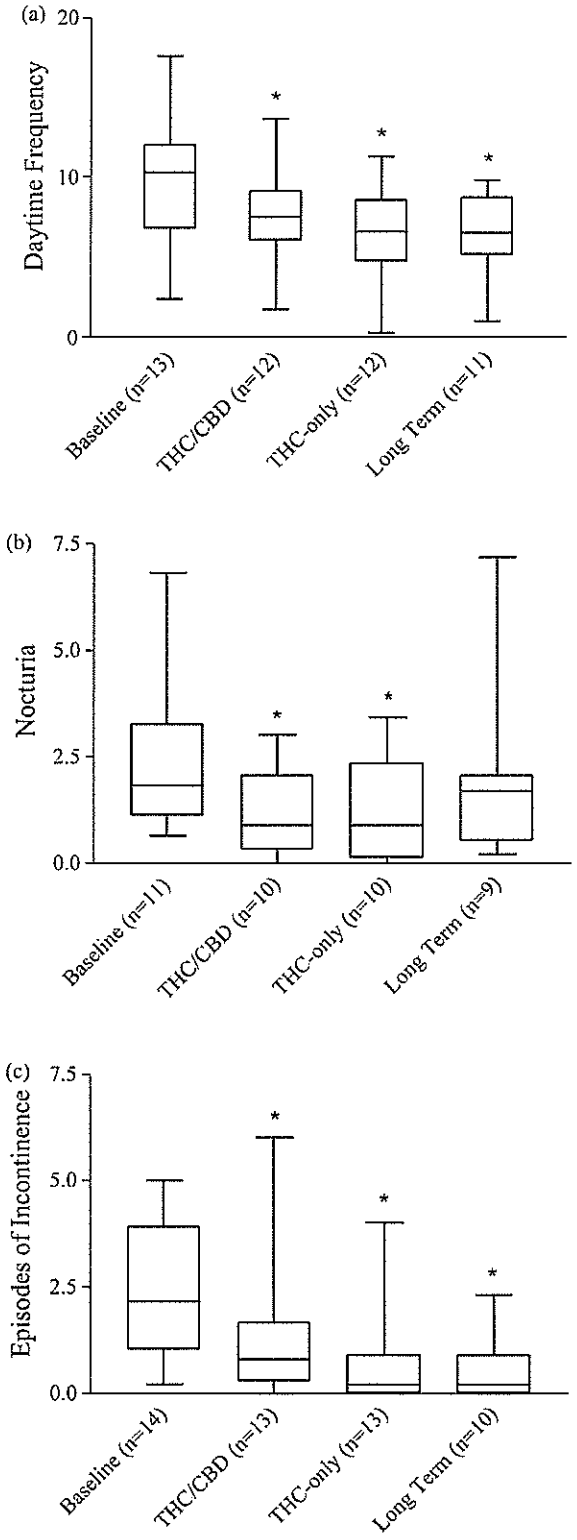

Figure 2 *The effects of THC/CBD and THC-only on the total number of daytime (a) and night-time (b) voids, and the number of incontinence episodes/24 hours (c) as recorded in voiding diaries at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only). The box extends from the 25th percentile to the 75th percentile, with a line at the median; the whiskers extend above and below the box to show the highest and lowest values (* where P < 0.05 compared to baseline using Wilcoxon's signed rank test).*

Figure 4) but the volumes recorded during weeks 7 and 8 were statistically significantly smaller than baseline volumes.

Bladder sensations The mean (median) proportion of voids for which the patient reported having the sensation of 'urgency' decreased significantly from 16% (11) to 6% (5) after eight weeks' treatment with THC/CBD, to 4% (2) after eight weeks of THC-only and to 2% (0.05) in the long-term. In concert, the proportion of 'planned or normal' voids increased significantly on both extracts following eight weeks' treatment and in the long-term ($P < 0.05$, Wilcoxon's signed rank test, Figure 3).

Other troublesome symptoms The most frequent additional troublesome symptoms that the patients identified during the tape recorded interview on entry to the study were spasticity, pain, tremor, difficulty sleeping and constipation (Table 2). Average VAS scores for pain ($n = 13$) improved after eight weeks' treatment with THC/CBD ($P < 0.05$, Wilcoxon's signed rank test). Scores for spasticity ($n = 13$), pain ($n = 12$) and difficulty sleeping ($n = 9$) all improved significantly ($P < 0.05$, Wilcoxon's signed rank test) after eight weeks' treatment with THC-only. No changes were noted for either tremor or constipation. Improvement in pain scores ($n = 10$) remained significant in the long-term for a mean (median) of 31(35) weeks. In addition, one patient complaining of severe idiopathic nausea refractory to all treatments had complete resolution of this symptom on both extracts, with continued benefit in the long-term. Improvements in other symptoms such as wellbeing were reported but the numbers were too small for analysis.

Urodynamic data

The maximum cystometric capacity (MCC) increased, but not significantly, from a mean of 296.6 mL (median 292,

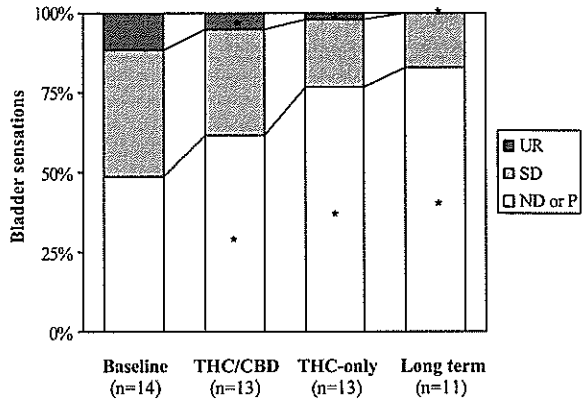

Figure 3 *The effects of THC/CBD (weeks 7 and 8) and THC-only (weeks 15 and 16, long-term) on the proportion of bladder sensations recorded in frequency/volume charts. UR = urgency, SD = strong desire to micturate, ND/P are normal desire to micturate and planned voids. The asterix denotes a statistically significant difference from baseline values (P < 0.05, Wilcoxon's signed rank test). Data from one patient with concomitant severe sensory urgency that persisted throughout the trial has been excluded.*

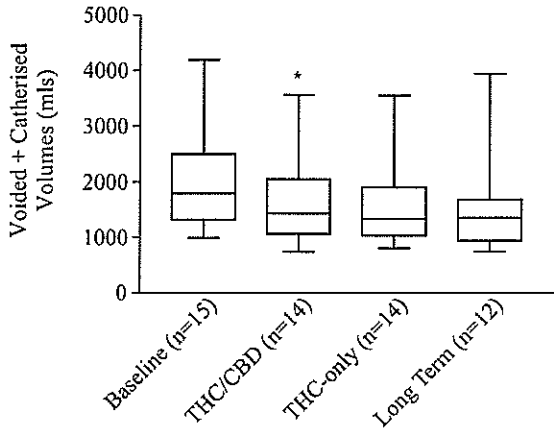

Figure 4 *Mean total voided and catheterized volumes/24 h at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only). (* where P < 0.05 compared to baseline using Wilcoxon's signed rank test).*

range 45–608, $n=15$) at baseline to 339 mL (312, 103–665, $n=14$) after chronic treatment with THC/CBD. Chronic treatment with THC-only resulted in a significant increase in mean MCC to 394 mL (294, 126–781, $n=14$; $P<0.05$, Wilcoxon's signed rank test). Acute treatment with the maximum tolerated dose of THC/CBD (mean dose, 10) increased mean MCC to 394 mL (324.5, 105–814, $n=14$) but this was not significant. However acute treatment with THC-only (mean dose, 7.5) significantly increased the mean MCC to 426 mL (384, 142–812, $n=12$; $P<0.05$).

Urinary symptom questionnaires

Responses to the questions relating to urinary frequency (Q1), nocturia (Q2) and urge incontinence (Q4) and to the impact of urinary symptoms on life (Q30 ICS-BPH, Q31 BFLUTS) changed significantly after eight weeks of treatment with both extracts ($P<0.05$, Wilcoxon's signed rank test), and reflected the improvements reported in diary data and pad tests. In addition, significant improvements were also noted in the responses to questions 3 (urgency) and 6 (number of incontinent episodes, BFLUTS only) after eight weeks' treatment with THC-only.

General and neurological assessments

There were no significant changes in any of the questionnaire based measures (SF36, MS Impact score, Barthel activities of daily living, Hospital Anxiety and Depression score) after eight weeks' treatment with THC/CBD. Ashworth and global comfort scores did not change after eight weeks' treatment with either extract (the patients having fasted from CME for 24 hours) or acute treatment with the maximum tolerated dose.

The physical examination measures remained unchanged in all patients. Mean Kurtzke score did not change throughout the early part of the trial (eight weeks' treatment each with THC/CBD and THC-only). No change in mean Ashworth scores from baseline were noted at the 8- and 16-week assessments, either following a 24-hours fast from CME or following maximum tolerated dose of CME.

Long-term safety and efficacy extension

CME did not have any adverse effects on laboratory safety blood tests after a mean of 36 weeks of follow-up. Three patients, all of whom were wheelchair bound at the time of recruitment, suffered significant MS-related physical deterioration during the long-term extension.

Discussion

In this open-label, pilot study in a select group of patients with advanced MS we investigated the safety and efficacy of self-titrated sublingual whole plant extracts of *C. sativa* for treatment of refractory lower urinary tract and other chronic symptoms. Side effects were minimal and tolerable, and over the short- and long-term periods of observation many symptoms improved and none worsened. Thus, self-titrated treatment with CME appears safe and efficacious.

Treatment with CME improved several MS-related urinary symptoms, with decreases in frequency, nocturia, incontinence and urgent voids, and increases in the proportion of voids that were 'planned' or occurred with a normal desire to void. However, total urinary output also decreased significantly during treatment with either extract, indicating that the patients were drinking less fluid. This may of course have contributed to the improvements in frequency, nocturia and episodes of incontinence, although it cannot have caused the observed increase in MCC that may also underlie these findings. The reduction in the number of urgent micturition events might also be related to decreases in fluid intake or the rate of bladder filling.

Table 2 Mean (SD) VAS scores for troublesome secondary neurogenic symptoms at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only)

	n	*Baseline*	n	*THC/CBD*	n	*THC-only*	n	*Long-term*
Spasticity	14	43.57 (18.74)	13	35.00 (22.59)	11	**30.18 (16.17)**	10	34.60 (24.95)
Pain	13	57.92 (21.17)	12	**42.75 (22.41)**	11	**41.91 (24.39)**	10	**39.9 (23.53)**
Tremor	10	43.90 (22.57)	9	40.22 (26.38)	8	39.75 (29.97)	6	46.67 (25.12)
Sleep	9	49.78 (26.05)	9	32.00 (25.95)	8	**28.50 (26.33)**	6	37.5 (30.19)
Constipation	6	50.50 (18.83)	6	36.33 (23.00)	6	37.17 (25.56)	6	34.33 (31.53)

Bold indicates statistically significant difference from baseline score ($P<0.05$, Wilcoxon's signed rank test).

An important aspect of this trial was the use of self-titration to establish a dosage most appropriate for each individual patient. This approach has also been used by both Nottcutt and Wade,[3,9] however, in our study patients were encouraged to gradually increase the dose of CME over a longer period (four weeks) until they had identified their maximum tolerated dose. The large dose range observed appeared to be determined by sensitivity to the side effects rather than by the amount of medication required to control LUTS, as there was no relation to final stable dose on either extract and baseline urological parameters, such as MCC. Similarly, patients who responded to CME in terms of symptom control were not all on a higher than average dose of CME, however the number of patients in this pilot study is too small for detailed analysis of responder and nonresponder groups.

The incidence of events due to intoxication (e.g., hallucinations) was low even though patients were encouraged to take the maximum tolerated dose. This suggests that the favourable pharmacokinetic profile of CME using the sublingual route allows patients to adjust their dose quite precisely such that symptom relief is achieved with minimal side effects, although it is possible that with such a large final dose range of CME, some patients might have been using a suboptimal dose. There was little intrapatient variation in the daily dose of either extract over time, which suggests that tolerance to CME did not occur and that efficacy was maintained at a stable dose.

All of the patients entered into the long-term safety and efficacy extension chose to take the THC-only extract as they found it more effective in controlling their urinary symptoms, particularly by reducing the intensity of urinary urgency. However no significant differences in efficacy between the extracts were identified on data analysis. In addition, patients preferred THC-only to THC/CBD as they took significantly less of this preparation to achieve the same therapeutic effect.

The positive effects of treatment on urinary symptoms, spasticity, pain and difficulty sleeping suggests that CME acts at numerous sites in the nervous system. Cannabinoids have been shown to inhibit gastrointestinal and uterine smooth muscle contraction and it is possible that CME has a direct inhibitory effect on detrusor contraction.[5–7,13,14] In addition, interaction of CME with the cholinergic receptor system and/or synergism with anticholinergic medication represent further mechanisms of action.[15–17]

The duration of action of cannabis on detrusor function or muscle spasticity is unknown. Anecdotally, many patients smoke cannabis for the rapid relief of acute symptoms (e.g., muscle spasms), or to attenuate chronic symptoms (e.g., tremor, pain), rather than as a preventative measure. This pattern of drug usage is probably related to the pharmacokinetic profile of the cannabinoids. However, we wanted to identify any chronic effects of the drug on parameters such as the Ashworth score and cystometric capacity, and therefore performed these measures after 24 hours off CME. Notwithstanding the obvious limitations of an open-label trial, given the half-life of the preparation (4–6 hours), a significant change from baseline could reasonably be attributed to chronic effects. We then assessed the acute effects of CME on these parameters following maximum tolerated dose.

We investigated changes in bladder function following treatment with CME using voiding diaries and cystometry. There was a considerable range in MCC and functional bladder capacity at baseline across the group and the numbers are insufficient to permit analysis of subgroups of bladder dysfunction, for example those patients with a very small bladder capacity or those with incomplete bladder emptying and a large residual. However all patients had detrusor overactivity. Although chronic treatment with THC-only produced significant increases in MCC, the increase seen with chronic treatment with THC/CBD did not reach statistical significance. This might be related to a failure to power the study adequately. Acute treatment with either extract did not further increase mean MCC significantly. Bladder emptying efficiency, an indirect measure of both detrusor contractility and outlet obstruction, did not change.

The improvements in urinary urgency in the absence of increasing voided volumes might be due to the action of cannabinoids on the putative suburothelial mechanosensory apparatus.[18] The endocannabinoid anandamide is an agonist at the vanilloid receptor (TRPV1) and it has recently been demonstrated that the density of TRPV1-immunoreactive c-fibres in the suburothelium is increased in patients with spinal cord lesions and bladder overactivity.[19–21] It is possible that cannabinoids or their metabolites in the blood or urine have an effect on vanilloid receptor-expressing afferents C fibres in the suburothelium. CME might also act directly on afferent fibers[6] or at the level of the spinal cord. It has been shown that intrathecal anandamide attenuates inflammation-induced bladder overactivity in an animal model.[22] Finally, cannabinoid receptors in the pons and other parts of the CNS involved in the control of micturition represent other potential pharmacological targets.[23]

Treatment with CME improved troublesome chronic neurological symptoms, in keeping with the results of other pilot studies using CME.[3,9] None of the other symptoms worsened. We observed significant improvements in VAS scores for pain, spasticity and ability to sleep after eight weeks' treatment with THC-only CME. Treatment with THC/CBD also significantly improved pain, but improvements in spasticity and sleeping did not reach statistical significance, probably a result of the small numbers of patients in the study. In the long-term study, there was a significant improvement in pain VAS only. The mean VAS scores for spasticity and quality of sleep decreased, but not significantly, in the long-term (Table 2). This is probably related to sample size, as patients did not take significantly less CME during this period. Other investigators have also reported improvements in these symptoms.[3,9] The positive results of VAS scores of spasticity and negative results of Ashworth scores complement the findings of Wade, and may reflect the limitations of the Ashworth scale in terms of its sensitivity.[3] In addition, whilst the Ashworth scale has

good intraobserver reliability, the results can be influenced by several factors (for example a long travelling time to the hospital in a seated position). Killestein has also reported negative results in Ashworth scores following treatment with both whole plant cannabis extracts and THC (Marinol) taken orally, although these results might be related to unpredictable bioavailability from the gastrointestinal tract as well as limitations in the Ashworth score itself.[24]

Weaknesses of this study are that there was no control group and it was not blinded. However, this is a potential problem in all such studies of novel treatments. An open-label design was necessary because this form of cannabis had not been used in a medical setting before and the dosage and onset of the symptoms of intoxication were unknown. Because of the open-label trial design, we were able to help patients identify symptoms of intoxication at an early stage during the dose titration period. A multicentre, placebo-controlled trial is now in progress.

Conclusion

In this open-label pilot study, treatment with cannabis-based medicinal extracts produced sustained improvements in urinary symptoms, in particular urinary urgency and urge incontinence, with significant improvements in symptom-specific quality of life scores. Decreased urinary output during treatment might account for part of the improvements in frequency and nocturia. Patient-reported pain, spasticity and quality of sleep all improved significantly in the short-term. The improvements in pain scores persisted in the long-term study. Unpleasant side effects such as hallucinations were uncommon and other side effects such as dry mouth were well tolerated.

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Role of Cannabinoids in Pain Management

18

Ethan B. Russo and Andrea G. Hohmann

Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

Introduction

Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

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The Endocannabinoid System

There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are "relax, eat, sleep, forget, and protect" [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

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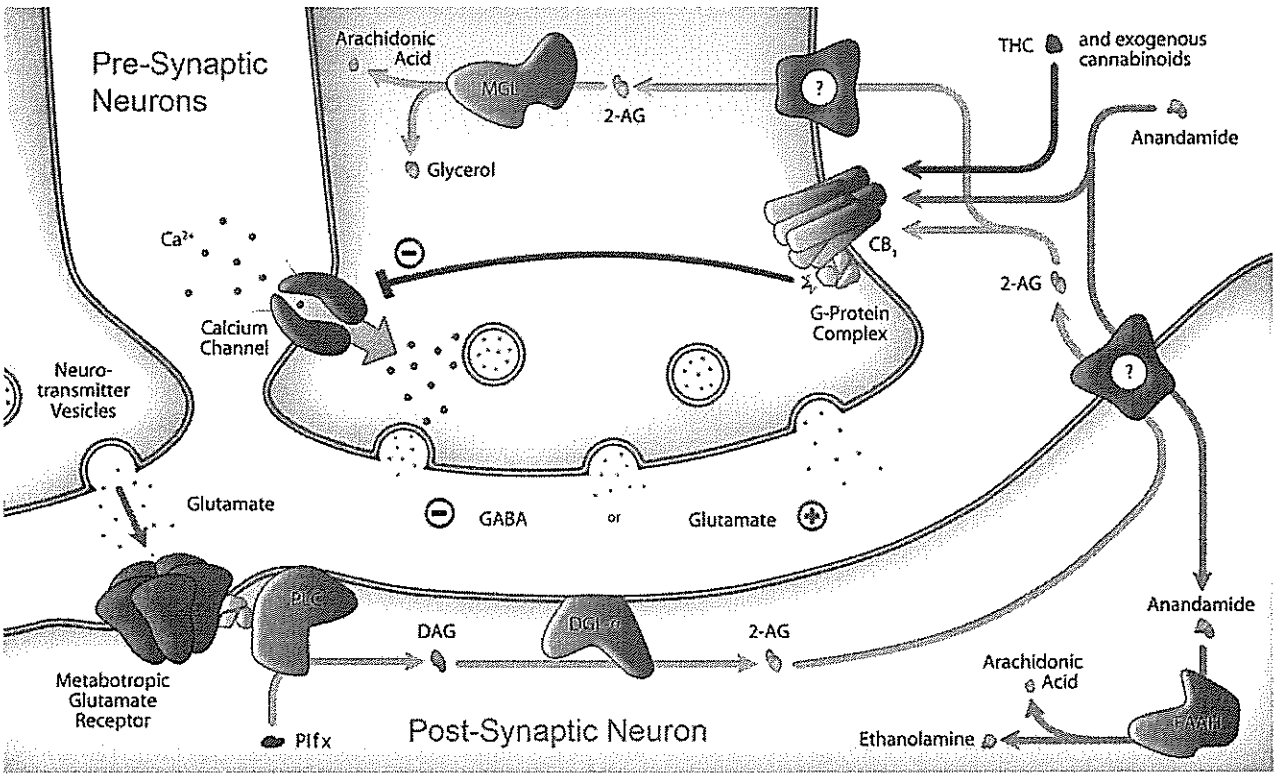

Fig. 18.1 Putative mechanism of endocannabinoid-mediated retrograde signaling in the nervous system. Activation of metabotropic glutamate receptors (*mGluR*) by glutamate triggers the activation of the phospholipase C (*PLC*)-diacylglycerol lipase (*DGL*) pathway to generate the endocannabinoid 2-arachidonoylglycerol (*2-AG*). First, the 2-AG precursor diacylglycerol (*DAG*) is formed from PLC-mediated hydrolysis of membrane phospholipid precursors (*PIPx*). DAG is then hydrolyzed by the enzyme DGL-α to generate 2-AG. 2-AG is released from the postsynaptic neuron and acts as a retrograde signaling molecule. Endocannabinoids activate presynaptic CB_1 receptors which reside on terminals of glutamatergic and GABAergic neurons. Activation of CB_1 by 2-AG, anandamide, or exogenous cannabinoids (e.g., tetrahydrocannabinol, *THC*) inhibits calcium influx in the presynaptic terminal, thereby inhibiting release of the primary neurotransmitter (i.e., glutamate or GABA) from the synaptic vesicle. Endocannabinoids are then rapidly deactivated by transport into cells (via a putative endocannabinoid transporter) followed by intracellular hydrolysis. 2-AG is metabolized by the enzyme monoacylglycerol lipase (*MGL*), whereas anandamide is metabolized by a distinct enzyme, fatty-acid amide hydrolase (*FAAH*). Note that MGL co-localizes with CB_1 in the presynaptic terminal, whereas FAAH is localized to postsynaptic sites. The existence of an endocannabinoid transporter remains controversial. Pharmacological inhibitors of either endocannabinoid deactivation (e.g., FAAH and MGL inhibitors) or transport (i.e., uptake inhibitors) have been developed to exploit the therapeutic potential of the endocannabinoid signaling system in the treatment of pain (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

postsynaptic enzyme, may control anandamide levels near sites of synthesis, whereas MGL, a presynaptic enzyme [8], may terminate 2-AG signaling following CB_1 receptor activation. These enzymes also represent therapeutic targets because inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at sites with ongoing synthesis and release [9]. The pathways controlling formation of AEA remain poorly understood. However, 2-AG is believed to be formed from membrane phospholipid precursors through the sequential activation of two distinct enzymes, phospholipase C and diacylglycerol lipase-α. First, PLC catalyzes formation of the 2-AG precursor diacylglycerol (DAG) from membrane phosphoinositides. Then, DAG is hydrolyzed by the enzyme diacylglycerol lipase-α (DGL-α) to generate 2-AG [199].

There are currently two well-defined cannabinoid receptors, although additional candidate cannabinoid receptors have also been postulated. CB_1, a seven transmembrane spanning G-protein-coupled receptor inhibiting cyclic AMP release, was identified in 1988 [10]. CB_1 is the primary neuromodulatory receptor accounting for psychopharmacological effects of THC and most of its analgesic effects [11]. Endocannabinoids are produced on demand in postsynaptic cells and engage presynaptic CB_1 receptors through a retrograde mechanism [12]. Activation of presynaptic CB_1 receptors then acts as a synaptic circuit breaker to inhibit neurotransmitter release (either excitatory or inhibitory) from the presynaptic neuron (*vide infra*) (Fig. 18.1). CB_2 was identified in 1992, and while thought of primarily as a peripheral immunomodulatory receptor, it also has important

effects on pain. The role of CB_2 in modulating persistent inflammatory and neuropathic pain [13] has been recently reviewed [14, 15]. Activation of CB_2 suppresses neuropathic pain mechanisms through nonneuronal (i.e., microglia and astrocytes) and neuronal mechanisms that may involve interferon-gamma [16]. THC, the prototypical classical cannabinoid, is a weak partial agonist at both CB_1 and CB_2 receptors. Transgenic mice lacking cannabinoid receptors (CB_1, CB_2, GPR55), enzymes controlling endocannabinoid breakdown (FAAH, MGL, ABHD6), and endocannabinoid synthesis (DGL-α, DGL-β) have been generated [17]. These knockouts have helped elucidate the role of the endocannabinoid system in controlling nociceptive processing and facilitated development of inhibitors of endocannabinoid breakdown (FAAH, MGL) as novel classes of analgesics.

A Brief Scientific History of Cannabis and Pain

Centuries of Citations

Cannabis has been utilized in one form or another for treatment of pain for longer than written history [18–21]. Although this documentation has been a major preoccupation of the lead author [22–25], and such information can provide provocative direction to inform modern research on treatment of pain and other conditions, it does not represent evidence of form, content, or degree that is commonly acceptable to governmental regulatory bodies with respect to pharmaceutical development.

Anecdotes Versus Modern Proof of Concept

While thousands of compelling stories of efficacy of cannabis in pain treatment certainly underline the importance of properly harnessing cannabinoid mechanisms therapeutically [26, 27], prescription analgesics in the United States necessitate Food and Drug Administration (FDA) approval. This requires a rigorous development program proving consistency, quality, efficacy, and safety as defined by basic scientific studies and randomized controlled trials (RCT) [28] and generally adhering to recent IMMPACT recommendations [29], provoking our next question.

Can a Botanical Agent Become a Prescription Medicine?

Most modern physicians fail to recognize that pharmacognosy (study of medicinal plants) has led directly or indirectly to an estimated 25 % of modern pharmaceuticals [30]. While the plethora of available herbal agents yield an indecipherable cacophony to most clinicians and consumers alike, it is certainly possible to standardize botanical agents and facilitate their recommendation based on sound science [31]. Botanical medicines can even fulfill the rigorous dictates of the FDA and attain prescription drug status via a clear roadmap in the form of a blueprint document [32], henceforth termed the *Botanical Guidance*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf. To be successful and clinically valuable, botanicals, including cannabis-based medicines, must demonstrate the same quality, clinical analgesic benefit, and appropriately safe adverse event profile as available new chemical entities (NCE) [28].

The Biochemical and Neurophysiological Basis of Pain Control by Cannabinoids

Neuropathic Pain

Thorough reviews of therapeutic effects of cannabinoids in preclinical and clinical domains have recently been published [33, 34]. In essence, the endocannabinoid system (ECS) is active throughout the CNS and PNS in modulating pain at spinal, supraspinal, and peripheral levels. Endocannabinoids are produced on demand in the CNS to dampen sensitivity to pain [35]. The endocannabinoid system is operative in such key integrative pain centers as the periaqueductal grey matter [36, 37], the ventroposterolateral nucleus of the thalamus [38], and the spinal cord [39, 40]. Endocannabinoids are endogenous mediators of stress-induced analgesia and fear-conditioned analgesia and suppress pain-related phenomena such as windup [41] and allodynia [42]. In the periphery and PNS [13], the ECS has key effects in suppressing both hyperalgesia and allodynia via CB_1 [43] and CB_2 mechanisms (Fig. 18.2). Indeed, pathological pain states have been postulated to arise, at least in part, from a dysregulation of the endocannabinoid system.

Antinociceptive and Anti-inflammatory Pain Mechanisms

Beyond the mechanisms previously mentioned, the ECS plays a critical role in peripheral pain, inflammation, and hyperalgesia [43] through both CB_1 and CB_2 mechanisms. CB_1 and CB_2 mechanisms are also implicated in regulation of contact dermatitis and pruritus [44]. A role for spinal CB_2 mechanisms, mediated by microglia and/or astrocytes, is also revealed under conditions of inflammation [45]. Both THC and cannabidiol (CBD), a non-euphoriant phytocannabinoid common in certain cannabis strains, are potent anti-inflammatory antioxidants with activity exceeding that of

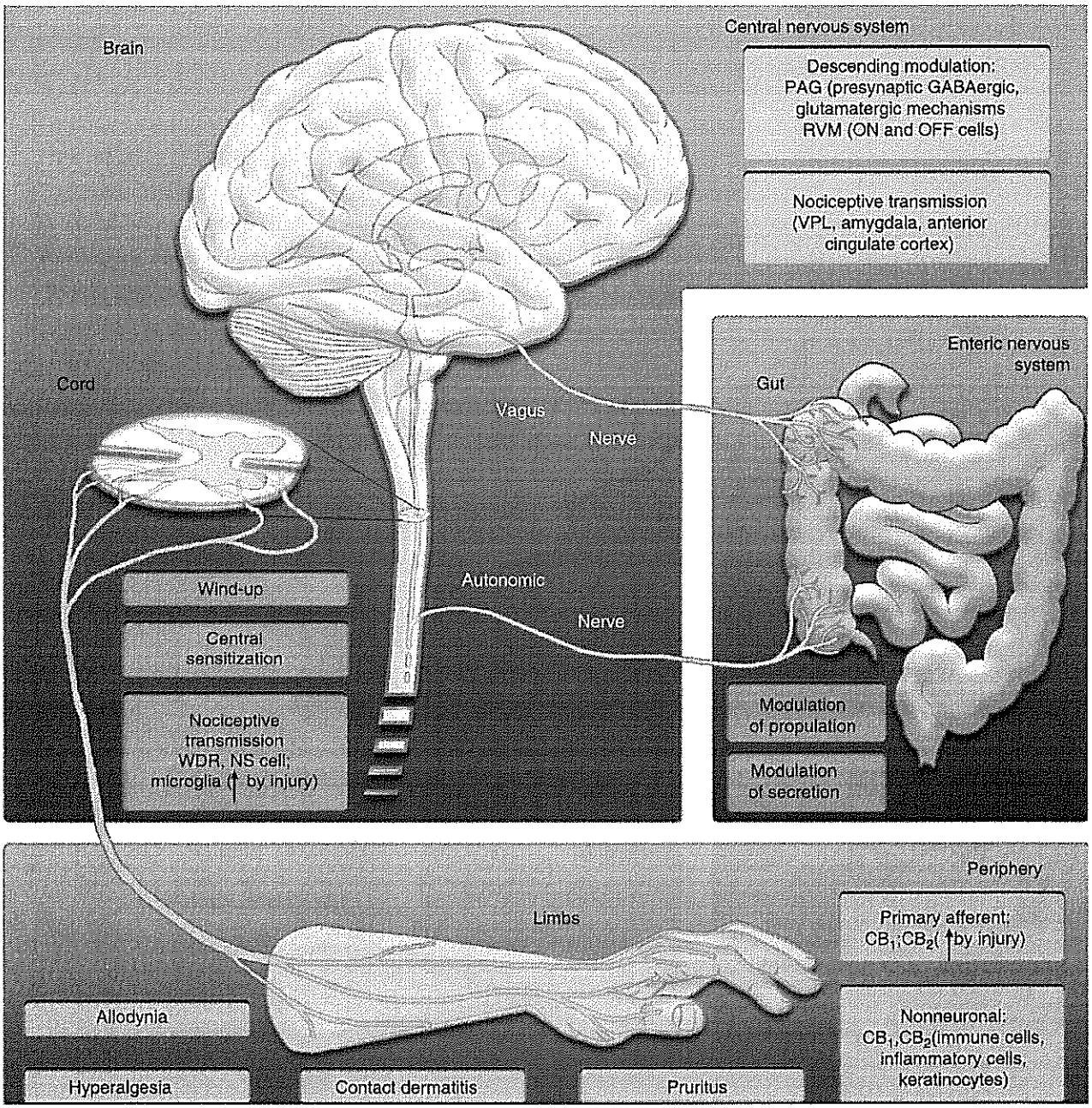

Fig. 18.2 Cannabinoids suppress pain and other pathophysiological (e.g., contact dermatitis, pruritis) and physiological (e.g., gastrointestinal transit and secretion) processes through multiple mechanisms involving CB_1 and CB_2 receptors. Peripheral, spinal, and supraspinal sites of cannabinoid actions are shown. In the periphery, cannabinoids act through both neuronal and nonneuronal mechanisms to control inflammation, allodynia, and hyperalgesia. CB_1 and CB_2 have been localized to both primary afferents and nonneuronal cells (e.g., keratinocytes, microglia), and expression can be regulated by injury. In the spinal cord, cannabinoids suppress nociceptive transmission, windup, and central sensitization by modulating activity in the ascending pain pathway of the spinothalamic tract, including responses of wide dynamic range (*WDR*) and nociceptive specific (*NS*) cells. Similar processes are observed at rostral levels of the neuraxis (e.g., ventroposterolateral nucleus of the thalamus, amygdala, anterior cingulate cortex). Cannabinoids also actively modulate pain through descending mechanisms. In the periaqueductal gray, cannabinoids act through presynaptic glutamatergic and GABAergic mechanisms to control nociception. In the rostral ventromedial medulla, cannabinoids suppress activity in ON cells and inhibit the firing pause of OFF cells, in response to noxious stimulation to produce antinociception (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

vitamins C and E via non-cannabinoid mechanisms [46]. THC inhibits prostaglandin E-2 synthesis [47] and stimulates lipooxygenase [48]. Neither THC nor CBD affects COX-1 or COX-2 at relevant pharmacological dosages [49].

While THC is inactive at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist. Like capsaicin, CBD is capable of inhibiting fatty-acid amide hydrolase (FAAH), the enzyme which hydrolyzes AEA and other fatty-acid amides that do not bind to cannabinoid receptors. CBD additionally inhibits AEA reuptake [50] though not potently. Thus, CBD acts as an endocannabinoid modulator [51], a mechanism that various pharmaceutical firms hope to emulate with new chemical entities (NCEs). CBD inhibits hepatic metabolism of THC to 11-hydroxy-THC, which is possibly more psychoactive, and prolongs its half-life, reducing its psychoactivity and attenuating attendant anxiety and tachycardia [51]; antagonizes psychotic symptoms [52]; and attenuates appetitive effects of THC [53] as well as its effects on short-term memory [54]. CBD also inhibits tumor necrosis factor-alpha (TNF-α) in a rodent model of rheumatoid arthritis [55]. Recently, CBD has been demonstrated to enhance adenosine receptor A2A signaling via inhibition of the adenosine transporter [56].

Recently, GPR18 has been proposed as a putative CBD receptor whose function relates to cellular migration [57]. Antagonism of GPR18 (by agents such as CBD) may be efficacious in treating pain of endometriosis, among other conditions, especially considering that such pain may be endocannabinoid-mediated [58]. Cannabinoids are also very active in various gastrointestinal and visceral sites mediating pain responses [59, 60].

Cannabinoid Interactions with Other Neurotransmitters Pertinent to Pain

As alluded to above, the ECS modulates neurotransmitter release via retrograde inhibition. This is particularly important in NMDA-glutamatergic mechanisms that become hyperresponsive in chronic pain states. Cannabinoids specifically inhibit glutamate release in the hippocampus [61]. THC reduces NMDA responses by 30–40 % [46]. Secondary and tertiary hyperalgesia mediated by NMDA [62] and by calcitonin gene-related peptide [40] may well be targets of cannabinoid therapy in disorders such as migraine, fibromyalgia, and idiopathic bowel syndrome wherein these mechanisms seem to operate pathophysiologically [63], prompting the hypothesis of a "clinical endocannabinoid deficiency." Endocannabinoid modulators may therefore restore homeostasis, leading to normalization of function in these pathophysiological conditions. THC also has numerous effects on serotonergic systems germane to migraine [64], increasing its production in the cerebrum while decreasing reuptake [65]. In fact, the ECS seems to modulate the trigeminovascular system of migraine pathogenesis at vascular and neurochemical levels [66–68].

Cannabinoid-Opioid Interactions

Although endocannabinoids do not bind to opioid receptors, the ECS may nonetheless work in parallel with the endogenous opioid system with numerous areas of overlap and interaction. Pertinent mechanisms include stimulation of beta-endorphin by THC [69] as well as its ability to demonstrate experimental opiate sparing [70], prevent opioid tolerance and withdrawal [71], and rekindle opioid analgesia after loss of effect [72]. Adjunctive treatments that combine opioids with cannabinoids may enhance the analgesic effects of either agent. Such strategies may permit lower doses of analgesics to be employed for therapeutic benefit in a manner that minimizes incidence or severity of adverse side effects.

Clinical Trials, Utility, and Pitfalls of Cannabinoids in Pain

Evidence for Synthetic Cannabinoids

Oral dronabinol (THC) has been available as the synthetic Marinol® since 1985 and is indicated for nausea associated with chemotherapy and appetite stimulation in HIV/AIDS. Issues with its cost, titration difficulties, delayed onset, and propensity to induce intoxicating and dysphoric effects have limited clinical application [73]. It was employed in two open-label studies of chronic neuropathic pain in case studies in 7 [74] and 8 patients [75], but no significant benefit was evident and side effects led to prominent dropout rates (average doses 15–16.6 mg THC). Dronabinol produced benefit in pain in multiple sclerosis [76], but none was evident in postoperative pain (Table 18.1) [77]. Dronabinol was reported to relieve pruritus in three case-report subjects with cholestatic jaundice [78]. Dronabinol was assessed in 30 chronic noncancer pain patients on opioids in double-blind crossover single-day sessions vs. placebo with improvement [79], followed by a 4-week open-label trial with continued improvement (Table 18.1). Associated adverse events were prominent. Methodological issues included lack of prescreening for cannabinoids, 4 placebo subjects with positive THC assays, and 58 % of subjects correctly guessing Marinol dose on test day. An open-label comparison in polyneuropathy examined nabilone patients with 6 obtaining 22.6 % mean pain relief after 3 months, and 5 achieving 28.6 % relief after 6 months, comparable to conventional agents [80]. A pilot study of Marinol in seven spinal cord injury patients with neuropathic pain saw two withdraw, and the remainder appreciate no greater efficacy than with diphenhydramine [81].

Table 18.1 Randomized controlled trials of cannabinoids in pain

Agent	N=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ($p=0.02$)/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ($p=0.03$) and hyperalgesia ($p=0.05$), 52 % with >30 % pain reduction vs. placebo ($p=0.04$)/Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ($p=0.023$)/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ($p=0.02$), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ($p=0.016$), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$)/Zajicek et al. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p=0.01$)/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ($p=0.02$), median pain relief improved ($p=0.035$) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ($p<0.05$) and 20 mg ($p<0.01$) with opioids, AE prominent/Narang et al. [79]
Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ($p<0.05$)/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$)/Skrabek et al. [89]
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs. placebo ($p<0.05$), symptom control best with Sativex ($p<0.0001$)/Wade et al. [132]
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$)/Notcutt et al. [133]
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p=0.002$) and Sativex ($p=0.005$) over placebo/Berman et al. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ($p=0.009$)/Rog et al. [135]

(continued)

Table 18.1 (continued)

Agent	N=	Indication	Duration/type	Outcomes/reference
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels ($p=0.004$), dynamic allodynia ($p=0.042$), and punctuate allodynia ($p=0.021$) vs. placebo/Nurmikko et al. [136]
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), DAS-28 ($p=0.002$), and SF-MPQ pain at present ($p=0.016$)/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory ($p=0.032$), and Patients' Global Impression of Change ($p=0.001$) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs. placebo ($p=0.0142$), Tetranabinex NSD/ Johnson et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo ($p=0.001$) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo ($p=0.006$)/ [201]

Nabilone, or Cesamet®, is a semisynthetic analogue of THC that is about tenfold more potent, and longer lasting [82]. It is indicated as an antiemetic in chemotherapy in the USA. Prior case reports in neuropathic pain [83] and other pain disorders [84] have been published. Sedation and dysphoria are prominent associated adverse events. An RCT of nabilone in 41 postoperative subjects dosed TID actually resulted in increased pain scores (Table 18.1) [85]. An uncontrolled study of 82 cancer patients on nabilone noted improved pain scores [86], but retention rates were limited. Nabilone improved pain ($p<0.05$) vs. placebo in patients with mixed spasticity syndromes in a small double-blind trial (Table 18.1) [87], but was without benefits in other parameters. In a double-blind crossover comparison of nabilone to dihydrocodeine (schedule II opioid) in chronic neuropathic pain (Table 18.1) [88], both drugs produced marginal benefit, but with dihydrocodeine proving clearly superior in efficacy and modestly superior in side-effect profile. In an RCT in 40 patients of nabilone vs. placebo over 4 weeks, it showed significant decreases in VAS of pain and anxiety (Table 18.1) [89]. A more recent study of nabilone vs. amitriptyline in fibromyalgia yielded benefits on sleep, but not pain, mood, or quality of life (Table 18.1) [90]. An open-label trial of nabilone vs. gabapentin found them comparable in pain and other symptom relief in peripheral neuropathic pain [91].

Ajulemic acid (CT3), another synthetic THC analogue in development, was utilized in a phase II RCT in peripheral neuropathic pain in 21 subjects with apparent improvement (Table 18.1) [92]. Whether or not ajulemic acid is psychoactive is the subject of some controversy [93].

Evidence for Smoked or Vaporized Cannabis

Few randomized controlled clinical trials (RCTs) of pain with smoked cannabis have been undertaken to date [94–97]. One of these [96] examined cannabis effects on experimental pain in normal volunteers.

Abrams et al. [94] studied inpatient adults with painful HIV neuropathy in 25 subjects in double-blind fashion to receive either smoked cannabis as 3.56 % THC cigarettes or placebo cigarettes three times daily for 5 days (Table 18.1). The smoked cannabis group had a 34 % reduction in daily pain vs. 17 % in the placebo group ($p=0.03$). The cannabis cohort also had a 52 % of subjects report a >30 % reduction in pain scores over the 5 days vs. 24 % in the placebo group ($p=0.04$) (Table 18.1). The authors rated cannabis as "well tolerated" due to an absence of serious adverse events (AE) leading to withdrawal, but all subjects were cannabis experienced. Symptoms of possible intoxication in the cannabis group including anxiety (25 %), sedation (54 %), disorientation (16 %), paranoia (13 %), confusion (17 %), dizziness (15 %), and nausea (11 %) were all statistically significantly more common than in the placebo group. Despite these findings, the authors stated that the values do not represent any serious safety concern in this short-term study. No discussion in the article addressed issues of the relative efficacy of blinding in the trial.

Wilsey et al. [95] examined neuropathic pain in 38 subjects in a double-blind crossover study comparing 7 % THC cannabis, 3.5 % THC cannabis, and placebo cigarettes via a complex cumulative dosing scheme with each dosage given

once, in random order, with at least 3 day intervals separating sessions (Table 18.1). A total of 9 puffs maximum were allowed over several hours per session. Authors stated, "Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication." Again, only cannabis-experienced subjects were allowed entry. No withdrawals due to AE were reported, but 1 subject was removed due to elevated blood pressure. No significant differences were noted in pain relief in the two cannabis potency groups, but a significant separation of pain reduction from placebo ($p=0.02$) was not evident until a cumulative 9 puffs at 240 min elapsed time. Pain unpleasantness was also reduced in both active treatment groups ($p<0.01$). Subjectively, an "any drug effect" demonstrated a visual analogue scale (VAS) of 60/100 in the high-dose group, but even the low-dose group registered more of a "good drug effect" than placebo ($p<0.001$). "Bad drug effect" was also evident. "Feeling high" and "feeling stoned" were greatest in the high-dose sessions ($p<0.001$), while both high- and low-dose differentiated significantly from placebo ($p<0.05$). Of greater concern, both groups rated impairment as 30/100 on VAS vs. placebo ($p=0.003$). Sedation also demarcated both groups from placebo ($p<0.01$), as did confusion ($p=0.03$), and hunger ($p<0.001$). Anxiety was not considered a prominent feature in this cannabis-experienced population. This study distinguished itself from some others in its inclusion of specific objective neuropsychological measures and demonstrated neurocognitive impairment in attention, learning, and memory, most noteworthy with 7 % THC cannabis. No commentary on blinding efficacy was included.

Ellis et al. [97] examined HIV-associated neuropathic pain in a double-blind trial of placebo vs. 1–8 % THC cannabis administered four times daily over 5 days with a 2-week washout (Table 18.1). Subjects were started at 4 % THC and then titrated upward or downward in four smoking sessions dependent upon their symptom relief and tolerance of the dose. In this study, 96 % of subjects were cannabis-experienced, and 28 out of 34 subjects completed the trial. The primary outcome measure (Descriptor Differential Scale, DDS) was improved in the active group over placebo ($p=0.016$), with >30 % relief noted in 46 % of cannabis subjects vs. 18 % of placebo. While most adverse events (AE) were considered mild and self-limited, two subjects had to leave the trial due to toxicity. One cannabis-naïve subject was withdrawn due to "an acute cannabis-induced psychosis" at what proved to be his first actual cannabis exposure. The other subject suffered intractable cough. Pain reduction was greater in the cannabis-treated group ($p=0.016$) among completers, as was the proportion of subjects attaining >30 % pain reduction (46 % vs. 18 %, $p=0.043$). Blinding was assessed in this study; whereas placebo patients were inaccurate at guessing the investigational product, 93 % of those receiving cannabis guessed correctly. On safety issues, the authors stated that the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.

A Canadian study [98] examined single 25-mg inhalations of various cannabis potencies (0–9.4 % THC) three times daily for 5 days per cycle in 23 subjects with chronic neuropathic pain (Table 18.1). Patients were said to be cannabis-free for 1 year, but were required to have some experience of the drug. Only the highest potency demarcated from placebo on decrements in average daily pain score (5.4 vs. 6.1, $p=0.023$). The most frequent AE in the high-dose group were headache, dry eyes, burning sensation, dizziness, numbness, and cough, but with "high" or "euphoria" reported only once in each cannabis potency group.

The current studies of smoked cannabis are noteworthy for their extremely short-term exposure and would be of uncertain relevance in a regulatory environment. The IMMPACT recommendations on chronic neuropathic pain clinical trials that are currently favored by the FDA [29] generally suggest randomized controlled clinical trials of 12-week duration as a prerequisite to demonstrate efficacy and safety. While one might assume that the degree of pain improvement demonstrated in these trials could be maintained over this longer interval, it is only reasonable to assume that cumulative adverse events would also increase to at least some degree. The combined studies represent only a total of 1,106 patient-days of cannabis exposure (Abrams: 125, Wilsey: 76, Ellis: 560, Ware 345) or 3 patient-years of experience. In contrast, over 6,000 patient-years of data have been analyzed for Sativex between clinical trials, prescription, and named-patient supplies, with vastly lower AE rates (data on file, GW Pharmaceuticals) [28, 99]. Certainly, the cognitive effects noted in California-smoked cannabis studies figure among many factors that would call the efficacy of blinding into question for investigations employing such an approach. However, it is also important to emphasize that unwanted side effects are not unique to cannabinoids. In a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies, the presence of intolerable side effects did not differ in groups receiving gabapentinoids, tricyclic antidepressants, anticonvulsants, cannabinoids (including nabilone, Sativex), and topical agents [80]. Moreover, no serious adverse events were related to any of the medications.

The current studies were performed in a very select subset of patients who almost invariably have had prior experience of cannabis. Their applicability to cannabis-naïve populations is, thus, quite unclear. At best, the observed benefits might possibly accrue to some, but it is eminently likely that candidates for such therapy might refuse it on any number of

grounds: not wishing to smoke, concern with respect to intoxication, etc. Sequelae of smoking in therapeutic outcomes have had little discussion in these brief RCTs [28]. Cannabis smoking poses substantial risk of chronic cough and bronchitic symptoms [100], if not obvious emphysematous degeneration [101] or increase in aerodigestive cancers [102]. Even such smoked cannabis proponents as Lester Grinspoon has acknowledged are the only well-confirmed deleterious physical effect of marihuana is harm to the pulmonary system [103]. However, population-based studies of cannabis trials have failed to show any evidence for increased risk of respiratory symptoms/chronic obstructive pulmonary disease [100] or lung cancer [102] associated with smoking cannabis.

A very detailed analysis and comparison of mainstream and sidestream smoke for cannabis vs. tobacco smoke was performed in Canada [104]. Of note, cannabis smoke contained ammonia (NH_3) at a level of 720 μg per 775 mg cigarette, a figure 20-fold higher than that found in tobacco smoke. It was hypothesized that this finding was likely attributable to nitrate fertilizers. Formaldehyde and acetaldehyde were generally lower in cannabis smoke than in tobacco, but butyraldehyde was higher. Polycyclic aromatic hydrocarbon (PAH) contents were qualitatively similar in the comparisons, but total yield was lower for cannabis mainstream smoke, but higher than tobacco for sidestream smoke. Additionally, NO, NO_x, hydrogen cyanide, and aromatic amines concentrations were 3–5 times higher in cannabis smoke than that from tobacco. Possible mutagenic and carcinogenic potential of these various compounds were mentioned. More recently, experimental analysis of cannabis smoke with resultant acetaldehyde production has posited its genotoxic potential to be attributable to reactions that produce DNA adducts [105].

Vaporizers for cannabis have been offered as a harm reduction technique that would theoretically eliminate products of combustion and associated adverse events. The Institute of Medicine (IOM) examined cannabis issues in 1999 [106], and among their conclusions was the following (p. 4): "Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems." One proposed technique is vaporization, whereby cannabis is heated to a temperature that volatilizes THC and other components with the goal of reducing or eliminating by-products of combustion, including potentially carcinogenic polycyclic aromatic hydrocarbons, benzene, acetaldehyde, carbon monoxide, toluene, naphthaline, phenol, toluene, hydrogen cyanide, and ammonia. Space limitations permit only a cursory review of available literature [107–115].

A pilot study of the Volcano vaporizer vs. smoking was performed in the USA in 2007 in 18 active cannabis consumers, with only 48 h of presumed abstinence [116]. NIDA 900-mg cannabis cigarettes were employed (1.7, 3.4, and 6.8 % THC) with each divided in two, so that one-half would be smoked or vaporized in a series of double-blind sessions. The Volcano vaporizer produced comparable or slightly higher THC plasma concentrations than smoking. Measured CO in exhaled vapor sessions diminished very slightly, while it increased after smoking ($p<0.001$). Self-reported visual analogue scales of the associated high were virtually identical in vaporization vs. smoking sessions and increased with higher potency material. A contention was advanced that the absence of CO increase after vaporization can be equated to "little or no exposure to gaseous combustion toxins." Given that no measures of PAH or other components were undertaken, the assertion is questionable. It was also stated that there were no reported adverse events. Some 12 subjects preferred the Volcano, 2 chose smoking, and 2 had no preference as to technique, making the vaporizer "an acceptable system" and providing "a safer way to deliver THC."

A recent [202, 117] examined interactions of 3.2 % THC NIDA cannabis vaporized in the Volcano in conjunction with opioid treatment in a 5-day inpatient trial in 21 patients with chronic pain (Table 18.1). All subjects were prior cannabis smokers. Overall, pain scores were reduced from 39.6 to 29.1 on a VAS, a 27 % reduction, by day 5. Pain scores in subjects on morphine fell from 34.8 to 24.1, while in subjects taking oxycodone, scores dropped from 43.8 to 33.6.

The clinical studies performed with vaporizers to date have been very small pilot studies conducted over very limited timeframes (i.e., for a maximum of 5 days). Thus, these studies cannot contribute in any meaningful fashion toward possible FDA approval of vaporized cannabis as a delivery technique, device, or drug under existing policies dictated by the *Botanical Guidance* [32]. It is likewise quite unlikely that the current AE profile of smoked or vaporized cannabis would meet FDA requirements. The fact that all the vaporization trials to date have been undertaken only in cannabis-experienced subjects does not imply that results would generalize to larger patient populations. Moreover, there is certainly no reason to expect AE profiles to be better in cannabis-naïve patients. Additionally, existing standardization of cannabis product and delivery via vaporization seem far off the required marks. Although vaporizers represent an alternate delivery method devoid of the illegality associated with smoked cannabis, the presence of toxic ingredients such as PAH, ammonia, and acetaldehyde in cannabis vapor are unlikely to be acceptable to FDA in any significant amounts. Existing vaporizers still lack portability or convenience [28]. A large Internet survey revealed that only 2.2 % of cannabis users employed vaporization as their primary cannabis intake method [118]. While studies to date have established that lower temperature vaporization in the Volcano, but not necessarily other devices, can reduce the relative amounts of noxious by-products of combustion, it has yet to be demonstrated that they are totally eliminated. Until or unless this goal is achieved, along with

requisite benchmarks of herbal cannabis quality, safety, and efficacy in properly designed randomized clinical trials, vaporization remains an unproven technology for therapeutic cannabinoid administration.

Evidence for Cannabis-Based Medicines

Cannador is a cannabis extract in oral capsules, with differing THC:CBD ratios [51]. Cannador was utilized in a phase III RCT of spasticity in multiple sclerosis (CAMS) (Table 18.1) [119]. While no improvement was evident in the Ashworth Scale, reduction was seen in spasm-associated pain. Both THC and Cannador improved pain scores in follow-up [120]. Cannador was also employed for postherpetic neuralgia in 65 patients, but without success (Table 18.1) [121, 122]. Slight pain reduction was observed in 30 subjects with postoperative pain (CANPOP) not receiving opiates, but psychoactive side effects were notable (Table 18.1).

Sativex® is a whole-cannabis-based extract delivered as an oromucosal spray that combines a CB_1 and CB_2 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids, and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring [51, 123]. It is approved in Canada for spasticity in MS and under a Notice of Compliance with Conditions for central neuropathic pain in multiple sclerosis and treatment of cancer pain unresponsive to opioids. Sativex is also approved in MS in the UK, Spain, and New Zealand, for spasticity in multiple sclerosis, with further approvals expected soon in some 22 countries around the world. Sativex is highly standardized and is formulated from two *Cannabis sativa* chemovars predominating in THC and CBD, respectively [124]. Each 100 µl pump-action oromucosal spray of Sativex yields 2.7 mg of THC and 2.5 mg of CBD plus additional components. Pharmacokinetic data are available [125–127]. Sativex effects begin within an interval allowing dose titration. A very favorable adverse event profile has been observed in the development program [27, 128]. Most patients stabilize at 8–10 sprays per day after 7–10 days, attaining symptomatic control without undue psychoactive sequelae. Sativex was added to optimized drug regimens in subjects with uncontrolled pain in every RCT (Table 18.1). An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain. One phase IIB dose-ranging study has already been completed [201]. Available clinical trials with Sativex have been independently assessed [129, 130].

In a phase II study of 20 patients with neurogenic symptoms [131], significant improvement was seen with both Tetranabinex (high-THC extract without CBD) and Sativex on pain, with Sativex displaying better symptom control ($p<0.0001$), with less intoxication (Table 18.1).

In a phase II study of intractable chronic pain in 24 patients [132], Sativex again produced the best results compared to Tetranabinex ($p<0.001$), especially in MS ($p<0.0042$) (Table 18.1).

In a phase III study of brachial plexus avulsion ($N=48$) [133], pain reduction with Tetranabinex and Sativex was about equal (Table 18.1).

In an RCT of 66 MS subjects, mean Numerical Rating Scale (NRS) analgesia favored Sativex over placebo (Table 18.1) [134].

In a phase III trial ($N=125$) of peripheral neuropathic pain with allodynia [135], Sativex notably alleviated pain levels and dynamic and punctate allodynia (Table 18.1).

In a safety-extension study in 160 subjects with various symptoms of MS [136], 137 patients showed sustained improvements over a year or more in pain and other symptoms [99] without development of any tolerance requiring dose escalation or withdrawal effects in those who voluntarily discontinued treatment suddenly. Analgesia was quickly reestablished upon Sativex resumption.

In a phase II RCT in 56 rheumatoid arthritis sufferers over 5 weeks with Sativex [137], medicine was limited to only 6 evening sprays (16.2 mg THC + 15 mg CBD). By study end, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain all favored Sativex (Table 18.1).

In a phase III RCT in intractable cancer pain on opioids ($N=177$), Sativex, Tetranabinex THC-predominant extract, and placebo were compared [138] demonstrating strongly statistically significant improvements in analgesia for Sativex only (Table 18.1). This suggests that the CBD component in Sativex was necessary for benefit.

In a 2-week study of spinal cord injury pain, NRS of pain was not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were positive (Table 18.1). Additionally, an RCT of intractable lower urinary tract symptoms in MS also demonstrated pain reduction (Table 18.1).

The open-label study of various polyneuropathy patients included Sativex patients with 3 obtaining 21.56 % mean pain relief after 3 months (2/3 > 30 %), and 4 achieving 27.6 % relief after 6 months (2/4 > 30 %), comparable to conventional agents [80].

A recently completed RCT of Sativex in intractable cancer pain unresponsive to opioids over 5 weeks was performed in 360 subjects (Table 18.1). Results of a Continuous Response Analysis (CRA) showed improvements over placebo in the low-dose ($p=0.08$) and middle-dose cohorts ($p=0.038$) or combined ($p=0.006$). Pain NRS improved over placebo in the low-dose ($p=0.006$) and combined cohorts ($p=0.019$).

Sleep has improved markedly in almost all Sativex RCTs in chronic pain based on symptom reduction, not a hypnotic effect [139].

The adverse event (AE) profile of Sativex has been quite benign with bad taste, oral stinging, dry mouth, dizziness, nausea, or fatigue most common, but not usually prompting discontinuation [128]. Most psychoactive sequelae are early and transient and have been notably lowered by more recent application of a slower, less aggressive titration schedule. While no direct comparative studies have been performed with Sativex and other agents, AE rates were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher, likely due to the presence of accompanying CBD [28, 51]. Similarly, Sativex displayed a superior AE profile compared to smoked cannabis based on safety-extension studies of Sativex [28, 99], as compared to chronic use of cannabis with standardized government-supplied material in Canada for chronic pain [140] and the Netherlands for various indications [141, 142] over a period of several months or more. All AEs are more frequent with smoked cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex [27, 28, 128]. A recent meta-analysis suggested that serious AEs associated with cannabinoid-based medications did not differ from placebo and thus could not be attributable to cannabinoid use, further reinforcing the low toxicity associated with activation of cannabinoid systems.

Cannabinoid Pitfalls: Are They Surmountable?

The dangers of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDS) of various design (e.g., gastrointestinal ulceration and bleeding vs. coronary and cerebrovascular accidents, respectively) [143, 144] are unlikely to be mimicked by either THC or CBD, which produce no such activity at therapeutic dosages [49].

Natural cannabinoids require polar solvents and may be associated with delayed and sometimes erratic absorption after oral administration. Smoking of cannabis invariably produces rapid spikes in serum THC levels; cannabis smoking attains peak levels of serum THC above 140 ng/ml [145, 146], which, while desirable to the recreational user, has no necessity or advantage for treatment of chronic pain [28]. In contrast, comparable amounts of THC derived from oromucosal Sativex remained below 2 ng/ml with much lower propensity toward psychoactive sequelae [28, 125], with subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 [100]. It is clear from RCTs that such psychoactivity is not a necessary accompaniment to pain control. In contrast, intoxication has continued to be prominent with oral THC [73].

In comparison to the questionable clinical trial blinding with smoked and vaporized cannabis discussed above, all indications are that such study blinding has been demonstrably effective with Sativex [147, 148] by utilizing a placebo spray with identical taste and color. Some 50 % of Sativex subjects in RCTs have had prior cannabis exposure, but results of two studies suggest that both groups exhibited comparable results in both treatment efficacy and side effect profile [134, 135].

Controversy continues to swirl around the issue of the potential dangers of cannabis use medicinally, particularly its drug abuse liability (DAL). Cannabis and cannabinoids are currently DEA schedule I substances and are forbidden in the USA (save for Marinol in schedule III and nabilone in schedule II) [73]. This is noteworthy in itself because the very same chemical compound, THC, appears simultaneously in schedule I (as THC), schedule II (as nabilone), and schedule III (as Marinol). DAL is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal, and dependency plus the drug's overall observed rates of abuse and diversion. Drugs that are smoked or injected are commonly rated as more reinforcing due to more rapid delivery to the brain [149]. Sativex has intermediate onset. It is claimed that CBD in Sativex reduces the psychoactivity of THC [28]. RCT AE profiles do not indicate euphoria or other possible reinforcing psychoactive indicia as common problems with its use [99]. Similarly, acute THC effects such as tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, and intraocular pressure decreases undergo prominent tachyphylaxis with regular usage [150]. Despite that observation, Sativex has not demonstrated dose tolerance to its therapeutic benefits on prolonged administration, and efficacy has been maintained for up to several years in pain conditions [99].

The existence or severity of a cannabis withdrawal syndrome remains under debate [151, 152]. In contrast to reported withdrawal sequelae in recreational users [153], 24 subjects with MS who volunteered to discontinue Sativex after a year or more suffered no withdrawal symptoms meeting Budney criteria. While symptoms such as pain recurred after some 7–10 days without Sativex, symptom control was rapidly reattained upon resumption [99].

Finally, no known abuse or diversion incidents have been reported with Sativex to date (March 2011). Formal DAL studies of Sativex vs. Marinol and placebo have been completed and demonstrate lower scores on drug liking and similar measures at comparable doses [155].

Cognitive effects of cannabis also remain at issue [155, 156], but less data are available in therapeutic applications. Studies of Sativex in neuropathic pain with allodynia have revealed no changes vs. placebo on Sativex in portions of the Halstead-Reitan Battery [135], or in central neuropathic pain in MS [134], where 80 % of tests showed no significant differences. In a recent RCT of Sativex vs. placebo in MS patients, no cognitive differences of note were observed

[157]. Similarly, chronic Sativex use has not produced observable mood disorders.

Controversies have also arisen regarding the possible association of cannabis abuse and onset of psychosis [156]. However, an etiological relationship is not supported by epidemiological data [158–161], but may well be affected by dose levels and duration, if pertinent. One may speculate that lower serum levels of Sativex combined with antipsychotic properties of CBD [52, 162, 163] might attenuate such concerns. Few cases of related symptoms have been reported in SAFEX studies of Sativex.

Immune function becomes impaired in experimental animals at cannabinoid doses 50–100 times necessary to produce psychoactive effects [164]. In four patients smoking cannabis medicinally for more than 20 years, no changes were evident in leukocyte, CD4, or CD8 cell counts [155]. MS patients on Cannador demonstrated no immune changes of note [165] nor were changes evident in subjects smoking cannabis in a brief trial in HIV patients [166]. Sativex RCTs have demonstrated no hematological or immune dysfunction.

No effects of THC extract, CBD extract, or Sativex were evident on the hepatic cytochrome P450 complex [167] or on human CYP450 [168]. Similarly, while Sativex might be expected to have additive sedative effects with other drugs or alcohol, no significant drug-drug interactions of any type have been observed in the entire development program to date.

No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/ml of THC [169]. Four oromucosal sprays of Sativex (exceeding the average single dose employed in therapy) produced serum levels well below this threshold [28]. As with other cannabinoids in therapy, it is recommended that patients not drive nor use dangerous equipment until accustomed to the effects of the drug.

Future Directions: An Array of Biosynthetic and Phytocannabinoid Analgesics

Inhibition of Endocannabinoid Transport and Degradation: A Solution?

It is essential that any cannabinoid analgesic strike a compromise between therapeutic and adverse effects that may both be mediated via CB_1 mechanisms [34]. Mechanisms to avoid psychoactive sequelae could include peripherally active synthetic cannabinoids that do not cross the blood-brain barrier or drugs that boost AEA levels by inhibiting fatty-acid amide hydrolase (FAAH) [170] or that of 2-AG by inhibiting monoacylycerol lipase (MGL). CBD also has this effect [50] and certainly seems to increase the therapeutic index of THC [51].

In preclinical studies, drugs inhibiting endocannabinoid hydrolysis [171, 172] and peripherally acting agonists [173] all show promise for suppressing neuropathic pain. AZ11713908, a peripherally restricted mixed cannabinoid agonist, reduces mechanical allodynia with efficacy comparable to the brain penetrant mixed cannabinoid agonist WIN55,212-2 [173]. An irreversible inhibitor of the 2-AG hydrolyzing enzyme MGL suppresses nerve injury-induced mechanical allodynia through a CB_1 mechanism, although these anti-allodynic effects undergo tolerance following repeated administration [172]. URB937, a brain impermeant inhibitor of FAAH, has recently been shown to elevate anandamide outside the brain and suppress neuropathic and inflammatory pain behavior without producing tolerance or unwanted CNS side effects [171]. These observations raise the possibility that peripherally restricted endocannabinoid modulators may show therapeutic potential as analgesics with limited side-effect profiles.

The Phytocannabinoid and Terpenoid Pipeline

Additional phytocannabinoids show promise in treatment of chronic pain [123, 163, 174]. Cannabichromene (CBC), another prominent phytocannabinoid, also displays anti-inflammatory [175] and analgesic properties, though less potently than THC [176]. CBC, like CBD, is a weak inhibitor of AEA reuptake [177]. CBC is additionally a potent TRPA1 agonist [178]. Cannabigerol (CBG), another phytocannabinoid, displays weak binding at both CB_1 and CB_2 [179, 180] but is a more potent GABA reuptake inhibitor than either THC or CBD [181]. CBG is a stronger analgesic, anti-erythema, and lipooxygenase agent than THC [182]. CBG likewise inhibits AEA uptake and is a TRPV1 agonist [177], a TRPA1 agonist, and a TRPM8 antagonist [178]. CBG is also a phospholipase A2 modulator that reduces PGE-2 release in synovial cells [183]. Tetrahydrocannabivarin, a phytocannabinoid present in southern African strains, displays weak CB_1 antagonism [184] and a variety of anticonvulsant activities [185] that might prove useful in chronic neuropathic pain treatment. THCV also reduced inflammation and attendant pain in mouse experiments [187]. Most North American [187] and European [188, 189] cannabis strains have been bred to favor THC over a virtual absence of other phytocannabinoid components, but the latter are currently available in abundance via selective breeding [124, 190].

Aromatic terpenoid components of cannabis also demonstrate pain reducing activity [123, 163]. Myrcene displays an opioid-type analgesic effect blocked by naloxone [191] and reduces inflammation via PGE-2 [192]. β-Caryophyllene displays anti-inflammatory activity on par with phenylbutazone via PGE-1 [193], but contrasts by displaying gastric cytoprotective activity [194]. Surprisingly, β-caryophyllene has proven to be a phytocannabinoid in its own right as a selective CB_2 agonist [195]. α-Pinene inhibits PGE-1 [196], and linalool acts as a local anesthetic [197].

Summary

Basic science and clinical trials support the theoretical and practical basis of cannabinoid agents as analgesics for chronic pain. Their unique pharmacological profiles with multimodality effects and generally favorable efficacy and safety profiles render cannabinoid-based medicines promising agents for adjunctive treatment, particularly for neuropathic pain. It is our expectation that the coming years will mark the advent of numerous approved cannabinoids with varying mechanisms of action and delivery techniques that should offer the clinician useful new tools for treating pain.

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to suffer from moderate to severe, non-cancer-related pain (51). Further, two-thirds of these people have been living with the pain for over 5 years and the pain was found to have a significant impact on the quality of life and emotional well-being, with patients experiencing significant improvements in these factors when their pain was well controlled. Other studies have shown the prevalence of chronic pain in the adult population ranging from 2% to 40%, with a median point prevalence of 15% (52,53). Persistent pain was reported with an overall prevalence of 20% of primary care patients, with approximately 48% reporting back pain (54). A systematic review of 4 international studies conducted in developed countries found prevalence rates of any type and severity level of chronic pain ranging from 10.5% to 55.2% of the population (55). A European survey of 46,000 individuals showed that 1 in 5 people reported suffering from chronic pain (56). This survey also showed that chronic pain sufferers reported 7 years of chronic pain on average, with some reporting pain lasting more than 20 years. A survey of Americans (57) showed 9% of Americans suffer with moderate-to-severe chronic non-cancer pain. An Australian study of over 17,000 people (53) showed the prevalence of chronic pain in 17.1% of males and 20% of females with the prevalence for males peaking at 27% in the 65–69 year age group and for females, prevalence peeking at 31% in the oldest age group of 80–84 years. Further, chronic pain is not only seen in adults, but it is also seen in the elderly and children (58-63). Various non-cancer pain problems include spinal pain, osteoarthritis, ischemic pain syndromes, visceral pain syndromes, neuropathic pain syndromes, and headache.

Recent publications have confirmed the above reported findings. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States (64,65), showed more than 21% of U.S. adults, or 46.4 million persons, were found to have self-reported, physician-diagnosed arthritis. This study estimated that rheumatoid arthritis affects 1.3 million adults (down from the estimate of 2.1 million for 1995), juvenile arthritis affects 294,000 children, spondylarthritides affects from 0.6 million to 2.4 million adults, systemic lupus erythematosus affects 161,000 to 332,000 adults, systemic sclerosis affects 49,000 adults, and primary Sjögren's syndrome affects from 0.4 million to 3.1 million adults (64). Part II of this study (65) also estimated that among U.S. adults, nearly 27 million have clinical arthritis (up from the estimate of 21 million for 1995), 711,000 have polymyalgia rheumatica, 228,000 have giant cell arteritis, up to 3.0 million have had self-reported gout in the past year (up from the estimate of 2.1 million for 1995), 5.0 million have fibromyalgia, 4 to 10 million have carpal tunnel syndrome, 49 million have had low back pain in the past 3 months, and 30.1 million have had neck pain in the past 3 months. These reports are considered to be the best available prevalence estimates for the United States, but for most specific conditions, more studies generalizable to the United States for addressing understudied populations are needed.

Neuropathic pain is apparently common, with an estimated prevalence in the general population of 7 to 8% (66-68). However, because neuropathic pain consists of a number of different disease-specific indications, each of which can have differing diagnostic definitions and cutoffs, it is difficult to estimate precisely its prevalence and incidence (69). Neuropathic pain also affects between 8% and 50% of all diabetics (70). Diabetic peripheral neuropathy shares certain similarities (both in clinical presentation and response to treatment) with other forms of neuropathic pain. The prevalence of neuropathic pain after thoracic surgery is high, with 57% complaining of neuropathic pain at 7–12 months, 36% at 4–5 years, and 21% at 6–7 years (71). Breast cancer patients may complain of "phantom" breast pain for months to years after surgery (72).

2.3 Chronicity

Duration of pain and its chronicity have been topics of controversy. Conventional beliefs are that most episodes of low back pain will be short-lived, with 80% to 90% of attacks resolving in about 6 weeks irrespective of the administration or type of treatment, and only 5% to 10% of patients developing persistent back pain (73-82). However, this commonly held belief has been questioned, as in reality, the condition tends to relapse, so that most patients will experience recurrent episodes. Almost 60% of spinal pain patients have suffered from chronic pain from 2 to 15 years (53,56,73-82). Further, overwhelming evidence shows that chronic persistent low back pain and neck pain in children and adults are seen in up to 60% of the patients, 5 years or longer after the initial episode (73,76-83).

2.4 Health and Economic Impact

Chronic non-cancer pain is associated with sig-

nificant economic, societal, and health impact (84-93). The cost of uncontrolled chronic pain is enormous, both to individuals and to society as it leads to a decline in the quality of life and disability. Estimates and patterns of direct healthcare expenditures among individuals with back pain in the United States reached $90.7 billion for the year 1998 (84). On average, individuals with back pain generate healthcare expenditures about 60% higher than do individuals without back pain ($3,498 per year versus $2,178). It has been estimated that the cost of healthcare for patients with chronic pain might exceed the combined cost of treating patients with coronary artery disease, cancer, and AIDS (94). In the United States, it was estimated that the cost of treatment in the first year after failed back surgery for pain was approximately $18,883 in 1997 (95). Even further, annual healthcare cost incurred by chronic pain patients, excluding cost for surgical procedures, may range from $500 to as high as $35,400, with averages ranging from $12,900 to $18,883 annually (96,97).

The economic costs for chronic pain in general have been estimated to be over $86 billion per year (97). A cross-sectional study, based on survey data from 28,902 working adults in the USA was reported in 2003 with 13% of the workforce experiencing a loss of productivity during a 2 week period due to a common pain condition (98). In monetary terms, this loss of productivity was calculated to cost $61.3 billion, with $14.4 billion due to absenteeism and the rest due to the survey participants being at work, but with impaired productivity due to the pain.

In a recent survey of expenditures and health status among adults with back and neck problems (92), self-reported back and neck problems accounted for a large proportion of health care expenditures and spine-related expenditures have increased substantially from 1997 to 2005, without evidence of corresponding improvement in self-assessed health status. In this national estimate based on annual samples of survey respondents with and without self-reported spine problems from 1997 through 2005, a total of 23,045 respondents were sampled in 1997, including 3,139 who reported spine problems. In 2005, the sample included 22,258 respondents, including 3,187 who reported spine problems. This survey showed that in 1997, the adjusted medical cost for respondents with spine problems was $4,695 (95% CI, $4,181 to $5,209), compared with $2,731 (95% CI, $2,557 to $2,904) among those without spine problems in terms in inflation-adjusted dollars. Conversely, in 2005, the adjusted medical expenditures among respondents with spine problems was $6,096 (95% CI, $5670 to $6,522), compared with $3,516 (95% CI, $3,266 to $3,765) among those without spine problems. Consequently, total estimated expenditures among respondents with spine problems increased 65% after adjusting for inflation from 1997 to 2005, more rapidly than overall health expenditures. This is in contrast to the estimated proportion of persons with back or neck problems with self-reported physical function and limitations increasing from 20.7% (95% CI, 19.9% to 21.4%) to 24.7% (95% CI, 23.7% to 25.6%) from 1997 to 2005, which is an increase of 4%.

In one study evaluating the burden and determinants of neck pain in the general population (91) and in workers (93) after evaluating numerous studies (101 for general population and 109 for workers), the 12-month prevalence of pain typically ranged between 30 and 50%, while, the 12-month prevalence of activity-limiting pain was 1.7% to 11.5% in the general population, in workers, the annual prevalence of neck pain varied from 27.1% to 47.8%, with between 11% and 14.1% of workers limiting their activities due to neck pain.

2.5 Comorbidities

Chronic pain sufferers are considered to be heavy users of healthcare services, often presenting with multiple or unexplained symptoms. Studies indicate that only 2% to 5% of chronic pain sufferers have been evaluated or treated by a pain specialist (56,99), whereas many patients seek alternative practitioners (100), and a high proportion take prescription or over-the-counter medications.

Chronic pain also has high functional impairment impact on the sufferer's day-to-day function, with a range of activities being curtailed. Patients with chronic pain report difficulties with daily chores, social life, and work, and a higher rate of unemployment (101-104). It has been shown that 19% of patients had lost their job because of chronic pain (56). In addition, chronic pain sufferers have been shown to have low scores for quality of life (105,106).

Increased comorbidity, disability, and costs have been described widely in the chronic pain population (107-126). In a study of 1,484 community dwelling Australian women 70 to 85 years of age, daily back pain was shown to be associated with reduced quality

of life, mobility and longevity, and increased risk of coronary heart events (107). In a descriptive report of the longitudinal course of depressive symptoms and pain experienced by continuing care retirement community residents, in 169 residents, 37% met the criteria for chronic activity-limiting pain, 21% met the criteria for chronic high depressive symptoms, and 13% were comorbid (63). In another study of an elderly population, both pain and depression affected physical performance, with depression having more an influential effect on the decline of physical performance and causing increased levels of functional impairment. This was also confirmed in a prospective study of patients with disabling low back pain and depressive symptoms in a community-dwelling population of over 90,000 elderly, more than 50,000 of whom were being surveyed for the follow-up purposes after 2 years (109). This study showed that among community-dwelling elderly persons, depressive symptoms and disabling low back pain were widespread, with depressive symptoms predicting disabling low back pain and vice versa. Multiple studies have addressed the impact of chronic spinal pain (112-114), headache (115,117,118), and various types of pain.

Extensive research of involvement of psychological disorders in the chronic pain population has been published (120-134). Since pain is defined as both a physiological sensation and a psychological condition or state (126), the neural event of pain is in many ways inextricable from the psychological or phenomenological experience of pain (127). Consequently, chronic pain in particular manifests a psychological constellation of cognitive, emotional, and behavioral characteristics. Numerous studies have shown that a significant proportion of pain patients present with depression, anxiety, and somatization disorder, either alone or in combination (120-125,128-133). In studies that have evaluated chronic pain patients, the comorbidity of major depression ranged from 15% to 56%, significantly higher than the occurrence of major depression within the general population, which ranged from 5% to 10%. Similarly, the occurrence of somatization disorder ranged from 20% to 31% in chronic pain patients, compared to 1% to 4% in the general population. Consequently, the prevalence of pain is noted to increase with the association of comorbidities, and the prevalence of pain continues to increase, along with psychological and substance abuse disorders.

3.0 Opioids Use in Chronic Pain

3.1 General Considerations

Inadequate treatment of pain has been attributed to a lack of knowledge about pain management options, inadequate understanding of addiction, or fears of investigation or sanction by federal, state, and local regulatory agencies (1-6,134-136). Proponents of opioid drug therapy for all types of pain contend that opioid analgesic therapy plays an important role in pain management and should be available when needed for the treatment of all kinds of pain, including noncancer pain, without restriction of dosage or frequency (135). Further, the Drug Enforcement Adminstration (DEA) has also taken the position that clinicians should be knowledgeable about using opioids to treat pain, and should not hesitate to prescribe them when opioids are the best clinical choice of treatment (137). In addition to the DEA, model guidelines adapted by the Federation of State Medical Boards also encourage opioid management with proper documentation (138).

3.2 Response to Alleged Undertreatment

The alleged undertreatment of pain as a major health problem in the United States led to the development of initiatives to address the multiple alleged barriers responsible for the undertreatment of pain. Consequently, numerous clinical guidelines have been developed, even though none of them were based on evidence-based medicine. In 2001, the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) introduced the concept that pain was the "fifth vital sign," in an effort to increase the awareness of pain in the hospitalized patient, and by design, improve the treatment of that pain. Unfortunately, the current emphasis on pain assessment as the fifth vital sign has resulted in the potential overmedication of a group of patients (139). The results of the effect of JCAHO regulations have been controversial (140-142). One study showed that opioid adverse drug reactions increased significantly from 11 to 24.5 per 100,000 inpatient hospital days (140). However another study (141) showed increased opioid consumption without an increase in the length of the stay, increase in the use of naloxone, or an increase in treatment for postoperative nausea and vomiting. Yet, another study (142) showed that routinely measuring pain by the fifth vital sign did not increase the quality of pain management.

Multiple reviews (6,9-19) have shown a lack of consistent effectiveness of opioids in reducing pain and improving functional status. A cost analysis of chronic spinal pain (143) suggested that treatment with medications alone did not significantly improve a patients' ability to stand, sit, walk, travel, socialize, and work both in and outside the home. However, complementary treatment components, such as anesthetic procedures, physical therapy, group education, and cognitive-behavioral psychotherapy, seemed to directly affect patients' pain-related functional impairments. It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering, because uncontrolled pain may have deleterious physical effects, and because persistent pain destroys peoples' autonomy, dignity, and decision-making capacity (6,14,144,145). Thus, the availability of opioids has skyrocketed dramatically in the past few decades, partly due to politics and the emotional issues involved with efforts to improve awareness and treatment of chronic pain. Despite equal recognition of the major side effects — drug abuse and addiction — by opponents and equally by proponents, proponents continue to promote extensive opioid use under the umbrella of undertreatment of pain, leading to an explosion in opioid therapy. As a result, most patients (over 90%) presenting to pain management settings, and receiving treatment at pain management centers have been receiving opioids, in spite of problems of abuse, diversion, and other side effects (120,146-170). The therapeutic use of opioids has exploded in the United States, witnessed by increased sales of hydrocodone by 244% from 1997 to 2006, while methadone usage increased 1,177% and oxycodone increased 732% (Table 3 and Fig. 1) (5). Coupled with increased retail sales in therapeutic opioid usage, the pattern of type of opioid usage also has changed. In 1997, the most commonly used opioid was codeine, followed by hydrocodone and oxycodone. However, in 2006, the most commonly used opioid was oxycodone, followed by hydrocodone and morphine.

Overall, opioids increased from 50.7 million grams of medication in 1997 to 115.3 million grams of medication in 2006, an overall increase of 127% (5). In addition, the estimated number of prescriptions filled for controlled substances increased from 222 million in 1994 to 354 million in 2003 (4,171,172). Prescriptions

Table 3. *Retail sales of opioid medications (grams of medication), 1997–2006.*

Drug	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% of change from 1997
Methadone	518,737	692,675 (34%)	964,982 (39%)	1,428,840* (48%)	1,892,691 (32%)	2,649,559 (40%)	3,683,881 (39%)	4,730,157 (28%)	5,362,815 (13%)	6,621,687 (23%)	1177%
Oxycodone	4,449,562	6,579,719 (48%)	9,717,600 (48%)	15,305,913 (58%)	19,927,286 (30%)	22,376,892 (12%)	26,655,152 (19%)	29,177,530 (9%)	30,628,973 (5%)	37,034,220 (21%)	732%
Fentanyl Base	74,086	90,618 (22%)	107,141 (18%)	146,612* (37%)	186,083 (27%)	242,027 (30%)	317,200 (31%)	370,739 (17%)	387,928 (5%)	428,668 (11%)	479%
Hydromorphone	241,078	260,009 (8%)	292,506 (12%)	346,574* (18%)	400,642 (16%)	473,362 (18%)	579,372 (22%)	655,395 (13%)	781,287 (19%)	901,663 (15%	274%
Hydrocodone	8,669,311	10,389,503 (20%)	12,101,621 (16%)	14,118,637 (17%)	15,594,692 (10%)	18,822,619 (21%)	22,342,174 (19%)	24,081,900 (8%)	25,803,543 (7%)	29,856,368 (16%)	244%
Morphine	5,922,872	6,408,322 (8%)	6,804,935 (6%)	7,807,511 (15%)	8,810,700 (13%)	10,264,264 (16%)	12,303,956 (20%)	14,319,243 (16%)	15,054,846 (5%)	17,507,148 (16%)	196%
Codeine	25,071,410	26,018,054 (4%)	23,917,088 (-8%)	23,474,865* (-2%)	23,032,641 (-2%)	22,633,733 (-2%)	21,865,409 (-3%)	20,264,555 (-7%)	18,960,038 (-6%)	18,762,919 (-1%	-25%
Meperidine (Pethidine)	5,765,954	5,834,294 (1%)	5,539,592 (-5%)	5,494,898* (-1%)	5,450,204 (-1%)	5,412,389 (-1%)	5,239,932 (-3%)	4,856,644 (-7%)	4,272,520 (-12%)	4,160,033 (-3%)	-28%
Total	50,713,010	56,273,194 (11%)	59,445,465 (6%)	35,962,089.84 (15%)	75,294,939 (11%)	82,874,845 (10%)	92,987,076 (12%)	98,456,163 (6%)	101,251,950 (6%)	115,272,706 (14%)	127%

Numbers in parenthesis are percentage of change from previous year. * For year 2000, data is not available; the average of 1999 and 2001 was taken. Source: www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html

Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11: S63-S88.

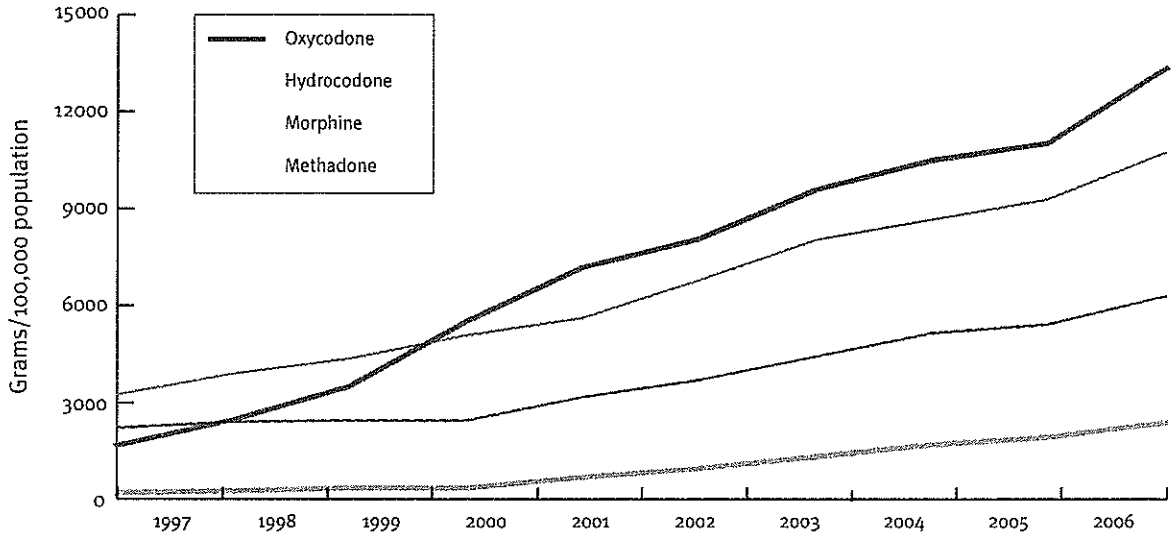


Fig. 1. *The increase in therapeutic opioid use in the United States (grams/100,000 population) from 1997 to 2006.*

Source: Based on data from US Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS); www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html

Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008: 11:S63-S89.

for controlled substances increased by 154%, compared to the number of prescriptions written for non-controlled drugs which increased by 57% (173-175). As a result, the milligram per person use of therapeutic opioids in the United States increased from approximately 74 mg in 1997 to 329 mg per person in 2006, an increase of 347% (Table 4) (5). Fig. 2 illustrates total prescriptions for selected narcotic analgesics for 2006 (5,176,177). In 2006, there were about 35-fold more hydrocodone prescriptions, 10-fold more oxycodone prescriptions, and 2-fold more fentanyl prescriptions compared to methadone prescriptions. In addition, Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply, along with two-thirds of the world's illegal drugs (1-5,178-181).

Multiple authors also have evaluated the increase in opioid use along with cost and health consequences which have been increasing substantially over the years (182-184). The analysis of the National Ambulatory Medical Care Survey, using data from 1980 to 1981 and 1999 to 2000, evaluating over 130,000 visits showed the doubling of opioid use for chronic pain from 8% to 16% and for acute pain the increase was from 8% to 11% (182). In addition, the study also showed that prescriptions for more potent opioids such as hydrocodone, oxycodone, and morphine increased from 2% to 9% in visits corresponding to 5.9 million visits in 2002 — an increase of 4.6 million visits from 1980 for chronic musculoskeletal pain. Further, in the analysis of analgesic use for low back pain and its impact on health care costs and service use (183), in 2001, 55.5%of members with claims for low back services received analgesics costing a total of $1.4 million, of which 68% were opioids. Opioid use was also associated with high volume usage of low back pain services and correlated with the higher use of opioids in patients with psychogenic pain and low back pain related to orthopedic devices such as fusion. There have been reports of association of opioid use with increased disability, medical costs, subsequent surgery, and continued or late opioid use (182-186). Webster et al (185) showed that patients receiving more than 450 mg equivalent of morphine over a period of several months were, on average, disabled 69 days lon-

ger than those who received no early opioids, and also had 3 times the increased risk for surgery, along with 6 times the increased risk of receiving late opioids. Greater self-reported disability and poor function was associated with opioid use (187). Finally, an epidemiological study from Denmark (188) demonstrated worse pain, higher health care utilization, and lower activity levels in opioid treated patients compared to a matched cohort of chronic pain patients not using opioids ,suggesting that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. Opioids are prescribed liberally for chronic pain in Denmark. In an evaluation of primary care patients, the frequency of opioid disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%) (189).

3.3 Prescription Opioids in Chronic Pain

Numerous reviews have critically evaluated the effectiveness of opioid therapy in chronic pain (1,6,11-19). In a meta-analysis of opioid use in patients with chronic low back pain, Martell et al (10) concluded that opioids do not provide effective pain relief and do not increase functional status in chronic low back pain. Ballantyne (6), after directly comparing the efficacy of different opioids, concluded that a non-significant reduction in pain was present. Chou et al (11) concluded there was insufficient and poor evidence to prove the safety or effectiveness or any opioids. Kalso et al (12) in their critical analysis concluded that the mean decrease in pain intensity in most studies was only 30%, whereas only 44% of the patients continued treatment for 7 to 24 months. Furlan et al (13) provided a more somber view of opioids concluding that strong opioids were more effective with pain relief and functional outcomes, even though drop-out rates averaged 33%. Two Cochrane reviews (15,16) showed unsatisfactory long-term results in managing neuropathic (15) and nociceptive pain (16). A recent systematic review and meta-analysis (9) of efficacy and safety of long-term opioid therapy for chronic non-cancer pain concluded that many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief. However, they also concluded that weak evidence suggests that oral opioids reduce pain long-term in the relatively small proportion of individuals with chronic non-cancer pain who continue treatment. Sandoval et al (18) in a systematic review of methadone found no randomized trials for long-term use of methadone and showed only limited evidence with observational reports.

Cepeda et al (17) performed a systematic review and meta-analysis of randomized clinical trials of tramadol and concluded that tramadol is more effective than placebo for the treatment of osteoarthritis when the pain is moderate. However, tramadol was only of limited benefit when the pain was severe.

Overall, the evidence supporting the long-term analgesic efficacy is weak at best based on the present evidence. In addition, not surprisingly, epidemiological

Table 4. *The increase in therapeutic opioids use in the U.S. (mg/person) from 1997 to 2006.*

Type	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% of Change from 1997
Morphine	22.20	24.01	24.50	28.11	31.72	36.95	44.30	51.55	54.20	63.03	184%
Methadone	1.94	2.60	3.47	5.14*	6.81	9.54	13.26	17.03	19.31	23.84	1,129%
Oxycodone	16.68	24.66	34.99	55.11	71.75	80.56	95.97	105.05	110.27	133.33	899%
Hydrocodone	32.49	38.93	43.57	50.83	56.15	67.77	80.44	86.70	92.90	107.49	231%
Fentanyl	0.28	0.34	0.39	0.53*	0.67	0.87	1.14	1.33	1.40	1.54	450%
Total	73.59	90.54	106.92	139.72	167.1	195.69	235.11	261.66	278	329.23	347%

* For year 2000 data is not available, the average of 1999 and 2001 was taken.

Source: Data taken from U.S. Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS); www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html. Access date: 3/13/08

Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11:S63-S88.

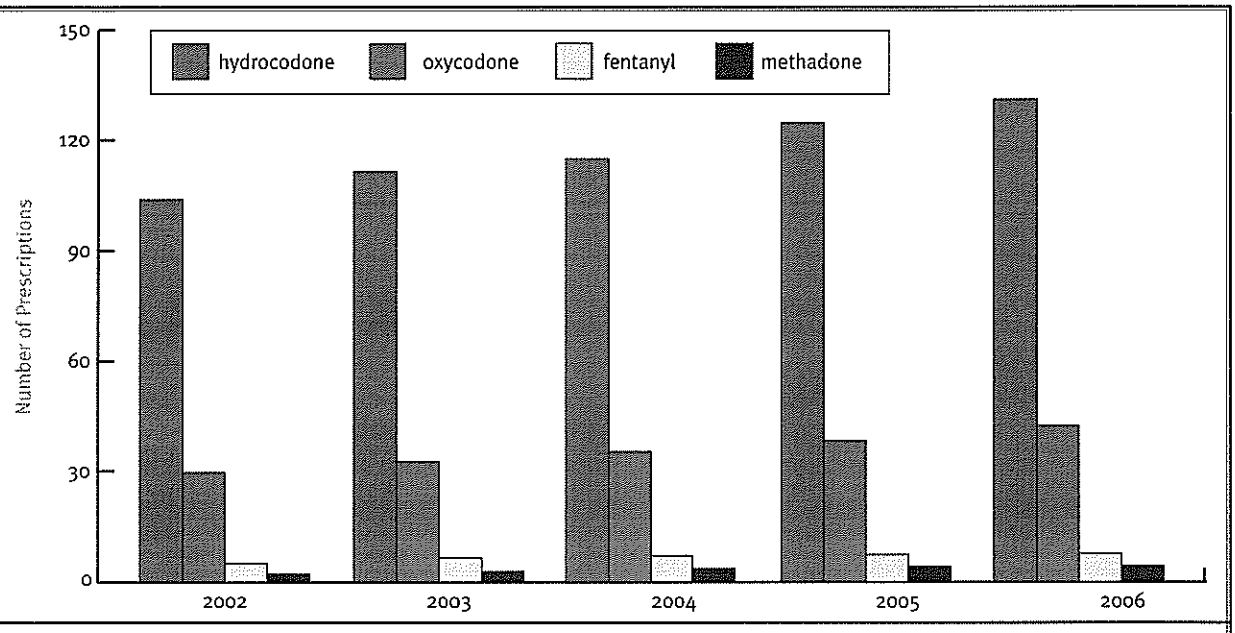


Fig. 2. *Total prescriptions of selected narcotic analgesics (29).*

Source: Methadone Morality Working Group Drug Enforecement Administration, Office of Diversion Control.
Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11:S63-S88.

studies while positive with pain are less positive with regards to function and quality of life and report the failure of opioids to improve quality of life in chronic pain patients (20).

3.4 Nonmedical Use of Prescription Drugs

The National Survey on Drug Use and Health of 2006 (190) showed that an estimated 20.4 million or 8.3% of Americans, ages 12 or older were current (past month) illicit drug users. Among the illicit drugs, psychotherapeutic drugs which include prescription type pain relievers, tranquilizers, stimulants, and sedatives are included. Marijuana and hashish are the most commonly used illicit drugs with 14.8 million current users, or 6% of the U.S. population. Cocaine was used by 2.4 million, whereas hallucinogens were used in the past month by 1 million persons. However, surprisingly, next to marijuana, 7.0 million (2.8%) persons aged 12 or older had used prescription-type psychotherapeutic drugs nonmedically in the past month. Of these, 5.2 million had used pain relievers, an increase from 4.7 million in 2005 (Table 5). The categories of nonmedical use of psychotherapeutics and pain relievers were well ahead of the illicit drug use of cocaine, hallucinogens, inhalants, methamphetamine, heroin, and LSD.

The increases for current nonmedical use of psychotherapeutics over a period of the last 10 years (1997 to 2006) was 162% compared to 33% for marijuana and hashish, and 61% for cocaine. Consequently, psychotherapeutics were the only ones that showed significant increases from 2002 to 2006, whereas, marijuana and cocaine were similar over a period of 5 years (5).

Statistics of new initiatives also continue to be grim with 2.6 million persons aged 12 or older using psychotherapeutic drugs nonmedically for the first time within the past year in 2006 (190). Similarly, numbers of new users for specific psychotherapeutics in 2006 were 2.2 million for pain relievers, 1.1 million for tranquilizers, 845,000 for stimulants, and 267,000 for sedative (Table 6).

Analysis of long-term statistics based on yearly use of illicit drugs are concerning (5). The past year use of illicit drugs in 2006 was 35.77 million or 4.5% of the population, whereas nonmedical use of psychotherapeutics for the past year in the 2006 survey was 16.287

Table 5. *Types of illicit drug use in the past month among persons aged 12 or older: Numbers in thousands, from 1997 to 2006.*

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% change from 1997 to 2006
Nonmedical Use of Psychotherapeutics[2]	2,665 (1.2%)	2,477 (1.1%)	3,952 (1.8%)	3,849 (1.7%)[c]	4,811[c] (2.1%)	6,210[a] (2.6%)	6,336 (2.7%)	6,007[b] (2.5%[b])	6,405 (2.6%)	6,991 (2.8%)	162%
Pain Relievers	--	--	2,621 (1.2%)	2,782 (1.2%)	3,497[c] (1.6%)	4,377[b] (1.9%[a])	4,693 (2.0%)	4,404[b] (1.8%[a])	4,658[a] (1.9%)	5,220 (2.1%)	NA
OxyContin®	--	--	--	--	--	--	--	325 (0.1%)	334 (0.1%)	276 (0.1%)	NA
Tranquilizers	845 (0.4%)	655 (0.3%)	1,097 (0.5%)	1,000 (0.4%)	1,358[c] (0.6%)	1,804 (0.8%)	1,830 (0.8%)	1,616 (0.7%)	1,817 (0.7%)	1,766 (0.7%)	109%
Stimulants	612 (0.3%)	633 (0.3%)	950 (0.4%)	788 (0.4%)	1,018 (0.5%)	1,218 (0.5%)	1,191 (0.5%)	1,189 (0.5%)	1,067 (0.4%)	1,191 (0.5%)	95%
Sedatives	187 (0.1%)	210 (0.1%)	229 (0.1%)	175 (0.1%)	306 (0.1%)	436 (0.2%)	294 (0.1%)	265 (0.1%)	272 (0.1%)	385 (0.2%)	106%
Marijuana and Hashish	11,109 (5.1%)	11,016 (5.0%)	10,458 (4.7%)	10,714 (4.8)	12,122[c] (5.4%)	14,584 (6.2%)	14,638 (6.2%)	14,576 (6.1%)	14,626 (6.0%)	14,813 (6.0%)	33%
Cocaine	1,505 (0.7%)	1,750 (0.8%)	1,552 (0.7%)	1,213 (0.5%)	1,667[c] (0.7%)	2,020[a] (0.9%)	2,281 (1.0%)	2,021[a] (0.8%)	2,397 (1.0%)	2,421 (1.0%)	61%
Total Illicit Drugs[1]	13,904 (6.4%)	13,615 (6.2%)	13,829 (6.3%)	14,027 (6.3%)	15,910[c] (7.1%)	19,522 (8.3%)	19,470 (8.2%)	19,071[a] (7.9%)	19,720 (8.1%)	20,357 (8.3%)	46%

-- Not available.
a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.
b Difference between estimate and 2006 estimate is statistically significant at the 0.01 level.
c Difference between estimate and previous year estimate is statistically significant at the 0.01 level.
1 Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.
2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.
Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11: S63-S88.

million compared to 15.172 million in 2005 and 14.643 million in 2004, or 6.6% of the population aged 12 or older in 2006, 6.2% in 2005, and 6.1% in 2004 with significant increases (Table 7). Similarly, lifetime use of psychotherapeutics drugs has been increasing over the years with nonmedical use of psychotherapeutic increasing from 20% of the population in 2005 to 20.3% in 2006 or almost 50 million. A review of therapeutic opioids with a 10-year perspective on the complexities and complications of escalating use, abuse, and nonmedical use of opioids describes in detail the issues related to therapeutic opioid abuse (5).

A survey of American adults by *USA Today* and HBO (192) in 2006 found that:

- One in 5 adults have a close relative who is or was addicted to drugs or alcohol.
- Three-quarters of American adults who have a family member suffering from the disease of drug or alcohol addiction think addiction is a disease.
- Emotional and Devastating/Horrible are the words that were most often used to describe the effects of a family member's addition.
- Almost one of 10 of those who say a family member's addiction has had a major negative impact on their financial situation say they have had to take out a loan or run up credit card bills as a direct result of this addiction.
- About a fifth of those who say a family member's addiction has had a major negative impact on their marriage, family relationships, or emotional health say they sought professional counseling.
- One third of American adults who have a family member suffering from the disease of drug or alcohol addiction say the addiction has caused estrangement among family members.
- Almost half of U.S. adults who have a family

Table 6. *Past year initiates for illicit drugs from 1997 to 2006 (numbers in thousands).*

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% change from 1997 to 2006
Pain Relievers[2]	1,316	1,548	1,810	2,268	2,400	2,320	2,456[a]	2,422[a]	2,193	2,150	63%
Tranquilizers	668	860	916	1,298	1,212	1,184	1,071	1,180	1,286	1,112	66%
Stimulants	553	648	706	808	853	783	715	793	647[a]	845	53%
Sedatives	120	147	164	191	225	209	194	240	247	267	123%
Marijuana	2,603	2,498	2,640	2,746	2,793	2,196	1,973	2,142	2,114	2,063	-21%
Cocaine	861	868	917	1,002	1,140	1,032	986	998	872	977	13%
Heroin	114	140	121	114	154	117	92	118	108	91	-20%

Note: 2002 to 2006 data is based on 2006 National Survey on Drug Use and Health Survey Report.
NOTE: Past year initiates are defined as persons who used the substance(s) for the first time in the 12 months prior to date of interview.
a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.
2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2002, 2003, 2004, 2005, and 2006.
Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11:S63-S88.

Table 7. *Types of illicit drug use in the past year among persons aged 12 or older from 1997 to 2006 (numbers in thousands).*

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% change from 1997 to 2006
Nonmedical Use of Psychotherapeutics[2]	6,111 (2.8%)	5,759 (2.6%)	9,220 (4.2%)	8,761 (3.9%)	11,102[c] (4.9%[c])	14,680[b] (6.2%)	14,986[b] (6.3%)	14,643[b] (6.1%[b])	15,172[a] (6.2%[a])	16,287 (6.6%)	167%
Pain Relievers	--	--	6,582 (3.0%)	6,466 (2.9%)	8,353[c] (3.7%[c])	10,992[b] (4.7%[b])	11,671[a] (4.9%)	11,256[b] (4.7%[b])	11,815[a] (4.9%)	12,649 (5.1%)	NA
OxyContin®	--	--	--	--	--	--	--	1,213 (0.5%)	1,226 (0.5%)	1,323 (0.5%)	NA
Tranquilizers	2,122 (1.0%)	1,940 (0.9%)	2,728 (1.2%)	2,731 (1.2%)	3,673[c] (1.6%[c])	4,849 (2.1%)	5,051 (2.1%)	5,068 (2.1%)	5,249 (2.2%)	5,058 (2.1%)	138%
Stimulants	1,687 (0.8%)	1,489 (0.7%)	2,291 (1.0%)	2,112 (0.9%)	2,486[c] (1.1%)	3,181 (1.4%)	2,751[b] (1.2%[a])	2,918[a] (1.2%)	2,771[b] (1.1%[b])	3,394 (1.4%)	101%
Sedatives	638 (0.3%)	522 (0.2%)	631 (0.3%)	611 (0.3%)	806 (0.4%)	981 (0.4%)	831 (0.3%)	737 (0.3%)	750 (0.3%)	926 (0.4%)	45%
Marijuana and Hashish	19,446 (9.0%)	18,710 (8.6%)	19,102 (8.6%)	18,589 (8.3%)	21,086[c] (9.3%[c])	25,755 (11.0%[a])	25,231 (10.6%)	25,451 (10.6%)	25,375 (10.4%)	25,378 (10.3%)	31%
Cocaine	4,169 (1.9%)	3,811 (1.7%)	3,742 (1.7%)	3,328 (1.5%)	4,186[c] (1.9%[c])	5,902 (2.5%)	5,908 (2.5%)	5,658 (2.4%)	5,523 (2.3%)	6,069 (2.5%)	46%
Total Illicit Drugs[1]	24,189 (11.2%)	23,115 (10.6%)	25,402 (11.5%)	24,535 (11.0%)	28,409 (12.6%[c])	35,132 (14.9%)	34,993 (14.7%)	34,807 (14.5%)	35,041 (14.4%)	35,775 (14.5%)	48%

Note: 2002 to 2006 data is based on 2006 National Survey on Drug Use and Health Survey Report.
Figures in () indicate percentage.
-- Not available.
a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2006 estimate is statistically significant at the 0.01 level. c Estimate is statistically different than previous year 1 Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. 2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.
Adapted from Manchikanti and Singh (5). Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11:S63-S88.

member suffering from the disease of drug or alcohol addiction say their family member has never sought treatment. Of those whose family member has sought treatment, 3 out of 10 only sought treatment after intervention.

- Of those whose family member sought treatment, almost half say the family member relapsed and almost one out of 10 say there was no improvement at all.
- Only 3 out of 10 respondents say their addicted family member consulted with a medical doctor or other medical professional specializing in the treatment of addiction.
- Over half of the respondents say their addicted family member was never evaluated for psychological illness.

The latest Center on Addiction and Substance Abuse (CASA) report (193) also presented alarming statistics finding that at 11 million high school students (80%) and 5 million middle school students (44%) attended drug-infested schools, where they have personally witnessed illegal drug use, illegal drug dealing, and students high on the grounds of the school. More than one in 3 (37%) teens say they can buy marijuana within a day, and 17% say they can buy marijuana within an hour. Even more concerning, students who identify themselves as "popular" and attended a drug-infested school, were 5 times more likely to get drunk in a typical month, and are much more likely to abuse prescription and illegal drugs. It is particularly concerning that 28.9% of pharmacists have been robbed within the past 5 years, and 20.9% no longer stock certain controlled drugs in order to prevent future robberies.

3.4.1 Physician Survey Highlights

In a 2006 survey (194) of 248 primary care physicians (PCP) regarding their attitudes toward the prescribing of opioids for chronic pain, their major concerns included prescription drug abuse (84.2%), addiction (74.9%), adverse effects (68%), tolerance (60.7%), and medication interaction (32%). A majority were comfortable prescribing opioids for cancer pain, but they were less comfortable prescribing opioids for back pain or for patients with a history of drug or alcohol abuse. Only 6.9% reported obtaining a urine screen prior to initiating opioid therapy, and only 15% performed urine screens on patients currently on opioids.

Similarly, in another survey (195) of 111 primary care attendings, residents, and nurse practitioners in 8 community clinics, the PCPs reported that 37.5% of their adult patients in a given week had chronic pain issues. But, they attributed these problems with pain care to patient related factors such as self-management and abuse issues instead of provider or practice system factors.

In a study published in 2007 (196) evaluating long-term opioid contract use for chronic pain management in primary care practice, illustrating a 5-year experience, contracts were discontinued in approximately 40% of the patients. However, only 17% were cancelled for substance abuse and noncompliance and 20% discontinued the contract voluntarily. In this population, urine toxicology screens were obtained in 42% of patients of whom 38% were positive for illicit substances. This report reveals a lack of a systematic approach to opioid administration and monitoring in primary care practices. In another article, it was questioned with regards to the dilemmas experienced when prescribing opioids in general practice (197). There have also been publications with regards to designing a primary care-based chronic pain management program from a scientific basis (198) and guidance for contractual approaches (198). Further, issues related to chronic pain patients, adherence monitoring, etc., have been described in detail in chronic pain management settings (1).

A CASA survey of 979 physicians regarding the diversion and abuse of controlled prescription drugs showed that physicians perceive the 3 main mechanisms of diversion to be doctor shopping, patient deception, or manipulation of doctors, and forged or altered prescriptions (180). Further, a good majority of physicians believe that patients account for the bulk of the diversion problem. In addition, less than 20% of surveyed physicians received any medical school training in identifying prescription drug diversion, and less than 40% received any training in medical school in identifying prescription drug abuse and addiction. It was also shown that 43% of physicians do not ask about prescription drug abuse when taking a patient's health history and over 70% of physicians have refrained from prescribing controlled drugs due to concerns that a patient may become addicted to them.

3.4.2 Pharmacist Survey Highlights

There have been no new studies of pharmacists since the CASA study of 2005 (180). At that time, 28.4% of pharmacists did not regularly validate the prescribing physician's DEA number when dispensing controlled drugs; one in 10 (10.5%) rarely or never do

so. Sixty-one percent did not regularly ask if the patient is taking any other controlled drugs, 25.8% rarely or never do. Seventy-eight percent become "somewhat or very" concerned about diversion or abuse when a patient asks for a controlled drug by name; 83.1% have refused to dispense a controlled drug in the past year because of suspicions of diversion; and 51.8% believed that patients account for the bulk of the diversion problems.

3.4.3 Drug Abuse Warning Network (DAWN) Reports

The Drug Abuse Warning Network (DAWN) (199) examined the involvement of opiates and deaths related to drug misuse. Nearly 1.3 million emergency department (ED) visits in 2005 were associated with drug misuse/abuse (200). Nonmedical use of pharmaceuticals was involved in nearly a half million of these ED visits with opioids constituting over 196,000 visits (an increase over 2004 of 24%). There was a 92% increase in visits due to hydromorphone products (most likely due to Palladone overdoses), and a 29% increase in methadone visits. Two-thirds or more of ED visits associated with opiates/opioids, benzodiazepines, and muscle relaxants involved multiple drugs, and alcohol was one of the other drugs in about a quarter of such visits. Toxic effects were reported in 10% of visits. The DAWN data also showed that opioids account for more overdose deaths in the United States than either heroin or cocaine.

In 2006, young adults aged 18 to 25 demonstrated rates of current use of illicit drugs to be higher (19.8%) than for youths aged 12 to 17 and adults aged 26 or older, with 16.3% using marijuana, 6.4% using psychotherapeutics nonmedically, 2.2% using cocaine, and 1.7% using hallucinogens (Fig. 3).

3.4.4 Healthcare and Social Costs

Unfortunately, the current emphasis on pain assessment as the fifth vital sign has resulted in the potential overmedication of a group of patients (139,140). Prescription drug abuse inflicts enormous costs on our society. The mortality from opioids cannot be ignored (201,202). In a study of the Centers for Disease Control (CDC) (203), increasing deaths were found from opioid analgesics in the United States. Unintentional drug poisoning mortality rates increased an average of 5.3% per year from 1979 to 1990 and 18.1% per year from 1990 to 2002. The rapid increase during the 1990s reflects the rising number of deaths attributed to opioids and unspecified drugs. Between 1999 and 2002 (the last date for which the information is available), the number of opioid analgesic poisonings on death certificates increased 91.2%, while heroin and cocaine poisonings increased 12.4% and

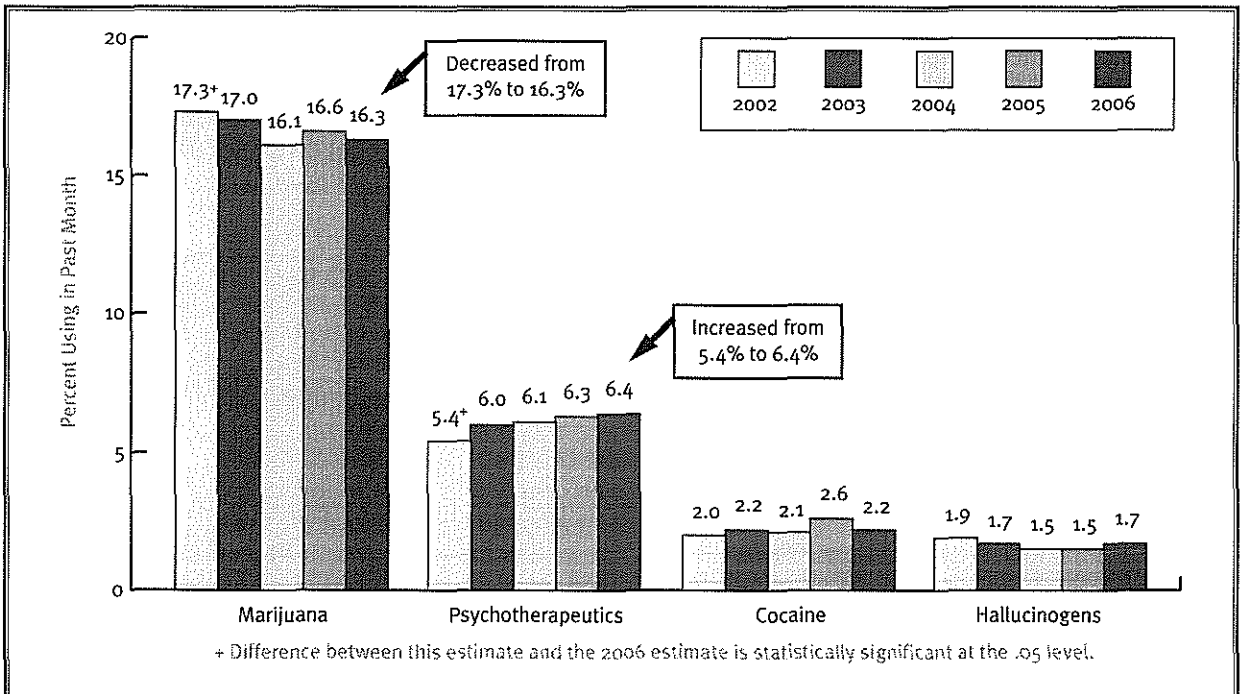


Fig. 3. *Past month use of selected illicit drugs among young adults aged 18 to 25: 2002 – 2006 (1).*

22.8%, respectively. In 2002, opioid analgesic poisoning was listed in 5,528 deaths – more than either heroin or cocaine. The follow-up evaluation in 2007 (200) revealed that unintentional drug poisoning was second only to motor vehicle crashes as a cause of death from unintentional injury in the United States. This updated study showed the number of unintentional poisoning deaths increased from 12,186 in 1999 to 20,950 in 2004, with an increase of age-adjusted rate of 62.5% from 4.4 per 100,000 population in 1990 to 7.1 in 2004. The highest rate of deaths (59.6) in 2004 were among persons aged 35 to 54 years. Among the opioids, methadone has been implicated in more unintentional poisoning deaths than any other opioid (176,177,204-207).

Methadone-related deaths from 1999 to 2004 increased 390%, whereas the number of all poisoning deaths increased 54% (203). In addition, methadone mentions in poisoning deaths increased from 4% of all poisoning deaths to 13% of all poisoning deaths. The increase in methadone deaths was 29% from 2002 to 2004, in contrast to all poisoning deaths of 6% during the same period (Table 8). Further, persons aged 15 to 24 years contributed to the largest increases of deaths with a rate of 11 times to that of 99 in 2004, even though most methadone deaths were in persons aged 35 to 44 and 45 to 54 years of age. However, reassessment of methadone mortality in 2007 also showed increasing use, misuse, diversion, and abuse (208,209). This led to a stricter warnings about methadone by the FDA (210).

3.5 Substance Abuse in Chronic Pain

The central question when prescribing opioids for chronic, non-cancer pain is how best to balance the risk of opioid abuse with the pain relief provided by these medications (7,159).

A prospective cohort study of 196 opioid treated, chronic, non-cancer pain patients identified predictors of opioid misuse (160). Misuse was defined as having: negative urine toxicologic screen (UTS) for prescribed opioids, UTS positive for controlled substances not prescribed, procurement of opioids from multiple providers, diversion of opioids, prescription forgery, or, UTS positive for stimulants. The strongest predictors of misuse were the self-reported histories of previous alcohol or cocaine abuse, or previous criminal drug or alcohol-related convictions. Demographics such as gender, race, literacy, disability, and socioeconomic status were not associated with misuse.

The Veterans Administration looked at longitudinal administrative data from 2000 to 2005 (15,000 patients), and found that nonopioid substance abuse (such as alcohol) was the strongest predictor of opioid abuse (211). Mental health disorders were moderately strong predictors; the incidence of mental health disorders was much higher than the prevalence of nonopioid substance abuse (45.3% vs 7.6%), suggesting that mental health disorders were indicative of a higher risk. Males, younger adults, and individuals with greater days supply of prescription opioids were more likely to develop opioid abuse. To look at the issue from the other side, a representative sample of

Table 8. *Number of poisoning deaths in which specific narcotic substances are mentioned, 1999 to 2004.*

Substance	1999	2000	2001	2002	2003	2004	1999-2004 % change	2003-2004 % change
Poisoning by all Narcotics and Psychodysleptics	9,995	10,173	11,480	14,247	15,731	16,735	68.1	6.4
Opium	4	2	5	3	4	1	-75.0	-75.0
Heroin	1,964	1,846	1,782	2,091	2,080	1,881	-4.2	-9.6
Other Opioids	2,757	2,932	3,484	4,431	4,877	5,242	90.1	7.5
Methadone	786	988	1,456	2,360	2,974	3,849	389.7	29.4
Other Synthetic Narcotics	732	784	962	1,301	1,406	1,668	127.9	18.6
Cocaine	3,832	3,565	3,840	4,612	5,212	5,461	42.5	4.8
Other Narcotics	2,902	2,880	2,881	3,143	3,117	2,761	-4.9	-11.4
Cannabis	37	41	37	50	61	99	167.6	62.3
LSD	3	3	2	0	1	1	-66.7	0.0
Other	9	8	7	5	6	5	-44.4	-16.7

Note: Substance-specific data are not additive because of death.
Source: National Center for Health Statistics, National Vital Statistics System

390 patients from 2 methadone maintenance treatment programs (MMTP) reveled that 37% of these patients suffered from severe, chronic pain (212). Correlates of chronic pain included age (odds ratio [OR] 2.08), chronic illness (OR 1.88), and lifetime psychiatric illness (OR 1.77).

Fleming et al (189) in a sample of primary care patients found that the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared to nonopioid therapy patients. They also showed that DSM-IV evidence of opioid use disorder was seen in 9.7% of patients, 4 times higher than the reported general population, and 24% of urine drug testings were positive for illicit drugs.

Even though occasional studies (213) and proponents claim extremely low levels of opioid abuse, opioids are by far the most abused drugs, especially in chronic pain management settings. Numerous investigations have illustrated drug abuse in 18% to 41% in patients receiving opioids for chronic pain (1-5,10,146-163,214-216).

Martell et al (10) in a systematic review of opioid treatment for chronic back pain, estimated the prevalence of lifetime substance use disorders to range from 36% to 56%, with a 43% current substance use disorder rate. Further, aberrant medication-taking behaviors ranged from 5% to 24%.

The abuse of drugs in chronic pain patients may also include illicit drugs in conjunction with controlled substances. Multiple investigators have studied the issue of illicit drug use in chronic pain patients receiving controlled substances (146,158,160-163). The results showed that illicit drug use in patients without controlled substance abuse was found in 14% to 16% of patients and illicit drug use in patients with controlled substance abuse was present in 34% of the patients (148,150,151). Illicit drug use was significant in chronic pain patients in general, but illicit drug use was similar in patients using either long-acting or short-acting opioids (161). In other evaluations, it was shown that adherence monitoring will in fact decrease controlled substance abuse and illicit drug use (158,163).

Along with the increase of prescriptions for controlled drugs from 1992 to 2002 of 154% (173-175,215-218), there was also a 90% increase in the number of people who admitted abusing controlled prescription drugs (219). Studies also evaluated opioid abuse in the insured population of the United States (218). Opioid abuse was determined to be present in 6.7 to 8 per 10,000 persons insured however, opioid abusers presented with multiple comorbidities and expenses 8 times higher than for non-abusers ($15, 884 vs $1,830).

3.6 Economic Impact

The cost of opioid abuse is enormous ranging as high as $300 billion a year as per the estimates of the White House Budget Office. The White House Office of National Drug Control Policy, a component of the Executive Office of the President, established by the Anti-Drug Abuse Act of 1990, has been spending $12 to $13 billion each year (2).

A study by the Office of Management and Budget estimated drug abuse costs to the United States at $300 billion a year, including government anti-drug programs and the costs of crime, healthcare, accidents, and lost productivity. In the Aid to Family with Dependent Children (AFDC), Medicaid and food stamp programs, the incidence of drug abuse varies from 9.4% to 16.4% (218).

3.7 Drug Diversion

Drugs can be diverted from their lawful purpose to illicit use at any point in the pharmaceutical manufacturing and distribution process. The diversion of prescription drugs among adults is typically described to occur through one of the following: doctor shopping, illegal internet pharmacies, drug theft, prescription forgery, and illicit prescriptions by physicians. Youths typically acquire drugs by stealing from their relatives or buying from classmates who sell their legitimate prescriptions.

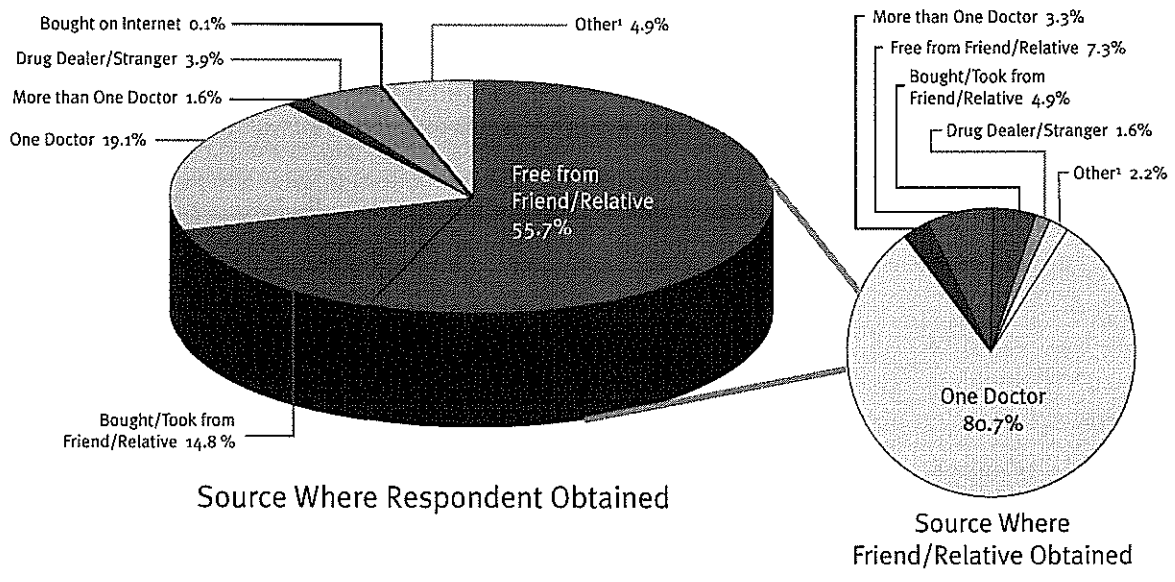
For the SAMHSA surveys (190,191), nonmedical users of prescription-type psychotherapeutic drugs were asked questions regarding how they obtained the drugs they recently used nonmedically. In both 2005 and 2006, over half of the nonmedical users of prescription-type pain relievers, tranquilizers, stimulants, and sedatives said they obtained the drugs they used most recently "from a friend or relative for free." A follow-up question added in 2006 asked these respondents where their friend or relative had obtained the drugs. In 80.7% of the cases, the individuals indicated that their friend or relative had obtained the drugs from just one doctor. Only 1.6% reported that the friend or relative had bought the drug from a drug dealer or other stranger (Fig. 4).

As long as long-acting forms of opioids can be converted into rapid-onset drugs, there will be a push to divert and abuse these medications (221). In

the wake of the OxyContin abuse scandals, the FDA has added warning labels to extended release formulations, admonishing against crushing and chewing tablets, which may have led to increased experimentation and abuse (222). The ease with which an active ingredient can be extracted form the parent medication has been seen as related to the medication's abuse potential; unfortunately, the pharmacy industry currently lacks standards to assess the tamper-resistance of a formulation, which makes it difficult to compare different formulations from different manufacturers. Katz and colleagues (223) have proposed 4 components of extractability: ease of extraction, purity of extract, efficiency of extraction, and potency of extract. They then developed a rating system, but concluded that more work needed to be done on the system before it could be used as an industry standard.

Doctor shopping by drug abusers is one of the most common ways of getting illegal controlled substances (224). Generally, this term refers to the visit by an individual—who may or may not have legitimate medical needs—to several doctors, each of whom writes a prescription for a controlled substance. The individual will visit several pharmacies, receiving more of the drug than intended by any single physician, typically for the purpose of feeding an addiction. Other illegal activities may include forged prescriptions and "pill mills" (facilities that prescribe large volumes of opioids without legitimate purpose, often for cash).

Illegal internet pharmacies have been available since about 1999. MarkMonitor, a company that analyzes online brands, estimates that consumers may be spending $4 billion annually on prescription medicines at uncertified online websites linked to spam emails (225). Of the 3,160 sites identified in the report, a third are ranked by the Alexa website tracking service as high volume sites and had an average of 32,000 visitors a day. MarkMonitor estimated that if just 0.5% of customers purchased on average $70 worth of medications, these ranked sites alone would earn $4 billion a year.



Note: Totals may not total to 100% because of rounding or because suppressed estimates are not shown.
¹The Other category includes the sources: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Fig.4. *Where pain relievers were obtained for most recent nonmedical use among past year users aged 12 or older: 2006 (1).* Source: Abuse and Mental Health Services Administration (2007) (190). Results from the 2006 National Survey on Drug Use and Health: National Findings.

3.8 Controlling Diversion and Abuse

For nearly 100 years, the laws governing the prescribing of medications with addictive potential (as described in the Harrison Narcotics Act of 1914) worked relatively well to control the access of these medicines while at the same time controlling their misuse. However, recent technologic developments, such as internet prescribing, have loosened the controls and increased the rate of diversion and abuse (226).

3.8.1 Drug Enforcement Administration

The Drug Enforcement Adminstration (DEA), as an agency within the United States Department of Justice, is the lead federal law enforcement agency responsible for enforcing the Controlled Substance Act (CSA). In cooperation with state authorities and other federal agencies, the DEA is responsible for preventing the diversion of controlled substances for illicit purposes. However, the DEA must comply with international treaties to the extent that they are not in conflict with constitutional provisions; it must also work closely with foreign, state, and local governments. The DEA has increased its monitoring of internet prescription drug sales. DEA investigations, enforcement, and intelligence programs have started to work more closely with other federal, state, and local agencies to target individuals and organizations involved in diversion and abuse of controlled prescription drugs.

High-profile arrests and prosecutions focus physicians' attention on the risks entailed in prescribing controlled substances in general, and have the specific effect of increasing physicians' and pharmacists' reluctance to prescribe, stock, or dispense opioid analgesics (227). However, a study published in 2006 looked at DEA arrest records in an effort to gauge the actual risk of DEA action (228). The review of the arrests and administrative actions of the DEA during fiscal year 2003 and 2004 showed that of the 963,385 physician registrants, there were 557 investigations with 6 civil fines, 22 letters of admonition, 21 administrative hearings, 34 license revocations, and 45 arrests.

3.8.2 State Laws and Regulations

Neither the DEA nor the federal government has the authority to regulate medical practice; this is the sole responsibility of the state government. States can require that a drug prescription be filled within a specified amount of time after it is written, and they can classify drugs at a higher level of abuse risk than the CSA schedule or place the drug on a state controlled substance list if not on the CSA list. State policies may conflict with or hamper the implementation of current treatment guidelines for the management of pain by limiting the amounts of opioid medications that can be prescribed, requiring special government-issued prescription forms, using outdated terminology, considering opioids only as the treatment of last resort, and suggesting incorrectly that the therapeutic use of opioids hastens death (229). State medical boards can address physician concerns about regulatory scrutiny and promote the balance between opioid benefits and risks. Before 1989, only a few state medical boards developed policies governing the use of controlled substances (230). Since then, 41 states have adopted such policies, which include regulations that have the force of law, as well as guidelines and policy statements.

3.8.3 Prescription Drug Monitoring Programs

States began to address the misuse and abuse of prescription medications in the 1940s by creating programs to monitor the dispensing of prescription drugs (3). These early programs required physicians to use special multiple-copy, 2- or 3-part prescription order forms, with a copy sent to a state monitoring program, and they only monitored Schedule II drugs. By 1999, 15 states had adopted prescription drug monitoring programs; but they were quite diverse. By the 1990s some programs were able to initiate electronic reporting, but, paper or electronic, most still used a variety of triggers such as number of prescriptions written or volume of medications prescribed to "flag" physicians or patients for further investigation. Kentucky established the Kentucky All Scheduled Prescription Electronic Reporting program (KASPER), an effective program that was limited by the 7 border states that surround Kentucky, allowing patients to take their prescriptions across state lines to thwart the program.

President Bush signed the National All Scheduled Prescription Electronic Reporting (NASPER) Act on August 11, 2005, making it the only statutorily authorized program to assist states in combating prescription drug abuse of controlled substances through a PDMP, and authorizing the U.S. Department of Health and Human Services (HHS) to award grants to States to construct prescription drug monitoring programs (PDMPs) and enhance communications between existing ones. Unfortunately, funding has not been provided for this activity (3).

A review of monitoring opioid adherence in chronic pain patients describes PDMPs (159). However, the effect and effectiveness of PDMPs is difficult to ascertain. The Medical Expenditure Panel survey showed

an effect from prescription drug monitoring programs on opioid prescriptions with 3% of people in a non-PDMP state purchased at least one Schedule II analgesic, compared to 1.6% in states that had a PDMP. A number of techniques, instruments, and tools have been described to monitor controlled substance use and abuse (159). Even though multiple factors may be involved in drug misuse and abuse, no single instrument or assessment method has universal evaluative or predictive utility. Thus, multiple techniques and tools are available, and have been used to monitor adherence. These include various screening tests, urine drug testing, and prescription monitoring programs. Each of these methods have some relative validity and utility in assessing patterns of drug use, misuse, abuse, and/or the potential occurrence of addiction. Consequently, it is important for the clinician to determine whether to assess compliance, misuse, abuse, and/or addiction, so that the appropriate evaluative methods can be employed.

4.0 Pharmacological Considerations

Opioids are analgesics compounds that attach to and modulate ascending and descending pain related pathways (231). Opioids may be classified by their function as agonists, mixed agonists-antagonists, or antagonists, and by their actions at opioid receptors, mu, kappa, and delta (231,232). Compounds can have differing degrees of affinity and efficacy at these various receptors (233).

4.1 Opioid Pharmacology

Opiates are naturally occurring alkaloids, such as morphine from the opium poppy seed. Opioid is the term used broadly to describe all compounds that exert activity at the opioid receptor. The term narcotic derives from the Greek word for stupor (227).

4.1.1 Opioid Receptors

There are opioid receptors within the central nervous system as well as throughout the peripheral tissues. These receptors are normally stimulated by endogenous peptides (endorphins, enkephalins, and dynorphins) produced in response to noxious stimulation. In addition, peripherally acting opioids (234) and combination of opioid analgesics have been described (235). Table 9 provides opioid receptors, related indigenous peptides, agonists, agonist/antagonist, and antagonists.

The opioid receptors were discovered in 1972, and the first endogenous opioid (enkephalin) was discovered in 1975. Their location in the CNS allows them to function as neurotransmitters, altering hormone secretion, thermoregulation, and cardiovascular control.

Opioids are classified by their action. These agents exhibit varying degrees of receptor affinity and efficacy, and can be pure agonist, agonist/antagonist, or antagonist.

Pure opioid agonists (e.g., morphine, hydromorphone, fentanyl) stimulate mu receptors and are the most potent analgesics. As the dose is increased, analgesia occurs in a log linear fashion; the degree of analgesia induced is limited only by intolerable dose-related adverse effects. Partial agonists and agonist/antagonists (example, nalorphine) exhibit a ceiling effect on the degree of analgesia that they can produce. Antagonists, as the name implies, counteracts effects at the opioid receptor.

4.1.2 Opioid Categories

The DEA classifies opioids into schedules related to potential abuse, and not potency (Table 10).

There has been concern that the lower scheduled opioids (Schedule III and IV) might have a higher addictive potential than some of the higher scheduled opioids (Schedule II). In a recent study (236), it was suggested that shorter-acting opioids had a lower potential for abuse. They looked at 140 patients on long-acting opioids (Schedule II) compared to 687 patients on short-acting opioids and 225 patients on nonopioids. More of the long-acting opioid patients (38%) were discharged from the practice for non-compliance compared to the short-acting opioid patients (32%) or the nonopioid patients (30%). In another study (161) in an interventional pain management setting evaluating the abuse of prescription and illicit drugs in chronic pain patients receiving either short-acting (hydrocodone) or long-acting (methadone), they concluded that prescription drug abuse as well as illicit drug use was similar in both groups of patients.

4.1.3 Opioid Metabolism

Many of the side effects of opioids, as well as their effects, may be related to the opioid metabolites. Most of the metabolism of opioids occurs in the liver. The CYP450 enzymes are a super-family of heme-containing, microsomal drug-metabolizing enzymes that are important in the biosynthesis and degradation of a wide variety of endogenous compounds, chemicals, toxins, and medications. More than 2,700 individual members of the CYP450 super-family have been identified, and 57 cytochrome P450 enzymes are recognized in humans (237). CYP3A4 is the isoenzyme most frequently involved in drug metabolism, and accounts

Table 9. Illustration of activity of opioid receptors.

	Mu (μ)	Delta (Δ)	Kappa (κ)
	• Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	• Analgesia, spinal analgesia	• Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous Peptides			
Enkephalins	Agonist	Agonist	
β-Endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl, sufentanil,	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Agonist-antagonists			
Nalorphine	Antagonist		Agonist
Antagonists			
Naloxone	Antagonist	Weak Antagonist	Antagonist
Naltrexone	Antagonist	Weak Antagonist	Antagonist

Table 10. *DEA schedules of controlled drugs.*

Schedule	Criteria	Examples
I	No medical use; high addiction potential	Heroin, marijuana, PCP
II	Medical use; high addiction potential	Morphine, oxycodone, methadone, fentanyl, amphetamines
III	Medical use; moderate addiction potential	Hydrocodone, codeine, anabolic steroids
IV	Medical use; low abuse potential	Benzodiazepines, meprobamate, butorphanol, pentazocine, propoxyphene
V	Medical use; low abuse potential	Buprenex, phenergan with codeine

for approximately 50% of marketed drug metabolism, and levels of CYP3A4 may vary as much as 30-fold between individuals (238), leading to large variability in blood levels. The metabolism of more than 90% of the most clinically important medications can be accounted for by 7 CYP isozymes (3A4, 3A5, 1A2, 2C9, 2C19, 2D6, and 2E1) (239). CYP1A2, CYP2C8, and CYP2C9 make up about 10% of the enzymes, CYP2D6 and CYP2E1 each around 5%, and CYP2C19 around 1%. CYP2D6 is entirely absent in some populations; for example, 6–10% of Caucasians are 2D6 deficient (240), while other persons have high levels of this enzyme, leading to rapid metabolism of the medicines.

4.2 Adverse Effects

Complications due to opioid administration concern all medical practitioners (7,8). Commonly known side effects of opioids include constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction, muscle rigidity and myoclonus (may be present in 3 to 87% of cancer patients, may be mediated by glycine inhibition in the dorsal horn neurons, and may be treated by opioid reduction or rotation, as well as benzodiazepines and baclofen) (241,242), sleep disturbance (243) (morphine has been shown to reduce REM sleep via inhibition of acetylcholine release in the reticular activating formation (244), pyrexia, diminished

psychomotor performance (which appears to be more of a problem with acute rather than chronic use) (245), cognitive impairment (246), dizziness and sedation, all reflecting the effects of opioids at multiple organ systems (247). Psychostimulants may improve psychomotor performance scores and subjective drowsiness (248). An imbalance in the cholinergic/dopaminergic CNS system is felt to be the mechanism of opioid-induced delirium (244). Hyperalgesia is a gradual increase in neural response to repeated stimulation (249).

Adverse events, in general, appear to fall into 2 broad categories: non-life threatening and life threatening. Hydrocodone may cause sensorineural hearing loss due to possible genetic polymorphisms. More serious adverse events such as respiratory depression and death have been seen with the use of fentanyl buccal tablets for breakthrough pain. Drug deaths from opioids are a serious and increasing issue. Strong patient compliance with medical treatment programs is needed to prevent rare but life-threatening adverse events.

4.3 Drug Interactions

A drug interaction occurs when the amount or the action of a drug is altered by the administration of another drug or multiple drugs. Multiple hepatic drug interactions may influence opioid drug levels (8,231,232) as illustrated in Table 11.

4.4 Drug Conversions

While there have been multiple opioid conversion charts developed, none are reliable and none take into consideration the vast individual differences in effect and metabolism between patients and within medications. Brand name and generic medications may have significant differences in bioavailability, and metabolism of medications may be influenced by genetic polymorphism and dug interactions. It is therefore important to recognize that "equipotent" doses of medications may have very different degrees of analgesia and side effects. In general, to switch between medications, the clinician must calculate a rough equiva-

Table 11. *Drug interactions of opioids.*

Tricyclic antidepressants	Inhibit morphine glucuronidation leading to ⇑blood levels --- Nortriptyline inhibits noncompetitively --- Amitriptyline and clomipramine inhibit competitively
Methadone and morphine	⇓ metabolism of TCAs, leading to toxicity
Quinine	⇓ conversion of codeine to morphine leading to analgesia
Metoclopramide	Earlier peak plasma levels with controlled-released opioids
Meperidine	MAO inhibitors trigger hyperpyrexia
Propoxyphene	⇑ carbamazepine, doxepin, metoprolol, propranolol levels ⇓ excretion of benzodiazepines, leading to accumulation and overdose
Erythromycin	⇑ opioid effects
Venlafaxine	⇑ methadone levels
Rifampin Phenytoin Carbamazepine	⇓ methadone levels
Phenytoin Phenobarbital	⇓ meperidine levels
CY2D6 inhibitors	⇑ tramadol levels ⇓ analgesia from hydrocodone/codeine
CY2D6 substrates	⇑ tramadol levels because of competition for metabolism
CYP3A4 inhibitors	⇑ methadone levels
CYP3A4 inducers	⇓ methadone levels
Methadone and morphine	⇓ metabolism of desipramine, leading to toxicity

lent 24-hour dose, divide by the dosing schedule, and then "under-dose," especially with methadone, with subsequent titration to effect.

4.5 Opioid Therapy and Side Effects

Multiple reviews (231-235,250) described opioid pharmacology of agonists, antagonists, partial agonists, agonists and antagonists, peripherally-acting opioids, combination opioid analgesics, and variations in opioid responsiveness. Implications and side effects of long-term opioid therapy include opioid-induced immunologic effects, hormonal changes, hyperalgesia, sedation, sleep disturbances, psychomotor disturbances, constipation, bladder dysfunction, and cardiac effects (8). Opioid complications and side effects in detail along with appropriate management of these side effects were described (8).

5.0 Terminology of Abuse and Addiction

5.1 Introduction

The terminology related to abuse and addiction of opioids and other controlled substances is considered confusing and reflects lack of understanding of multiple issues related to abuse and addiction. There are 3 fundamental concepts related to addiction:

1) the determination of addiction rests with the user even though some drugs produce pleasurable reward:
2) addiction is a multidimensional disease with neurobiological and psychosocial dimensions: and
3) addiction is a phenomenon distinct from physical dependence and tolerance.

Addiction is related to the "reward center" located within the mesocorticolimbic dopamine systems in the brain (251). Up-regulation of cAMP pathways in the brain (locus coeruleus) and spinal cord leads to acute physical withdrawal symptoms when the administered opioid is reduced or stopped, resulting in excessive central norepinephrine release, and its manifestations (252). Addiction is therefore a physiologic response, influenced by a variety of psychosocial issues (such as depression and anxiety) as well as genetic issues (family history of addiction).

5.2 History

More than a century ago, the debate over how best to address the misuse and abuse of prescription medications began, at a time when the most commonly abused drugs were freely available (253). As an example, heroin (diacetyl morphine) was developed to help morphine addicts; "heroin was sold over the counter as a soothing syrup for colicky babies and cocaine was the reason a then-new beverage invented in an Atlanta pharmacy was called 'Coke' (254)."

5.3 Terminology

Despite significant growth in understanding of the scientific basis of addiction, definitions and diagnostic criteria based on obsolete conceptualization of addiction persist. The following terms have been defined by World Health Organization (WHO), DSM-IV, and United States Federal and State policies, and other organizations by means of consensus statements.

There continues to be confusion and misunderstanding concerning the term "addiction." The Controlled Substance Act defined addiction as a term meaning any individual who habitually uses any narcotic drug so as to endanger the public morals, health, safety, or welfare or who is so far addicted to the use of narcotic drugs as to have lost the power of self-control with reference to his or her addiction (255).

5.3.1 Substance Abuse

DSM-IV defines substance abuse as a maladaptive pattern of substance use leading to significant impairment or distress in the last 12 months with one (or more) events such as failure to fulfill major role obligations, using inappropriate substances, participating in hazardous situations, being involved in recurrent substance related legal problems, and/or continuing use in the face of adverse consequences.

5.3.2 Substance Dependence

DSM-IV defines substance dependence as a maladaptive pattern of substance use leading to significant impairment or distress in the last 12 months meeting the criteria for substance abuse plus 3 or more of the following 7 criteria during the same 12-month period: tolerance, withdrawal, inability to control use, unsuccessful attempts to decrease or discontinue use, a great deal of time lost in obtaining the substance, using the substance, or recovering from its effects, important activities are given up because of use, continued use despite physical or psychological problems caused by use, and continued use of a substance.

5.3.3 Tolerance

The need for an increased dosage of a drug to produce the same level of analgesia that previously existed is defined as tolerance. Tolerance also suspect-

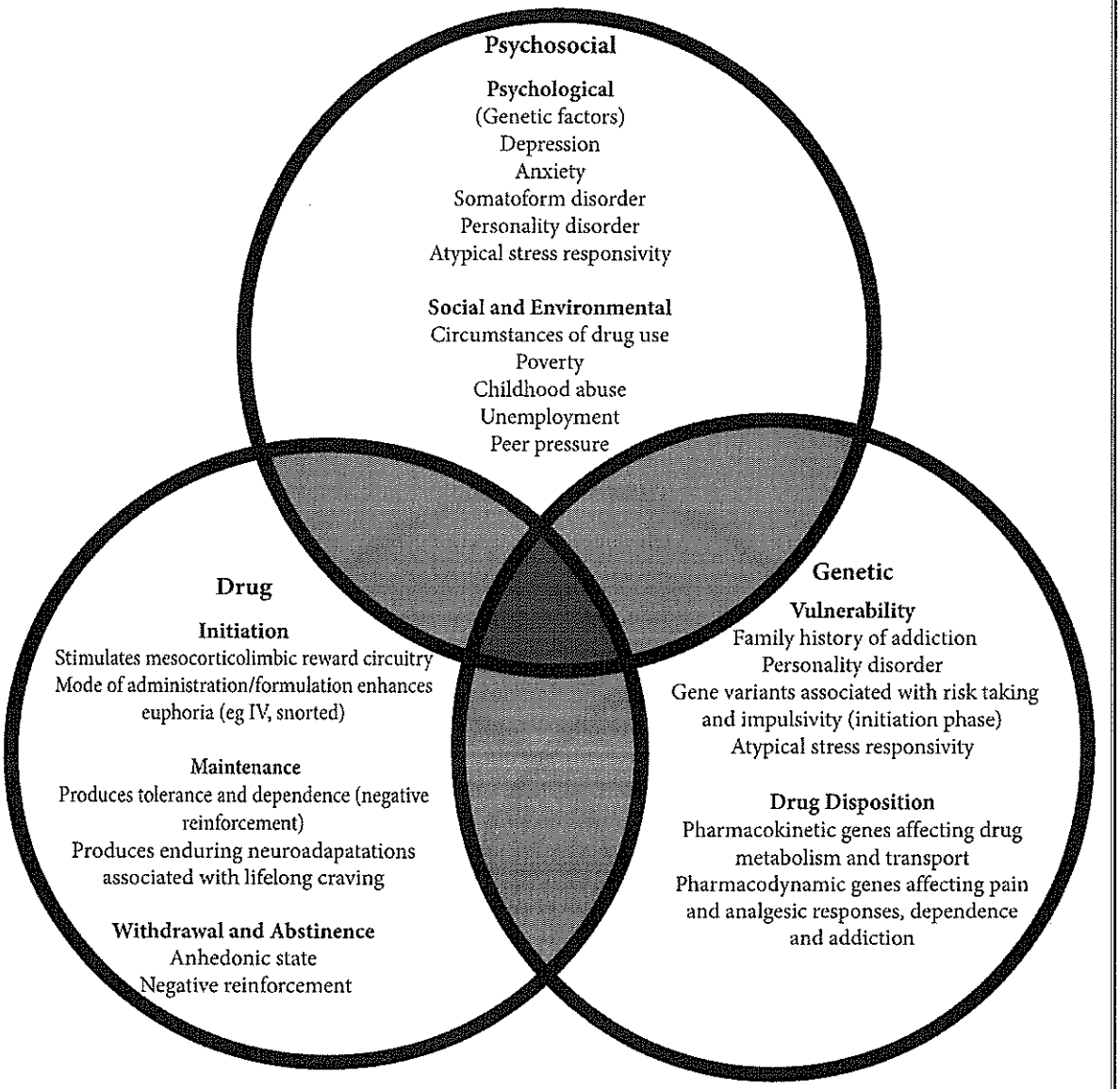


Fig. 5. *Contributions to addiction.*
Adapted from Ballantyne (6). Opioid analgesia: Perspectives on right use and utility. *Pain Physician* 2007; 10:479-491.

ed when a reduced physiologic effect is observed with constant dosing. Analgesic tolerance is not always evident during opioid treatment, and is not to be confused with addiction, which occurs as a dysfunctional craving of a drug action by physiologic action and psychologically driven factors.

5.3.4 Withdrawal

Withdrawal describes a characteristic set of symptoms that occur when a substance is withdrawn, and those symptoms disappear when the substance is reintroduced.

5.3.5 Physical Dependence

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by a drug cessation, rapid dose reduction, decreasing blood level of the

drug, and/or administration of an antagonist. Physical dependence is a normal adaptation to the drug, reinforced by continued use. Physical dependence is most commonly associated with withdrawal symptoms when the substance is abruptly discontinued, and is seen in many classes of medication not associated with addiction, such as beta blockers.

5.3.6 Addiction

In contrast to tolerance, withdrawal, and physical dependence, addiction is compulsive use of a drug despite physical harm, and the terms tolerance and addiction are not interchangeable. The terminology may share similar characteristics, as many addicts do become tolerant of their chosen drug, which can be expected with regular use. Addiction is a dysfunctional use behavior that includes one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving, while tolerance is a physiologic alteration of metabolism.

In a chronic pain state, a patient may be exposed to a controlled substance for a prolonged period of time, developing tolerance and physical dependence. Addiction may occur, but is an unlikely event. Dependence does not foreshadow harm, or intent at self-destructive behavior. It is therefore, incumbent upon the pain management physician to determine that these definitions and their physiologic undertones are well understood, and that the overlap of these definitions does not necessarily define a controlled substance risk or an inappropriate patient. In other words, tolerance and dependence share many common physiologic characteristics, and addiction may be associated with, but not defined by, either or both. Physical dependence, addiction, and tolerance are physiologic, social, and psychological considerations with prolonged substance management.

5.4 Opioid Agonist Therapy

Opioid agonist therapy (OAT) is a term used when a prescribed drug is given to occupy the receptor sites that otherwise would respond to an illicit agent such as heroin (229). OAT is a widely accepted medical treatment for opioid addiction, with efficacy that has been documented in many studies over many years (256). The best-known and most widely used form of OAT involves methadone maintenance treatment (MMT), though a second and newer form of OAT employs buprenorphine (a partial agonist), which is able to block the effects of morphine and other opioids, while offering mild opioid-like effects (232,257).

6.0 Clinical Effectiveness

6.1 Introduction

Considerable controversy over the prescription of opioids for chronic non-cancer pain continues despite the growing acceptance of this practice and claims that pain is undertreated. WHO developed a step-ladder approach to the management of pain. It recommends nonopioid analgesics initially, and then suggests the addition of mild opioids (e.g., hydrocodone) for mild to moderate pain, reserving strong opioids such as morphine for severe pain (258). In addition, opioids have been endorsed by multiple societies and advocacy organizations as appropriate treatment for refractory chronic non-cancer pain in the general population, when used judiciously and according to guidelines similar to those used for cancer patients. The DEA has also taken the position that clinicians should be knowledgeable about using opioids to treat pain, and should not hesitate to prescribe them when opioids are the best clinical choice of treatment (255). However, these endorsements of opioids in chronic non-cancer pain vary widely based on the philosophy of organizations, advocacy, ethical, and financial interests. Variations are evident with regards to the selection criteria, documentation, drug dosages, frequency, duration, and break through pain management. While all agree that opioids are indicated in cancer pain, numerous questions continue to arise about opioid usage in non-cancer pain on a long-term basis. Consequently, there is wide disagreement on who should be treated, how much should be provided, and who should be monitoring the controlled substances, their abuse, diversion, and side effects.

The clinical effectiveness of opioid medications for non-cancer pain in humans is difficult to measure. Since the publication of the ASIPP Opioid Guidelines by Trescot et al (1) in 2006, several new studies, including systematic reviews, observational studies, and controlled trials, evaluated the clinical effectiveness of medications.

6.2 Systematic Reviews

As illustrated in Table 3 and Fig. 1, from 1997 to 2006 the use of methadone increased exponentially followed by oxycodone, fentanyl base, hydromorphone, hydrocodone, morphine, and codeine. However, the highest use of per milligram per person in the United States for 2006 was methadone followed by oxycodone, fentanyl, hydrocodone, and morphine (Table 4).

Further, the proportion of the highest use of opioids is oxycodone, followed by hydrocodone, whereas the highest growth is in methadone with an increase of 1,129% from 1997 to 2006 (Table 4) (5).

The available evidence is highly variable. There is literature support for long-term use of opioids in chronic non-cancer pain with improvement in function and reduction in pain for longer than 6 months for transdermal fentanyl and sustained-release morphine (albeit weak) (9,19). However, the evidence is limited for the most commonly used opioid, i.e., oxycodone, in the United States. Further, for the second most commonly used opioid in the United States, hydrocodone, the evidence is non-existent. The evidence for methadone and other drugs is also non-existent. This lack of evidence for the most commonly used opioids and weak evidence for morphine and transdermal fentanyl are insurmountable factors in the synthesis of evidence-based guidelines for opioid use for long-term management of chronic non-cancer pain.

Noble et al (9) in a systematic review and meta-analysis of efficacy and safety of long-term opioid therapy for chronic non-cancer pain, published in 2008, reviewed the clinical evidence on patients treated with opioids for chronic non-cancer pain for at least 6 months. They identified 115 studies from 11 databases until April 7, 2007. Of these, 17 studies met the inclusion criteria. Seven studies of 1,504 patients evaluated oral opioids (259-265), whereas 3 studies with 1,993 patients (259,266,267) evaluated transdermal opioids. Table 12 illustrates characteristics of the included studies in the evaluation of long-term ef-

Table 12. *Characteristics of included studies in evaluation of the long-term effectiveness by Noble et al (9).*

Reference	Opioid	Type of Predominant Pain	Number of Patients Enrolled	Outcomes Used in Evidence Synthesis			
				Withdrawal Due to Adverse Events	Withdrawal Due to Insufficient Pain Relief	Pain	
						Continuous/ Categorical	>50% Relief
Oral Administration							
Allan et al (259)	Morphinea	Low back pain	342	✓	✓	b	✓
Caldwell et al (260)	Morphinea	Osteoarthritis	(295)c181	✓	✓	d	
Harati et al (261)	Tramadol	Diabetic neuropathy	(131)c117	✓	✓	✓	
Fredheim et al (262)	Methadone	Low back pain	12	✓	✓	e	
McIlwain and Ahdieh (263)	Extended-release oxymorphone	Osteoarthritis	(491)c153	✓	✓	✓	
Roth et al (264)	Controlled-release oxycodone	Osteoarthritis	(133)c106	✓	✓	✓	
Zenz et al (265)	Dihydrocodeine,a buprenorphine, or morphinea	Neuropathic or back pain	100		✓		✓
Transdermal Administration							
Allan et al (259)	Fentanyl	Low back pain	338	✓	✓	b	
Milligan et al (266)	Fentanyl	Unspecified	532	✓	✓	f	
Mystakidou et al (267)	Fentanyl	Unspecified	529	✓	✓	✓	

a Sustained release.
b Not analyzed because of number of patients at follow-up times not reported.
c N in parentheses denotes number of patients randomized in original RCT; second number is that enrolled in open-label extension.
d Not meta-analyzed because reported units are statistically incompatible with the 3 other studies meeting inclusion criteria.
e Not analyzed because data were reported for fewer than 10 patients at follow-up times.
f Not analyzed because instrument used not validated.

Adapted and modified from Noble et al (9). Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage* 2008; 35:214-228.

fectiveness of morphine and transdermal fentanyl by Noble et al (9). Trescot et al (19) evaluated specifically the role long-term opioid therapy.

Tables 13 and 14 illustrate effectiveness of long-term sustained-release morphine and transdermal fentanyl. They concluded that sustained-released morphine and transdermal fentanyl provided weak

Table 13. *Results of studies evaluating the long-term effectiveness of morphine.*

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Allan et al (259) Open, randomized, parallel group multicenter study 13 months	Chronic low back pain N=680	Sustained release oral morphine versus transdermal fentanyl	Pain relief, bowel function, quality of life, disease progression, and side effects	Significant proportion of patients on sustained release morphine experienced pain relief	Sustained release strong opioids can safely be used in opioid naïve patients	Most common adverse events leading to discontinuation were nausea (37%), vomiting and constipation.
Caldwell et al (260) Double-blind trial, followed by open-label extension trial	184 with chronic osteoarthritis 181 patients entered the open-label trial	Placebo, Avinza, or MS Contin in double-blind trial	Pain relief; physical functioning; stiffness	Significant improvement in pain relief and sleep measures	Efficacy was comparable between two modes of administration.	Most common adverse effects were constipation and nausea
Zenz et al (265) Narrative descriptive report	100 patients who were chronically given opioids for treatment of nonmalignant pain, with 23 patients receiving morphine SR	Sustained release morphine, sustained release dihydrocodeine, buprenorphine	VAS, Karnofsky Performance Status Scale used to assess function	Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy	Results indicate that opioids can be effective in chronic nonmalignant pain, with side effects that are comparable to those that complicate the treatment of cancer pain	Common side effects were constipation and nausea
Maier et al (296) Narrative descriptive report	121 patients with chronic non-cancer pain	Sustained release morphine	Pain relief and quality of life	Significantly lower pain intensity and improved physical state and quality of life	Pain relief correlated with improvement in functional status	There was no development of tolerance
Tassain et al (297) Long-term prospective study	28 chronic non-cancer pain patients, 18 received oral sustained morphine, 10 patients stopped morphine due to side effects and were followed as control group	Oral sustained morphine	Pain relief and cognitive functioning Follow-up period of 12 months	Morphine produced persistent pain relief and improved quality of life and mood	There was no impairment of any neuropsychological variables over time	Side effects included constipation, loss of appetite, nausea, dry mouth, drowsiness, somnolence, fatigue, subjective memory impairment, sweating, and pruritus

Adapted from Trescot et al (19). Effectiveness of opioids in the treatment of chronic non-cancer pain. Pain Physician 2008; 11:S181-S200.

Table 14. *Results of studies evaluating long-term effectiveness of transdermal fentanyl.*

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Allan et al (259) Open, randomized, parallel group multicenter study 13 months	338 patients were studied with transdermal fentanyl with chronic low back pain	Evaluation of transdermal fentanyl in strong-opioid naïve patients with chronic low back pain	Pain relief, bowel function, quality of life, disease progression, and side effects	Transdermal fentanyl provided significant pain relief	Transdermal fentanyl can safely be used in opioid naïve patients	Most common side effects included constipation, nausea, and vomiting
Milligan et al (266) International, multicenter, open label trial	532 pts w/ chronic non-cancer pain studied over 12 months 51% completed trial. 25% withdrew because of adverse events	Transdermal fentanyl compared to previous medication (over 40 different opioids)	Preference of medication, pain control, SF-36, global satisfaction, requirement for break-through pain	67% rated pain relief as very good to moderate on transdermal fentanyl, 86% preferred transdermal fentanyl, SF-36 showed improvement for body pain only	Long-term treatment with transdermal fentanyl offered majority of patients at least moderate relief	Nausea 31%; constipation 19%; somnolence 18%; respiratory depression, abuse, or less 1%; withdrawal 3%
Mystakidou et al (267) Prospective open-label study	529 patients being treated with oral codeine or oral morphine	Transdermal therapeutic system fentanyl	Quality of Life-Short Form 12	Transdermal therapeutic system-fentanyl significantly improves quality of life within 28 days, and pain management within 48 hours	Transdermal therapeutic system-fentanyl is a safe and effective pain management	Side effects, with constipation (range 4.6%-23.1%) and nausea were the most frequent

Adapted from Trescot et al (19). Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008; 11:S181-S200.

evidence for improvement in physical status and decrease in pain on a long-term basis, whereas, tramadol provided weak evidence in osteoarthritis patients. However, the most commonly used, oxycodone, provided only limited evidence, while, the second most commonly used, hydrocodone, had no published evidence. Similarly, other commonly used opioids had no published evidence of effectiveness with long-term therapy.

Overall, many patients withdrew from the clinical trials due to adverse effects with 32.5% with oral therapy and 17.5% with transdermal therapy; 11.9% in the oral therapy group and 5.8% in the transdermal group withdrew due to insufficient pain relief. They concluded that there was an insufficient amount of data on transdermal opioids to quantify pain relief. For patients able to maintain on oral or intrathecal opioids for at least 6 months, pain scores were reduced long-term with a 38% mean reduction in pain scores in the intrathecal group and 63.4% mean reduction in pain scores in oral opioid group when treatment lasted 6–18 months. However, there was substantial heterogenicity in the oral studies, which could not be resolved using meta-regression by follow-up time. Further, the summary effect estimate of pain relief from oral opiates was not robust to sensitivity analysis. Consequently, due to lack of robustness upon sensitivity analysis and unexplained heterogenicity, the quantitative estimates of the amount of pain relief associated with opioid therapy may be unstable. Even then,

long-term opioids were associated with some degree of pain relief. Many patients in the included studies were so dissatisfied with adverse events or insufficient pain relief from opioids that they withdrew from the studies. Even then, for patients able to continue on opioids, evidence (albeit weak) suggested that their pain scores were lower than before therapy began and that this relief would be maintained long-term over 6 months. The data describing long-term safety and efficacy of opioids was insufficient, providing only weak evidence. The evaluations shown for oral opioids (259-265) studied the effectiveness of morphine in 2 studies (259,260), tramadol in one study (261), methadone in one study (262), extended-release oxymorphone in one study (263), controlled-release oxycodone in one study (264), and dihydrocodeine, buprenorphine and morphine in one study (265). Thus, overall morphine was studied in 2 studies and all others in one; however, hydrocodone was not studied. Transdermal studies included only fentanyl (259,266,267).

The first systematic review of comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain was published by Chou et al (11), the Oregon Health Resources Commission (OHRC). A total of 16 randomized trials evaluating comparative efficacy and adverse events, enrolling 1,427 patients, and 8 observational studies of adverse events of 1,190 patients were included in this review through October 2002. They were unable to rate any randomized trial as good quality, whereas observational studies were generally of poorer quality than randomized trials. They concluded that there was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or safety profiles. Further, there was also insufficient evidence to determine whether long-acting as a class are more effective or safer than short-acting opioids. They found a subgroup of 3 studies on long-acting versus short-acting oxycodone was more homogenous and provided fair evidence that these formulations were equally effective for pain control (268-270). They included studies with evaluation for as early as 6 days and the longest in randomized trials was 16 weeks. In this study, 2 of the 16 trials compared one long-acting opioid to another one (260,271), one of the trials (271) compared transdermal fentanyl to long-acting morphine, whereas the second trial (260) compared a once daily morphine preparation to a twice daily morphine preparation. Seven trials compared a long-acting opioid to a short-acting opioid (268-270,272-275), and 7 compared a long-acting opioid to a nonopioid or placebo (264,276-281). They identified trials on long-acting oxycodone (264,268-270,281), long-acting morphine (260,271,274,277-279), long-acting dihydrocodeine (273,275), long-acting codeine (272,276,280), and transdermal fentanyl (271). The authors did not identify any trials on methadone, levorphanol, and hydrocodone. The average of enrollment in these trials was 79, which ranged from 12 (278) to 295 (260). Only 3 trials evaluated heterogenous chronic non-cancer pain (271,276,279), whereas 5 trials focused on back pain (269,270,273,274). Two trials focused on neuropathic pain (277,281) and 5 trials focused on osteoarthritis (260,263,268,275,280) with only one study focusing on phantom limb pain (278). All of the trials were of relatively short duration, ranging from 5 days (272) to 16 weeks (274). Thus, these results may not even be applied to chronic pain management settings. Even then, withdrawal rates ranged from 0% to 45%.

In a systematic review of opioid treatment for chronic back pain evaluating prevalence, efficacy, and association with addiction, Martell et al (10) evaluated multiple studies through 2005 and concluded that opioids are commonly prescribed for chronic back pain and maybe efficacious for short-term pain relief. However, long-term efficacy of more than 16 weeks was reported to be unclear. They also reported substance use disorders were common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24% of cases. Thus, this systematic review also has not provided any long-term evidence for opioid therapy of longer than 6 months.

Kalso et al (12) analyzed available randomized, placebo-controlled trials of the WHO step 3 opioids for efficacy and safety in chronic non-cancer pain through September 2003. Among the 15 randomized placebo-controlled trials they identified, 11 studies with 1,025 patients compared oral opioids with placebo for 4 days to 8 weeks. However, 8 of the 14 included trials had an open-label follow-up, 4 of oral morphine, 3 of oral oxycodone, and 1 of fentanyl (282-289). The mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain. About 80% of patients experienced at least one adverse event with constipation (41%), nausea (32%), and somnolence (29%) being most common. Only 44% of the 388 patients on open-label treatment were still on opioids after therapy for between 7 and 24 months. They concluded that the short-term efficacy of opioids was good in both neuro-

pathic and musculoskeletal pain conditions, whereas, only a minority of patients in these studies were onto long-term management with opioids, precluding any conclusion with regards to effectiveness on a long-term basis. Overall, they concluded that the mean relief with opioid was about 30%. The lowest maximum doses, morphine 30 mg and oxycodone 20 mg daily were used in musculoskeletal pain and were not effective. Only 3 of the 8 studies found improvement in function or disability.

Furlan et al (13) also performed a meta-analysis of effectiveness and side effects of opioids with the inclusion of 41 randomized trials involving 6,019 patients with 80% of the patients suffering with nociceptive pain of osteoarthritis, rheumatoid arthritis, or back pain; 12% with neuropathic pain of post herpetic neuralgia, diabetic neuropathy, or phantom limb pain; 7% fibromyalgia; and 1% with mixed pain. They reported methodological quality of 87% of the studies as high. They also classified opioids as weak, which included tramadol, propoxyphene, and codeine or strong, which included morphine and oxycodone. However, hydrocodone was not included in either category. In this meta-analysis, they found that dropout rates averaged 33% in the opioid groups and 38% in the placebo group with average duration of treatment of 5 weeks, ranging from 1 to 16 weeks.

Ballantyne (6) and Ballantyne and Mao (14) performed a review of opioid therapy for chronic pain. In their review, they included 8 studies evaluating for 4 weeks or less, 7 studies for 12 weeks or less, and only 2 studies evaluated for a period of 14 weeks or longer with the longest duration being 24 weeks. They concluded that the only knowledge of long-term analgesic efficacy comes from surveys, case series, open-label follow-up studies in association with some RCTs, and epidemiological studies. Further, they concluded that surprisingly, only a few of the existing opioid studies have focused on function and quality of life.

Sandoval et al (18) performed a systematic review of methadone involving 21 papers with 545 patients with multiple non-cancer pain conditions. The methadone starting dose ranged from 0.2 mg to 80 mg per day with maximum doses of 20 mg to 930 mg per day. They reported statistical improvement in pain for methadone with 20 mg per day compared to placebo in 59% of the cases, side effects in 225 patients with nausea and/or vomiting in 23%, sedation in 18%, itching and/or rash in 13%, and constipation in 11% The results of oral methadone for chronic non-cancer pain are illustrated in Table 15 (18,290-294).

Cepeda et al (17) performed a systematic review and meta-analysis of 11 RCTs to determine the analgesic effectiveness, effect on physical function, the duration of benefit and safety of oral tramadol in patients with osteoarthritis. The study only included RCTs that evaluated the effect of tramadol or tramadol plus acetaminophen on pain levels in patients with opioid addiction (OA). Studies that evaluated other types of arthritis (e.g., rheumatoid arthritis), non-osteoarthritic joint pain, or back pain were excluded. The study concluded that tramadol is more effective than placebo for the treatment of OA when pain is moderate. However, when OA pain is severe, there is only a small benefit to the patient. The study also notes that tramadol tolerability is increased when a slow titration regimen is implemented (e.g. 100 mg/day for 7–10 days, then 200 mg/day). The study found this approach halves the proportion of people who interrupt therapy because of adverse events. Since only 2 studies evaluated tramadol for more than 8 weeks, the authors were unable to determine whether the clinical effectiveness of tramadol decreases with chronic use. Finally, another noted limitation was that only one of the 11 systematic reviews included in this study was not industry funded. Thus, it is possible for an overestimation of treatment effects of tramadol in patients with osteoarthritis.

Eisenberg et al (15) in a systematic review of opioids for neuropathic pain included 23 trials with 267 patients for short-term and 460 patients for intermediate term defining short-term as less than 8 days and intermediate term as 8 days to 10 weeks. They evaluated short-term trials of morphine, alfentanil, fentanyl, meperidine, and codeine, whereas, intermediate trial studies included morphine, oxycodone, methadone, and levorphanol. They reported mixed results with short-term trials of less than 8 days, whereas intermediate trials of 8 days to 10 weeks showing consistent opioid analgesic efficacy. They also reported nausea in 33%, constipation in 33%, drowsiness in 29%, dizziness in 21%, and vomiting in 15% with withdrawals in 11% of the patients.

Based on the information available from an extensive review of the literature, it appears that it is necessary to utilize less rigorous forms of evidence to evaluate long-term effectiveness, since it is not feasible to conduct RCTs over prolonged periods. Even in the open studies of long-term effectiveness, as many as 56% of patients abandon the treatment because

Table 15. *Characteristics of case series evaluating the effectiveness of methadone over 6 months.*

Study	Participants	Intervention	Outcomes	Effectiveness (no. Patients)
Robbins (290) Ambulatory setting	66 patients (53 F, 13 M), ages 26 to 58 y/o, with chronic headaches. Indication for methadone was ineffective pain relief with previous treatments: NSAIDs, calcium channel blockers, beta-blockers, valproate, and antidepressants	Average dose was 10 mg/day. Co-interventions: not described. Time: 6 months Side effects: fatigue, confusion nausea, constipation, profuse sweating, lightheaded/ dizziness, and rash	Pain relief scale: 1-25% = no relief: 27 patients (41%) 25-50% = mild relief*: 5 patients (8%) 50–75% = moderate relief: 16 patients (24%) 75-100% = excellent relief: 18 patients (27%)	Meaningful = 34 Non-meaningful = 32 Unclassifiable = 0
Robbins (291) Ambulatory setting	148 patients. Only 42 remained on methadone after 6-mos period (33 F, 9 M). With chronic daily headache refractory to standard therapies such as NSAIDs, calcium channel blockers, divalproex, antidepressants, and methysergide	Average dose was 10 mg/day. Co-interventions: not described. Time: 6 months Complications and side effects: not described	42 reported moderate or excellent relief. Quality of work and home life in these 42 patients: 86% of patients had improvement in work performance; 71% improvement in relationship with partner; 81% improvement in relationship with children and friends; 60% improvement in sexuality	Meaningful = 42 Non-meaningful = 106 Unclassifiable = 0
Mironer et al (292) Ambulatory setting	47 patients (18 F, 29 M), 57 y/o on average (from 29 to 88), with neuropathic pain. Indication for methadone was ineffectiveness with previous treatments: opioids, anticonvulsants, antidepressants, calcium channel blockers, intravenous and oral lidocaine, etc.	Average daily intake of methadone was 27 mg/day (range 10-60 mg/day) The most common co-intervention: gabapentin (12 patients). Duration of treatment varied from 6 to 37 months	Patients reported on average 30% to 90% pain relief, with 34 out of 47 having more than 50% improvement in their pain scores. Side effects: not significant	Meaningful = 47 Non-meaningful = 0 Unclassifiable = 0
Quang-Cantagrel et al (293) Ambulatory setting	Methadone was given to 29 patients out of 86 (50 F, 36 M) with various non-cancer pain syndromes (back pain neuropathy: joint pain, visceral pain, reflex sympathetic dystrophy, headache, and fibromyalgia Indication for methadone was ineffectiveness with previous treatments	Doses of methadone were 39.0 6 17.0 mg/day. Co-interventions: not described. Duration of the treatment was an average of 49.4 wks	There was 1 case of addiction and no case of tolerance Complications and side effects (52%) included: nausea, vomiting, sedation, itching, and kidney alterations	Meaningful = 8 Non-meaningful = 21 Unclassifiable = 0
Moulin et al (294) Ambulatory setting	50 patients (22 F, 28 M) with mean age of 52.7 and a variety of intractable neuropathic pains. The indications were ineffectiveness of previous medications and side effects	Initial dose of 20 mg/day. Maximum dose 160 mg/ day Maintenance dose 121 mg/day. Co-interventions: tricyclic antidepressants, NSAIDs, SSRI, benzodiazepines, and anticonvulsants. Mean duration of treatment: 17.3 months	26 (52%) improved with methadone: 3 mild, 16 moderate, 6 marked, and 1 complete pain relief 16 patients (32%) reported improvement in function Complications and side effects: not described	Meaningful = 23 Non-meaningful = 27 Unclassifiable = 0

Adapted from Trescot et al (19). Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008; 11:S181-S200.

of lack of efficacy or side effects (9,12). In addition, it has been described that many opioid trials utilize enrichment in their protocols with removal of patients who do not respond, also known as selecting out during the pre-trial phase with an additional unusually high drop-out rate across opioid trials during enrichment, compromising the internal validity of these trials (6,295). Further, functional status improvement has been studied meagerly and the results have been poor.

6.2.1 Effectiveness of Individual Drugs

In the United States, the most commonly used therapeutic opioids in the order of maximum use are as follows: oxycodone, hydrocodone, codeine, morphine, and methadone. Transdermal fentanyl is the least used opioid behind meperidine and hydromorphone. However, the available evidence is better for sustained-release morphine and transdermal fentanyl, compared to all other drugs, though weak.

Morphine

Allan et al (259) evaluated sustained release oral morphine in 342 strong-opioid naïve patients with chronic low back pain with assessment of pain relief, quality of life, disease progression, and side effects, including bowel function. Sustained release morphine provided significant improvement of mean VAS scores for patients who remained in the study for 56 weeks. However, use of concomitant, strong, short-acting opioids was frequent in 50% of the patients as rescue medication. While quality of life scores showed improvement in physical health, there was no significant difference with mental health. They concluded that strong opioids may be indicated for chronic low back pain that is not relieved by other forms of analgesia

Caldwell et al (260), in an open-label extension trial evaluated Avinza® an extended-release morphine formulation, in 181 patients during the 26-week open-label extension trial. Significant reductions in pain intensity and improved sleep measures were observed. However, improvements were not observed in physical function. Twenty-eight or 15% of patients were excluded entirely from the subset analysis due to concomitant therapy with NSAIDs and/or acetaminophen use. Constipation and nausea were the most frequent adverse effects reported in over 80% of the patients.

Zenz et al (265) evaluated long-term oral opioid therapy in 100 patients with chronic non-cancer pain, utilizing either sustained-release morphine, dihydrocodeine, or buprenorphine, with 23 patients in the morphine group. Good pain relief was obtained in 51 patients, partial pain relief was reported by 28 patients, and 21 patients reported no beneficial effect from opioid therapy. The most common side effects were constipation and nausea.

Maier et al (296) evaluated long-term efficacy of morphine in 121 patients with chronic non-cancer pain, 5 years after the onset of medical treatment. Frequency of withdrawal was 14.8% mainly due to lack of efficacy with an average treatment time of 66 months (37–105 months with 87% more than 5 years). The study showed that patients with long-term opioid intake exhibited significantly lower pain intensity and higher contentment with the pain management and improvement in physical status and quality of life. There were inconsistent changes in opioid dosages over the period of 5 years, without any change in 33% of the patients, with decrease in 16%, slight increase in 27%, and high increase in 19%. The survey demonstrated a very low frequency of withdrawal in patients with long-term opioid medication after initial response without evidence for tolerance development, especially if their treatment was controlled in a pain center.

Tassian et al (297) evaluated the long-term effects of sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Of the 28 patients initially included in the study, 18 patients received oral sustained morphine on a long-term basis with significant improvement in pain, function, and mood. Morphine induced persisting effects on pain, and to a lesser extent on quality of life and mood at 12 months, with no disruption of cognitive function.

Table 13 illustrates results of multiple studies evaluating the long-term effectiveness of morphine.

Transdermal Fentanyl

Allan et al (259) evaluated 338 patients with chronic low back pain with transdermal fentanyl for a period of 13 months.The proportion of patients experiencing a 50% or greater improvement in back pain was observed to be 40% in the patients with rest, 47% on movement and during the day, and 53% in patients at night. Concomitant medication with possible analgesic effect and rescue medication during the trial was seen in greater than 80% of the patients with 52% using strong opioids.

Milligan et al (266) evaluated long-term efficacy and safety of transdermal fentanyl in the treatment of chronic non-cancer pain in an international, multicenter, open-label trial over a period of 12 months,

with completion of the trial by 301 (57%) of the patients. An average of 67% of patients within the efficacy analysis group (n=524) reported very good, good, or moderate pain control, with global satisfaction reported in 42% of the patients. The majority (86%) of patients reported a preference for transdermal fentanyl over their previous treatment. There was significant improvement in the bodily pain scores of Short Form 36. The most frequent treatment-related adverse events were nausea (31%), constipation (19%), and somnolence (18%).

Mystakidou et al (267) evaluated the effectiveness of transdermal fentanyl in the long-term management of non-cancer pain, in 529 patients in a prospective open-label study. The mean duration of therapy for effective pain management was 10 months, and 90% of patients sustained effectiveness with improvement in quality of life scores and pain. Further, the improvements were not influenced by pain type or etiology.

Table 14 illustrates the results of studies evaluating long-term effectiveness of transdermal fentanyl.

Oxycodone

The effectiveness of oxycodone was evaluated in multiple studies (286,298-300).

Portenoy et al (300) looked at sustained release oxycodone use over a 3-year period in 233 non-cancer patients who had participated earlier in clinical trials regarding the same medication. At study's end, pain was the same or improved in 70% to 80% of the patients. They noted that approximately 50% of the patients stopped the opioids due to side effects in the first 6 months. Adverse effects were seen in 88% of the patients on sustained release oxycodone.

Rauck et al (298), in a randomized, open-label, multicenter trial, studied the effectiveness of sustained release oxycodone comparing it with sustained release morphine in 266 patients up to 8 months. Both groups showed significant improvement. The concluded that compared to twice daily sustained release oxycodone, once daily sustained release morphine resulted in significantly better physical function and quality of life.

Roth et al (264) studied 133 patients with osteoarthritis with follow-up lasting up to 6 months. Fifty-eight patients completed 6 months of treatment and 41 completed 12 months of follow-up, whereas 15 completed 18-month follow-up. They concluded that sustained release oxycodone provided sustained analgesia.

Hermos et al (299) in an observational review reported the results of 47,000 veterans receiving opioids through the VA system of which 2,200 received oxycodone for over 9 months however, 31% of these patients were diagnosed with cancer with mean daily doses of 3.9 tablets per day with a range of 0.5 to 13 with minimum change over time.

Table 16 illustrates the results of studies evaluating oxycodone.

Hydrocodone

There were no studies evaluating the effectiveness of hydrocodone even though this is the most commonly used drug.

Methadone

Fredheim et al (262) studied 8 chronic non-cancer patients experiencing insufficient pain control or intolerable side effects during treatment with oral morphine who switched to oral methadone. They showed that opioid switching from low doses of oral morphine to an equi-analgesic oral methadone causes a small but statistically significant increase in QTc time.

Fredheim et al (301) showed that, after switching 12 patients from morphine to methadone, their blood levels and metabolite levels remained steady for the 9-month study period, contradicting the hypothesis of metabolic tolerance and auto-induction of hepatic enzymes during long-term methadone therapy. However, they noted that the oral dose had a poor correlation with serum blood levels, confirming a large inter-individual variability of metabolism.

Sandoval et al (18), in a systematic review of oral methadone for chronic non-cancer pain described the effectiveness of methadone in multiple observational studies as shown in Table 15.

Tramadol

Cepeda et al (17) performed a systematic review and meta-analysis of multiple randomized trials.

Controlled-release tramadol was evaluated by Beaulieu et al (302) in a multi-center, randomized, double blind, double dummy, 8-week crossover study, comparing it to immediate release tramadol. Overall pain scores were significantly better with the controlled release formulation. Since tramadol has a serotonin and norepinephrine reuptake inhibition action, continuous dosing (such as seen with extended release formulations) would be expected to be more effective than intermittent dosing (since the intermediate dosing does not allow for accumulation of serotonin and norepinephrine).

Adams et al (303), in a study funded by Ortho-McNeil, performed a double blind, 12-month crossover trial, looking at 3 different treatment arms: tramadol alone, tramadol randomized against

Table 16. *Results of studies evaluating long-term effectiveness of oxycodone.*

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Rauck et al (298) Randomized, open-label, multicenter trial	Chronic, severe low back pain (n=266) Sustained release morphine vs. sustained release oxycodone Up to 8 months	Randomized to sustained release morphine (Avinza) or sustained release oxycodone (Oxycontin) period of dose titration, then 8 week evaluation and optional 4 month extension (n=174)	Short Form-12, Work Limitation Questionnaire	Improvements seen in both groups (> in sustained release morphine)	Compared to twice a day sustained release oxycodone, once daily sustained release morphine resulted in significantly better physical function and quality of life activities.	None described
Roth et al (264) Randomized, double blind, placebo controlled	133 patients with osteoarthritis 6 to 12 months 58 patients completed 6 months treatments, 41 completed 12 months, 15 completed 18 months	Sustained release oxycodone bid 10 mg (n=44) 20 m (n=44) vs placebo (n=45)	VAS, mood, sleep, quality of life	Mood and quality of life improved. Analgesia was maintained and dose was stable	Sustained release oxycodone provided sustained analgesia	Typical opioid side effects were noted and decreased over time
Hermos et al (299) Observational review	47,000 veterans receiving opioids through the VA system	Oxycodone with APAP; concurrent use of long acting narcotics, benzodiazepines, tricyclic antidepressants, and anti-epileptic drugs	Number of doses	About 2,200 received oxycodone with APAP for > 9 months (31% with diagnosis of cancer); mean daily dose 3.9 tabs/day (0.5-13.0) with minimal change over time	Among patients without cancer, patients with concurrent benzodiazepines, psychogenic pain, alcohol abuse, and HIV/AIDS had more prescription management problems	None described
Portenoy et al (300) Open label, uncontrolled registry	233 patients non-cancer pain Low back pain (68 patients) Neuropathic (67 patients) Osteoarthritis (84 patients)	Sustained release oxycodone 1 yr (141 pts) 2 yrs (86 pts) 3 yrs (39 pts)	Brief Pain Inventory Short Form, VAS, med acceptability, adverse events, aberrant drug behavior (abuse, misuse, withdrawal)	Brief Pain Inventory Short Form scores decreased after starting oxycodone. Pain scores improved in approximately 70 to 80% thru month 33 and 54% at month 36.	There need to be more data regarding efficacy of long-term opioids	Adverse events seen in 88% sustained release oxycodone. Constipation (15%), nausea (12%), somnolence (8%), vomiting (7%), depression (2%). 7 patients died, presumably not related to medication.

Adapted from Trescot et al (19). Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008; 11:S181-S200.

NSAIDs, and tramadol randomized against hydrocodone. They looked at pain scores, SF-36, and what they called an "abuse index." They found that the prevalence of abuse/dependence over the 12-month period was equal for the tramadol and NSAIDs, but, as expected, the hydrocodone had twice as much abuse.

Table 17 illustrates results of studies of tramadol.

Table 17. *Results of studies evaluating long-term effectiveness of tramadol.*

Study/methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Harati et al (261) 6-month open extension followed a 6-week double-blind randomized trial	117 with painful diabetic neuropathy A total of 117 patients (56 former tramadol and 61 former placebo) entered the study.	Tramadol	Self-administered pain intensity scores (scale 0-4; none to extreme pain) and pain relief scores (scale -1-4; worse to complete relief) were recorded the first day of the open extension (last day of the double-blind phase) and at 30, 90, and 180 days.	Tramadol reduced mean pain scores which were maintained throughout the study	Tramadol provides long-term relief of the pain of diabetic neuropathy	The most common adverse events were constipation, nausea, and headache
Adams et al (213) Prospective	A total of 11,352 subjects were enrolled	NSAIDs, tramadol, hydrocodone	Abuse	Tramadol was effective with less abuse potential than hydrocodone	These results support the hypothesis that the rate of abuse identified with tramadol is less than the rate associated with hydrocodone	None described
Beaulieu et al (302) Multicenter randomized double blind, double dummy, cross over trial of tramadol controlled-release and tramadol immediate-release	Chronic non cancer pain patients: (n= 122) Completed study: n=65 8 weeks	Pts randomized to 2 groups: active tramadol controlled-release + placebo 4-6 hours prn or placebo plus active tramadol immediate-release 4-6 hours prn for 4 weeks and then switched to alternate treatment for another 4 weeks	Pain intensity; pain disability index; sleep quality and quantity; analgesic effectiveness; adverse events at each visit	Overall pain intensity scores significantly better with controlled-release tramadol. No differences in total pain disability index, or overall pain and sleep scores	Significantly better pain control in chronic benign pain with tramadol controlled-release every 24 hours vs. Tramadol immediate-release every 4-6 hours prn Funded by Purdue Pharma	3 patients experienced serious adverse events. The only difference in adverse events was nausea seen more often in the tramadol controlled-release ($p<0.021$). 2 patients hospitalized with vomiting from the immediate-release group; one hospitalized for asthenia in the controlled-release group

Adapted from Trescot et al (19). Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008; 11:S181-S200.

Oxymorphone

Rauck et al (304) studied oxymorphone in an open-label 6-month study looking at efficacy and side effects. They reported 75% of patients could be stabilized on a dose of oxymorphone that provided effective pain relief with tolerable side effects.

McIlwain and Ahdieh (263), in a 52-week, multicenter open-label extension study of 153 patients with moderate to severe chronic osteoarthritis-related pain, showed improvement in pain. They found that oxymorphone ER provides a new 12-hour analgesic for the treatment of moderate to severe, chronic osteoarthritis-related pain in patients who may require long-term opioid therapy.

6.3 Summary of Evidence

Based on the review of multiple systematic reviews and the available literature, the evidence for the effectiveness of long-term opioids in reducing pain and improving the functional status for 6 months or longer is variable. The evidence for transdermal fentanyl and sustained-release morphine is Level II-2 based on the quality of evidence criteria described by the U.S. Preventive Services Task Force as illustrated in Table 1 (26). For oxycodone, the level of evidence is II-3, however, for hydrocodone and methadone, the level of evidence is III.

6.4 Recommendation

Based on the review of multiple systematic reviews and the available literature, the recommendation is 2A — weak recommendation, high-quality evidence with benefits closely balanced with risks and burden; derived from RCTs without important limitations or overwhelming evidence from observational studies; with the implication that with a weak recommendation, best action may differ depending on circumstances or patients' or societal values.

7.0 Adherence Monitoring

7.1 Introduction

Important issues in opioid therapy in chronic pain revolve around appropriate use of prescription opioids. Patients that describe symptoms of pain, and lack of relief, are one of the most common patient populations in the primary care community. Perceived interference of activities of daily living creates the perception of a need of drugs, and sometimes these patients are divulging signs and symptoms that may threaten the patient-physician relationship that is built on trust. The primary care physician is ill equipped to handle these patients, they rapidly lose control, and then they often are referred to the pain management physician as a "risk shift." These patients expect something to be done, and are often promised that the pain clinic will maintain the same level of care. It is the pain physician's responsibility to define their personal risk tolerance. Many times the primary care physician will not engage in opioid agreements and not fully explore non-narcotic medication alternatives. Adherence monitoring is crucial to avoid abuse of the drugs and at the same time to encourage appropriate use, and involves the initiation of drug screening, pill counts, and patient care agreements, with the motto of "trust but verify."

A high-risk practice, such as a pain management practice, will readily activate an adherence monitoring program, utilize advanced documentation, have a strong office policy, a threshold policy, and will define how many patients of this nature will be treated in the practice. If available, a second opinion from an addictionologist or psychologist may be advised, and a high-risk practice should understand that these charts should be readily available for the Board of Medical Examiners to review for legitimate need. Frequent functional assessments are mandatory. The risk environment is increased with Medicaid and disabled patients, patients with a previous history of substance abuse, and psychiatric disorders, particularly bipolar personalities, borderline personalities, history of alcohol abuse, and chaotic home environment. Boundary violations, which unfortunately do occur in this patient population, are never acceptable, and a difficult patient is best chaperoned at each visit.

The high-risk patient may have an abnormal pill count or drug screen. The patient that is discharged from a previous practice will have a documented historical reason, and records from this previous practice are recommended. High risk includes discharge from a previous practice, chaotic lifestyle, recent arrival to the area, poor response to multimodality approach to pain, sedentary lifestyle, cigarette smoker, and possibly obesity. Also patients that are litigating, disabled, and on Medicaid may also be at higher risk and may require more adherence monitoring. Patients should be expected to take a proactive role in their own healthcare. The risk/reward of the relationship is constantly reassessed. The patient should understand that pills kill, pain does not. The concept of legitimate

medical need is reviewed with the patient, and function, adherence, compliance, and comanaging physicians are sometimes called upon.

Confusion surrounding a specific operational definition of opioid misuse among chronic pain patients has complicated the process of effectively assessing and predicting its occurrence (159). The typical elements of drug diversion involve theft, forgery, counterfeit prescriptions, fraud imposed against physician/pharmacy for other patients, and promoting pill mills (1-4).

There is a need for better tamper-proof opioids. As long as long-acting opioids can be easily converted into a rapidly absorbed form, there will be a effort to divert these medications for illicit use.

7.2 Screening for Opioid Abuse

The decision to use opioids for chronic pain patients, like all medical decisions, is based on a balance between risk and potential benefit. Screening for opioid misuse and abuse is an exercise to strengthen the patient-physician relationship. This should not be confrontational, and the patient has to understand that this is like any other lab test. A physician would respond to abnormal liver functions or anemia, just as a pain physician responds to a screening questionnaire, urine drug screen, or pill count.

Even though several investigators have described multiple screening instruments in detecting opioid abuse or misuse in chronic pain patients, there is no widely used screening instrument in the current practice. Most look at problematic behaviors such as focusing on opioids, escalation of opioid use, multiple phone calls and visits, lack of improvement with increased medications, multiple prescription problems (lost or stolen scripts), and opioids from multiple providers (159).

7.3 Urine Drug Testing (UDT)

Although drug testing may be performed by testing the urine, serum, or hair, urine is considered as the best biologic specimen for detecting the presence or absence of certain drugs due to specificity, sensitivity, ease of administration, and the cost. However, controversies exist regarding the clinical value of UDT, partly because most current methods were designed for, or adapted from, forensic or occupational deterrent-based testing for illicit drug use and are not necessarily optimized for clinical applications in chronic pain management. In chronic pain management, UDT should be used with an appropriate level of understanding (which can improve a physician's professional ability to manage therapeutic prescription drugs with controlled substance), and to diagnose substance abuse or appropriate intake of drugs, thereby leading to proper treatment. They should be random, well organized, and synchronized with a well-understood testing lab. The lab understands you, and you understand what they are testing. False-positives, negatives, and the scope of testing should also be understood.

It is also critical to understand the metabolism of opioids, to avoid falsely accusing patients of abuse. For instance, codeine is metabolized to morphine, and hydrocodone to hydromorphone. However, it has only been recognized recently that morphine (in high doses) can be metabolized to hydromorphone (305). The hydromorphone is usually about 2% of the morphine dose (which can be determined by quantitative testing), and is usually seen in patients taking at least 100 to 200 mg morphine per day. In a retrospective case-control study (306), 66% of patients on morphine showed evidence of hydromorphone in the UDT; this was seen more commonly in females, despite the fact that the females were taking lower doses of morphine.

In principle, UDTs can detect the parent drug and/or its metabolite(s) and, therefore, demonstrate recent use of prescription medications and illegal substances. For most clinical applications, initial testing is done with class-specific immunoassay drug panels, which typically do not identify individual drugs within a class. However, this may, and perhaps should, be followed by a more specific technique such as a gas chromatography/mass spectrometry (GC/MS) to identify or confirm the presence or absence of a specific drug and/or its metabolite(s). Numerous differences between various tests and even among the laboratories and manufacturers of various rapid drug screen tests include the number of drugs tested, cross-reactivity patterns, cut-off concentrations, and drug interferences. Clinicians should remember that the cut-off concentrations used for drugs in federally regulated testing, particularly opioids, are too high to be of value in clinical practice. Federally regulated testing includes 5 drugs or drug classes that are tested for in federal employees and federally regulated industries, including marijuana, cocaine, opiates, PCP, and amphetamines/methamphetamines, with pre-determined cut-off levels with mandatory reconfirmation with the results by GC/MS, along with split sample in chain of custody requirements. In contrast, nonregulated testing is used for many purposes, including monitoring pain patients clinically.

In clinical practice, UDT is used for accurate record keeping, to identify use of undisclosed substances, to uncover diversion or trafficking, and to determine appropriate intake of prescribed substances. There are typically 2 types of UDT. These approaches used in proper combination can reduce cost, ensure accuracy, and improve efficiency. The 2 main types of UDT methods are:

1) Immunoassay drug testing, either laboratory based or by rapid drug testing ("site of service").
2) Laboratory-based specific drug identification with GC/MS, high-performance liquid chromatography (HPLC), etc.

Immunoassays, which are based on the principle of competitive binding, use antibodies to detect the presence of a particular drug or metabolite in a urine sample. Immunoassay drug testing is provided either in the laboratory or by means of rapid drug testing at the point of service. An immunoassay's ability to detect drugs will vary according to the drug concentration in the urine and the assay's cut-off concentration. Any response above the cut-off is deemed positive and any response below the cutoff is negative. Further, immunoassays are subject to cross-reactivity. For example, tests for cocaine are highly predictive of cocaine use. In contrast, tests for amphetamine/methamphetamine are highly cross-reactive and unreliable. They may detect other sympathomimetic amines such as ephedrine and pseudoephedrine and, therefore, are not very predictive for amphetamine/methamphetamine use. Further, standard tests for opiates are very responsive for morphine and codeine (but do not distinguish the difference), but show a lower sensitivity for semisynthetic/synthetic opioids such as oxycodone, fentanyl, methadone, and buprenorphine, such that a negative response does not exclude use of these opioids. Specific immunoassay tests for semisynthetic/synthetic opioids are available.

Table 18 illustrates cut-off levels for various drugs detected by urine analysis. Ideally, a panel in chronic pain management settings for rapid drug screening should include not only opiates, but also oxycodone and methadone. In addition, the panel should include cocaine, marijuana, amphetamines and methamphetamines for illicit drugs and benzodiazepines and barbiturates for other controlled substances. If

Table 18. *Urine drug testing: Typical screening and confirmation cutoff concentrations and detection times for drugs of abuse.*

Drug	Screening cutoff concentrations ng/mL urine	Analyte tested in confirmation	Confirmation cutoff concentrations ng/mL (non-regulated)	Confirmation cutoff concentrations ng/mL (federally regulated)	Urine detection time
Amphetamine	1,000	Amphetamine	500	1,000	2-4 days
Barbiturates	200	Amobarbital, secobarbital, other barbiturates	200	300	2-4 days for short acting; up to 30 days for long acting
Benzodiazepines	200	Oxazepam, diazepam, other benzodiazepines	200	300	Up to 30 days
Cocaine	300	Benzoylecgonine	150	300	1-3 days
Codeine	300	Codeine, morphine	300; 300	2,000; 300	1-3 days
Heroin	300	Morphine, 6-acetylmorphine	300; 10	2,000; 300	1-3 days
Marijuana	100; 50; 20	Tetrahydrocannabinol	15	50	1-3 days for casual use; up to 30 days for chronic use
Methadone	300	Methadone	300	300	2-4 days
Methamphetamine	1000	Methamphetamine, amphetamine	500; 200	1;000; 50	2-4 days
Phencyclidine	25	Phencyclidine	25	25	2-7 days for casual use; up to 30 days for chronic use

a custom panel is not available, multiple tests may have to be performed as rapid drug screening.

Cross-reactants with cannabinoids include Orudis KT, Aleve, Sustiva, Protonix, Marinol, ibuprofen, promethazine, and riboflavin. Opioid cross-reactivity includes poppy seeds, chlorpromazine, rifampin, dextromethorphan, and quinine. Cross-reactants to amphetamines include ephedrine, methylphenidate, pseudoephedrine, trazodone, desipramine, bupropion, fenfluramine, propranolol, labetalol, mexiletine, selegiline, tyramine, amantadine, ranitidine, phenylephrine, and Vicks Vapor Spray. PCP cross-reactants include chlorpromazine, thioridazine, dextromethorphan, diphenhydramine (Benadryl), and venlafaxine (Effexor). Benzodiazepine cross-reactants include oxaprozin (Daypro) and sertraline (Zoloft) and some herbal agents, while opioid cross-reactants include ofloxacin (Floxin), papaverine, and rifampin, as well as the oft-described poppy seeds. ETOH cross-reactants sometimes include asthma inhalers. Since false-negatives and false-positives are possible, when questions arise, prior to taking any actions, a confirmatory test or no threshold test must be performed in the laboratory.

Urine is sometimes adulterated. Collected within 4 minutes, the temperature range should be between 90° and 100° F. The pH should be between 4.5 and 8, and creatinine norm is 20 mg/dl and up. Dilute urine creatinine is <20 mg/dl and adulterated urine is <5 mg/dl. Urine testing has difficulty identifying LSD, hallucinogens, inhalants, and anabolic steroids. A new emerging therapy for fibromyalgia, flunitrazepam (Rohypnol), is the "date-rape" drug that is utilized sometimes for sleep; it may show up on urine screening as a benzodiazepine. Urine can be adulterated with glutaraldehyde detergent, potassium nitrate acid, and Pyridium chlorochromate, which are readily available over the internet.

Physicians may establish zero or low tolerance, but this should be discussed with the patient on the initial visit, and should be part of the written clinic policy. This may include referral to an addictionologist or psychologist, or may result in the refusal to prescribe opioids. However, it usually does not warrant dismissal of the patient. The practice limits for presence of cocaine and marijuana may range from only one positive screen (zero tolerance) to 3 positive screens and appropriate action later. Improper use of prescription drugs and doctor shopping should be dealt in the same manner.

7.4 Periodic Review and Monitoring

7.4.1 Periodic Review

Periodic reviews should assess the medical diagnosis, psychological diagnosis, informed consent, treatment agreement, appropriate opioid therapy with or without adjuvant medications or with or without interventional techniques, pre- and post-intervention assessment of pain level, and function and reassessment of pain score and level of function.

Regular assessment of the patient along with periodic review of the diagnosis is extremely important. Routine assessment of the "4 As" (analgesia, activity, aberrant behavior and adverse effects) will help to direct therapy and support pharmacologic actions taken (PASSIK reference add here).

Further assessment should be performed by periodic monitoring, pill counts, and UDT (see below).

7.4.2 Periodic Monitoring

At reasonable intervals depending on specific circumstances of a given patient, the physician should review the course of treatment and any new information about the etiology of the pain. Continuation or modification of therapy should depend on the physician's evaluation of progress towards the stated treatment goals, such as a reduction in a patient's pain scores and improved physical and/or psychosocial function (i.e., ability to work, utilization of healthcare resources, activities of daily living, and quality of social life). If treatment goals are not being achieved despite medication adjustments, the physician should reevaluate the appropriateness of continued treatment with the current medications. The physician should monitor patient compliance in medication usage and related treatment plans.

Some physicians have long embraced long-term opioid therapy, sometimes naïve of the consequences. Even the term pseudoaddiction involved only one case and one patient, and from there evolved into the philosophy of pseudoaddiction which took on its own meaning: "I think, therefore it is." Patients are becoming more demanding and the question is raised whether the detection of aberrant use is contradictory to the physician's goal, which is developing a sacred relationship.

7.4.3 Prescription Drug Monitoring

Prescription drug monitoring programs collect information to assist state law enforcement and regulatory agents in identifying and investigating illegal practices related to controlled substances. However, some of the existing prescription programs and the

recently passed NASPER should also assist physicians and pharmacists in identifying controlled substance abuse. The purpose of NASPER is to ensure access to care, delegate the appropriate use of opioids to those in the most need, and identify potential abusers that misuse, divert, or doctor shop.

7.4.4 Periodic Education

Drug education for the physicians, providers, and patients is crucial. While it appears that certain medications have revolutionized the treatment of chronic pain in the United States, physicians must balance the medical need with the possibility of abuse and diversion, as well as the necessity to comply with the state and federal regulations. It is obvious that healthcare practitioners are not only expected to prescribe medications when there is medical need and document appropriately, but also they are expected to prevent illegal diversion and identify drug abuse. Consequently, education is a critical component of any program to control the diversion of prescription drugs.

7.4.5 Pill Counts

Random pill counts, along with UDT and prescription monitoring, would greatly reduce controlled substance abuse. Pill counts are essential in patients with suspicion of abuse. However, these can also be performed randomly on high-risk patients.

A pill count is performed by notifying the patient a day before or on the day of the appointment of the patient, requesting the patient to bring with them their unused pills. The inability to provide pills or providing a reduced number will indicate use beyond the prescription. Pill counts above the expected ranges would indicate inappropriate low intake (suggesting that the medications are being over-prescribed). Recently, it has been reported that some unsuspected elderly patients may be selling controlled substances to supplement their income.

8.0 Principles of Opioid Usage

8.1 Introduction

In interventional pain management, patients may receive not only opioid analgesics, but also other controlled or noncontrolled drugs. Further, patients may be receiving controlled substances as an adjunct to interventional techniques, as well as to manage comorbid psychiatric and psychological disorders. Thus, the effectiveness studies published thus far may not apply in the majority of interventional pain management patients. Indeed, in an interventional pain practice, controlled substances may be prescribed at lower doses, particularly opioid analgesics, in conjunction with interventional techniques. It has also been shown that interventional techniques reduce psychological distress and improve functional status (307-330). More likely than not, the requirement for opioids and adjuvant drugs may be reduced or at least become stable. Hence, interventional pain physicians probably should not compare patients in their settings undergoing interventional techniques with others receiving drug therapy as mainstay. Monotherapy, particularly with opioids, may be appropriate for only a small subgroup of those with chronic pain.

The concept of "universal precautions," first seen in medicine with the explosion of HIV and hepatitis tainted blood, was introduced to counter the misconception that a provider would be able to predict "by looking" who might have a communicable bloodborne disease. This led to the use of "precautions" (gloves, etc.) for all patients, regardless of their age or socieoeconomic class. A rational approach to the treatment of chronic pain with opioids has been described using a pain and addiction continuum and a substance use assessment in a pain patient leading to the implementation of "universal precautions" in pain medicine (331).

8.2 Recommendation

Based on the grading recommendations provided by Guyatt et al (37) and illustrated in Table 2, the recommendation is 2A — weak recommendation, high-quality evidence: with benefits closely balanced with risks and burden; derived from RCTs without important limitations or overwhelming evidence from observational studies, with the implication that with a weak recommendation, best action may differ depending on circumstances or patients' or societal values.

8.3 Basic Philosophy

Principles for prescribing opioids must require a comprehensive evaluation (mandatory physical and optional psychological), appropriate documentation at regular intervals to assess the efficacy of therapy, with specific evaluation of the impact on functional status, degree of pain relief, identification and treatment of undesirable side effects, and monitoring for abuse behaviors. In addition, there must be adherence to a controlled substance agreement and with

regulatory guidelines promulgated by various agencies. Fig. 6 shows an algorithmic approach to patient evaluation and management. Table 19 shows an algorithmic approach for chronic opioid therapy.

8.4 Evaluation

Appropriate history, physical examination, and medical decision-making based on the initial evaluation of a patient's presenting symptoms are essential. The guidelines of the Centers for Medicare and Medicaid Services (CMS) provide various criteria for 5 levels of evaluation and management services (E&M) (332-335), with 3 crucial components: history, physical examination, and medical decision-making. Other components include counseling, coordination of care, nature of presenting problem, and time required for face-to-face evaluation. While there are numerous techniques to evaluate a chronic pain patient, which vary from physician to physician, institution to institution, and textbook to textbook, following the guidelines established by CMS will assist a physician in performing a comprehensive and complete evaluation complying with regulations.

Some of the aspects specific in controlled substance abuse and chronic pain include evaluation of the effect of pain on physical and psychological function, such as activities of daily living (336,337).

8.4.1 Diagnostic and Therapeutic Injections

Diagnostic interventional techniques will assist in making the proper diagnosis by following an algorithmic approach (338-345). It has been shown that in approximately 70% to 85% of the patients with spinal pain an accurate diagnosis may not be provided in spite of the available history, physical examination, EMG nerve conduction studies, and radiological evaluation. With precise diagnostic interventional

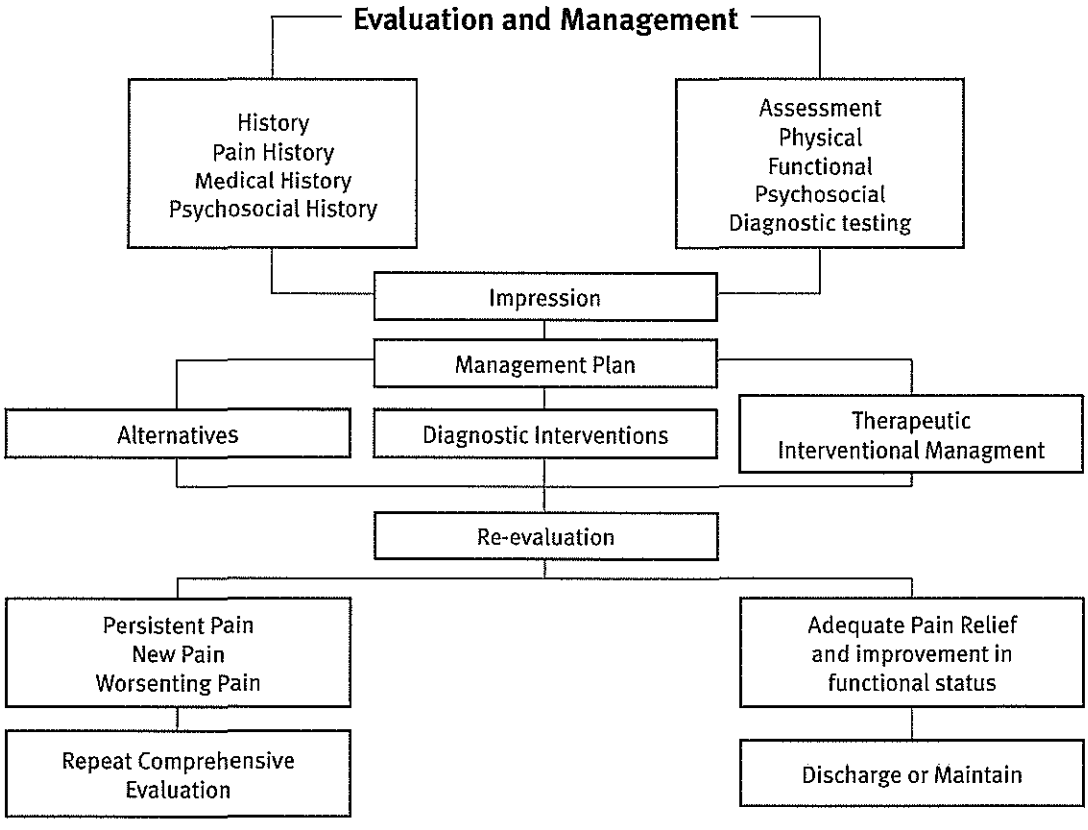


Fig. 6. *Suggested algorithm for comprehensive evaluation and management of chronic pain.*

techniques, the chances of correct diagnosis may be improved substantially, and proper treatment may be offered (346-350).

Therapeutic interventional techniques also may be used in a monotherapeutic way rather than using opioids for pain management and functional improvement. The effectiveness of various interventional techniques has been evaluated in systematic reviews (307-330).

A written treatment plan should document objectives that will be used to evaluate treatment success, including pain relief and improved physical and psychosocial function, and should indicate if additional diagnostic tests, consultations, or treatments are planned. After starting treatment, the physician should adjust with care the drug therapy to the individual medical needs of each patient. In the continuum of treatment, other modalities, including interventional techniques, rehabilitation, and psychological therapy may be necessary depending on the etiology of the pain and the extent to which pain is associated with physical, functional, and psychosocial impairment.

8.4.2 Consultation

Physicians should be willing to refer a patient as clinically indicated for additional evaluation to achieve treatment objectives. Special attention should be given to those patients who are at risk of misusing their medications and those whose living arrangements create a risk for medication misuse or diversion. The management of patients with a history of substance abuse or with a coexisting psychiatric disorder may require extra care, monitoring, documentation, and consultation with, or referral to, an addictionologist. The lack of well-trained psychologists and psychiatrists in many regions of the country may make this referral difficult to obtain. Likewise in many locations there are no clinically trained addiction specialists with whom to collaborate.

8.4.3 Informed Consent and Controlled Substance Agreement

At the initial visit, the physician should discuss the risks and benefits of the use of controlled substances with the patient or surrogate, including the risk of tolerance and drug dependence. It is advisable to employ the use of a written agreement between physician and patient outlining patient responsibilities. Agreements are helpful, specifically if the patient is determined to be at high risk for medication abuse or have a history of substance abuse. Possible items of a controlled substance agreement between a physician and patient include:

1. One prescribing doctor and one designated pharmacy.
2. Urine/serum drug screening when requested.
3. No early refills and no medications called in.
4. If medications are lost or stolen, then a police report could be required before considering additional prescriptions.

Table 19. *Ten-step process: An algorithmic approach for long-term opioid therapy in chronic pain.*

STEP I	Comprehensive initial evaluation
STEP II	Establish diagnosis ♦ X-rays, MRI, CT, neuro-physiologic studies ♦ Psychological evaluation ♦ Precision diagnostic interventions
STEP III	Establish medical necessity (lack of progress or as supplemental therapy) ♦ Physical diagnosis ♦ Therapeutic interventional pain management ♦ Physical modalities ♦ Behavior therapy
STEP IV	Assess risk-benefit ratio ♦ Treatment is beneficial
STEP V	Establish treatment goals
STEP VI	Obtain informed consent and agreement
STEP VII	Initial dose adjustment phase (up to 8-12 weeks) ♦ Start low dose ♦ Utilize opioids, NSAID's and adjuvants ♦ Discontinue • Lack of analgesia • Side effects • Lack of functional improvement
STEP VIII	Stable phase (stable – moderate doses) ♦ Monthly refills ♦ Assess for four A's • Analgesia • Activity • Aberrant behavior • Adverse effect ♦ Manage side effects
STEP IX	Adherence monitoring ♦ Prescription monitoring programs ♦ Random drug screens ♦ Pill counts
STEP X	Outcomes ♦ Successful – continue • Stable doses • Analgesia, activity • No abuse, side effects ♦ Failed – discontinue • Dose escalation • No analgesia • No activity • Abuse • Side effects • Non-compliance

The reasons for which opioid drug therapy may be discontinued, such as violation of a documented doctor/patient agreement, should be delineated. Additional items to be included in an agreement are listed in Table 20.

Table 20. *Sample Controlled Substance Agreement*

We are committed to doing all we can to treat your chronic pain condition. In some cases, controlled substances are used as a therapeutic option in the management of chronic pain and related anxiety and depression, which is strictly regulated by both state and federal agencies. This agreement is a tool to protect both you and the physician by establishing guidelines, within the laws, for proper controlled substance use. The words "we" and "our" refer to the facility and the words "I", "you", "your", "me", or "my" refer to you, the patient.

1. i. I understand that chronic opioid therapy has been associated with not only addiction and abuse, but also multiple medical problems including the suppression of endocrine function resulting in low hormonal levels in men and women which may affect mood, stamina, sexual desire, and physical and sexual performance.

   ii. For female patients, if I plan to become pregnant or believe that I have become pregnant while taking this medication, I am aware that, should I carry the baby to delivery while taking these medications; the baby will be physically dependent upon opioids. I will immediately call my obstetrician and this office to inform them of my pregnancy. I am also aware that opioids may cause a birth defect, even though it is extremely rare.

   iii. I have been informed that long-term and/or high doses of pain medications may also cause increased levels of pain known as opioid induced hyperalgesia (pain medicine causing more pain) where simple touch will be predicted as pain and pain gradually increases in intensity and also the location with hurting all over the body. I understand that opioid-induced hyperalgesia is a normal, expected result of using these medicines for a long period of time. This is only treated with addition of non-steroidal anti-inflammatory drugs such as Advil, Ibuprofen, etc., or by reducing or stopping opioids.

   iv. I understand that physical dependence is not the same as addiction. I am aware physical dependence means that if my pain medicine use is markedly decreased, stopped, or reversed by some of the agents mentioned above, I will experience a withdrawal syndrome. This means I may have any or all of the following: runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, irritability, aches throughout my body and a flu-like feeling. I am aware that opioid withdrawal is uncomfortable, but not life threatening.

   v. I am aware that tolerance to analgesia means that I may require more medicine to get the same amount of pain relief. I am aware that tolerance to analgesia does not seem to be a big problem for most patients with chronic pain; however, it has been seen and may occur to me. If it occurs, increasing doses may not always help and may cause unacceptable side effects. Tolerance or failure to respond well to opioids may cause my doctor to choose another form of treatment, reduce the dose, or stop it.

2. i. All controlled substances must come from the physician whose signature appears below or during his/her absence, by the covering physician, unless specific authorization is obtained for an exception.

   ii. I understand that I must tell the physician whose signature appears below or during his/her absence, the covering physician, all drugs that I am taking, have purchased, or have obtained, even over-the-counter medications. Failure to do so may result in drug interactions or overdoses that could result in harm to me, including death.

   iii. I will not seek prescriptions for controlled substances from any other physician, health care provider, or dentist. I understand it is unlawful to be prescribed the same controlled medication by more than one physician at a time without each physician's knowledge.

   iv. I also understand that it is unlawful to obtain or to attempt to obtain a prescription for a controlled substance by knowingly misrepresenting facts to a physician or his/her staff or knowingly withholding facts from a physician or his/her staff (including failure to inform the physician or his/her staff of all controlled substances that I have been prescribed).

Table 20 (continued). *Sample Controlled Substance Agreement*

3. All controlled substances must be obtained at the same pharmacy where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is:

   _____Phone: _____

4. i. You may not share, sell, or otherwise permit others, including your spouse or family members, to have access to any controlled substances that you have been prescribed.

   ii. Early refills will not be given. Renewals are based upon keeping scheduled appointments. Please do not make excessive phone calls for prescriptions or early refills and do not phone for refills after hours or on weekends.

5. Unannounced pill counts, random urine or serum, or planned drug screening may be requested from you and your cooperation is required. Presence of unauthorized substances in urine or serum toxicology screens may result in your discharge from the facility and its physicians and staff.

6. I will not consume excessive amounts of alcohol in conjunction with controlled substances. I will not use, purchase, or otherwise obtain any other legal drugs except as specifically authorized by the physician whose signature appears below or during his/her absence, by the covering physician, as set forth in Section 2 above. I will not use, purchase, or otherwise obtain any illegal drugs, including marijuana, cocaine, etc. I understand that driving while under the influence of any substance, including a prescribed controlled substance or any combination of substances (e.g., alcohol and prescription drugs), which impairs my driving ability, may result in DUI charges.

7. Medications or written prescriptions may not be replaced if they are lost, stolen, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen, it will not be replaced unless explicit proof is provided with direct evidence from authorities. A report narrating what you told the authorities is not enough.

8. In the event you are arrested or incarcerated related to legal or illegal drugs (including alcohol), refills on controlled substances will not be given.

9. I understand that failure to adhere to these policies may result in cessation of therapy with controlled substances prescribed by this physician and other physicians at the facility and that law enforcement officials may be contacted.

10. I also understand that the prescribing physician has permission to discuss all diagnostic and treatment details, including medications, with dispensing pharmacists, other professionals who provide your health care, or appropriate drug and law enforcement agencies for the purpose of maintaining accountability.

11. I affirm that I have full right and power to sign and to be bound by this agreement, that I have read it, and understand and accept all of its terms. A copy of this document has been given to me.

_____
Patient's full name

_____ _____
Patient's signature Date

_____ _____
Physician's signature Date

9.0 Documentation and Medical Records

The physician should keep accurate and complete medical records, which include all aspects of interventional pain management and medical care. These comprise, but are not limited to:

- The medical history and physical examination
- Diagnostic, therapeutic, and laboratory results
- Evaluations and consultations
- Treatment objectives
- Discussion of risks, benefits, and limitations of treatments
- Details of different treatments, medications, including date, type, dosage, and quantity prescribed
- Instructions to the patient
- Periodic reviews of outcomes, including documentation of functional status, preferably using validated tools

Records should remain current and be maintained in an accessible manner and readily available for review, not only for the physician and other members of the practice, but also for authorities.

To be in compliance with controlled substance laws and regulations required to prescribe, dispense, or administer controlled substances, the physician must have an active license in the state and comply with applicable federal and state regulations. Various boards have published regulations and recommendations for prescribing controlled substances. Physicians are advised to refer to those regulations for their respective state. Physicians should not prescribe scheduled drugs for themselves or immediate family except in emergency situations.

The following criteria should be considered carefully in providing controlled substances:

1. Complete initial evaluation, including history and physical examination
2. Psychological evaluation
3. Physiological and functional assessment, as necessary and feasible
4. Definition of indications and medical necessity:
   - Pain of moderate-to-severe degree
   - Suspected organic problem
   - Documentation of failure to respond to non-controlled substances, adjuvant agents, physical therapy, and interventional techniques
   - For patients with interventional techniques as primary modality, controlled substance drugs may be used as a second line treatment.
   - For nonopioid controlled substances, appropriate documentation of psychological disorders should be maintained.
   - Continued opioid prescription requires monitoring of "the 4 As":
     - Analgesia
     - Activity
     - Aberrant behavior
     - Adverse effect
5. The use of the lowest possible dose to provide adequate analgesia with minimum side effects should be the goal of opioid therapy.
6. In general, do not combine opioids with sedative-hypnotics, benzodiazepines, or barbiturates for chronic, non-cancer pain unless there is a specific medical indication for the combination.
7. Adherence to the controlled substance agreement with patients understanding the risks and benefits of controlled substances and the policy and regulations of the practitioner, including controlled substances being prescribed by only one practitioner and being obtained from only one pharmacy.
8. Monitoring for drug abuse or diversion should be routine and if confirmed, referral to rehabilitation centers may be made, with termination of prescriptions of controlled substances.
9. Use caution when prescribing acetaminophen-containing opioids, especially given the ubiquitousness of acetaminophen in over-the-counter medications. Short-term use (< 10 days) should be less than 4,000 mg/day, while chronic use should probably be limited to 2,500 mg/day.

While there are no universally accepted tools to assess opioid responsiveness, it is important to use a tool that monitors both function and pain relief.

Although opioids may be useful for the treatment of chronic pain, aberrant behavior and/or no improvement in function and pain after an adequate trial of opioids should trigger a consideration to discontinue the opioids, tapered over a several week period to avoid withdrawal symptoms. Evidence of diversion or illegal use warrants an immediate discontinuation of the medication. Clonidine po or transdermal 0.1 mg can be offered to counteract the majority of withdrawal symptoms.

10.0 Key Points

1. These opioid guidelines for the treatment of chronic non-cancer pain were developed to improve the quality and appropriateness of care, improve patient access, improve patient quality of life, improve efficiency and effectiveness, and achieve cost containment by improving the cost-benefit ratio.
2. Opioids are extensively used in managing chronic pain.
3. There is significant evidence of opioid abuse in conjunction with or without illicit drugs.
4. Abuse terminology is variable. This document attempts to standardize and provide a common sense definition.
5. Opioid pharmacology is variable and essential to understand for proper management of patients.
6. Among the rules of opioid administration, comprehensive evaluation and diagnostic assessment is crucial, including diagnosis by interventional techniques.
7. Establishing goals of treatment and using a controlled substance agreement are essential in the practice of pain management with opioids.
8. Periodic review of the patient on opioids is essential, using appropriate adjustments, with routine assessment of analgesia, activity, aberrant behavior, and adverse effects.
9. Documentation, keeping accurate and complete medical records with all the essential elements to provide proper patient care and also meet regulatory and legal requirements, is essential.
10. The rationalization and importance of these guidelines lies in the fact that most available evidence documents a wide degree of variance in the prescribing patterns of opioids for chronic pain. The strength of available evidence in the use of opioids for chronic non-cancer pain is weak.

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Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines

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Background: Opioid abuse has continued to increase at an alarming rate since our last opioid guidelines were published in 2005. Available evidence suggests a continued wide variance in the use of opioids, as documented by different medical specialties, medical boards, advocacy groups, and the Drug Enforcement Administration.

Objectives: The objectives of opioid guidelines by the American Society of Interventional Pain Physicians (ASIPP) are to provide guidance for the use of opioids for the treatment of chronic non-cancer pain, to bring consistency in opioid philosophy among the many diverse groups involved, to improve the treatment of chronic non-cancer pain, and to reduce the incidence of abuse and drug diversion.

Design: A broadly based policy committee of recognized experts in the field evaluated the available literature regarding opioid use in managing chronic non-cancer pain. This resulted in the formulation of the review and update of the guidelines published in 2006, a series of potential evidence linkages representing conclusions, followed by statements regarding the relationships between clinical interventions and outcomes.

Methods: The elements of the guideline preparation process included literature searches, literature synthesis, consensus evaluation, open forum presentations, formal endorsement by the Board of Directors of the American Society of Interventional Pain Physicians, and peer review. Based on the criteria of the U.S. Preventive Services Task Force, the quality of evidence was designated as Level I, II, and III, with 3 subcategories in Level II, with Level I described as strong and Level III as indeterminate. The recommendations were provided from 1A to 2C, varying from strong recommendation with high quality evidence to weak recommendation with low-quality or very low-quality evidence.

Results: After an extensive review and analysis of the literature, which included systematic reviews and all of the available literature, the evidence for the effectiveness of long-term opioids in reducing pain and improving functional status for 6 months or longer is variable. The evidence for transdermal fentanyl and sustained-release morphine is Level II-2, whereas for oxycodone the level of evidence is II-3, and the evidence for hydrocodone and methadone is Level III. There is also significant evidence of misuse and abuse of opioids.

The recommendation is 2A – weak recommendation, high-quality evidence: with benefits closely balanced with risks and burdens; with evidence derived from RCTs without important limitations or overwhelming evidence from observational studies, with the implication that with a weak recommendation, best action may differ depending on circumstances or patients' or societal values.

Conclusion: Opioids are commonly prescribed for chronic non-cancer pain and may be effective for short-term pain relief. However, long-term effectiveness of 6 months or longer is variable with evidence ranging from moderate for transdermal fentanyl and sustained-re-

lease morphine with a Level II-2, to limited for oxycodone with a Level II-3, and indeterminate for hydrocodone and methadone with a Level III.

These guidelines included the evaluation of the evidence for the use of opioids in the management of chronic non-cancer pain and the recommendations for that management. These guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Because of the changing body of evidence, this document is not intended to be a "standard of care."

Key words: Chronic pain, persistent pain, non-cancer pain, controlled substances, substance abuse, prescription drug abuse, dependency, opioids, prescription monitoring, drug testing, adherence monitoring, diversion

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1.0 Introduction

1.1 Purpose

The American Society of Interventional Pain Physicians (ASIPP) has developed guidelines for the use of opioids in the management of non-cancer pain. They were last updated and published in *Pain Physician* journal in 2006 (1). These guidelines have been developed by ASIPP, so that physicians, lawmakers, and law enforcement agencies would better understand the role of opioids in non-cancer pain management algorithms. A better understanding of the risks and benefits of this class of medications should conceivably improve access to treatment for patients with chronic pain whose quality of life could be improved with opioids. In addition, a better understanding of the risks and benefits should also conceivably lead to a reduction in the abuse and diversion of this class of medications, consequences which are of grave importance. Many opioid proponent experts and some policy makers maintain that chronic pain remains undertreated with opioids and that the extent of the problem may have been underestimated. Similarly, some experts and many policy makers maintain that chronic pain may have been overtreated with opioids and the extent of the problem of abuse, diversion, and deaths may have been underestimated (2-8). Regardless of these widely diverse opinions, there is incontrovertible evidence that we are in the midst of an epidemic of prescription drug abuse and this has become a public health issue as well (2-5).

1.2 Rationale and Importance

The use of opioids in the management of cancer pain and palliative care has been widely accepted. The use of opioids to treat moderate to severe acute pain is also widely accepted. The use of opioids to treat chronic non-cancer pain, however, remains controversial (6,7,9-18). The most significant consequences of long-term therapy include, but are not limited to, tolerance, physical and psychological dependence, abuse, and diversion (6,7-18). When utilized to treat cancer pain or in palliative care, the treatment objectives of pain control can typically be met, and the major concerns regarding the prolonged use of opioids do not have as much impact on therapeutic decision-making. This is also usually true when treating acute pain. These issues, however, are of grave consequence when considering the prescription of opioids for chronic benign pain with evidence of lack of effectiveness and significant complications (6-19).

Another significant factor that accounts for the discrepancy in the acceptance of the use of opioids for chronic benign pain is the actual goals of treatment in this patient population. The treatment objectives in chronic benign pain are subtly, but significantly, different and more complex than the goals of opioid therapy in the settings of terminal conditions or acute pain. The objective of the treatment of chronic pain of a non-cancer origin include, when possible, not only management of painful symptoms but an emphasis on maintaining functionality and continued participation in society. These objectives can be thwarted by the use of opioids depending on multiple factors. These factors include, but are not limited to, the psychological make up of the patient, the type of pain being treated, and the skills, knowledge, and resources of the clinician.

1.3 Objectives and Benefits

The objective of these guidelines is to provide clear and concise guidelines to physicians, to improve patient access, and avoid diversion and abuse. The perceived benefits of these guidelines include:

- Increased physician awareness about the current issues involving opioids and non-cancer pain
- Improved patient access
- Reduced level of opioid abuse
- Improved ability to manage patient expectations
- Reduced diversion
- Improved understanding by law enforcement about proper prescribing patterns
- Improved cooperation among patients, providers, and regulatory agencies
- Improved understanding by patients regarding their rights as well as their responsibilities when taking opioid medications

1.4 Population and Preferences

The population covered by these guidelines includes all patients with chronic moderate to severe pain of non-cancer origin who may be eligible for appropriate medically necessary opioid analgesic management. This management may include or be independent of interventional techniques.

1.5 Implementation and Review

The dates for implementation and review were established:

- Effective date – February 1, 2008
- Scheduled review – July 1, 2011
- Expiration date – January 31, 2012

1.6 Application

These guidelines were developed to be used by physicians practicing interventional pain management and do not constitute inflexible treatment recommendations. These guidelines are not intended to address all possible clinical situations where opioids might be used for non-cancer pain in clinical practice. It is expected that a provider will establish a plan of care on a case-by-case basis, taking into account an individual patient's medical condition, personal needs, and preferences, as well as the physician's experience. Based on an individual patient's needs, treatment different from that outlined here could be warranted. These guidelines do not represent "standard of care."

1.7 Focus

The focus of these guidelines is the effective management of chronic non-cancer pain, as well as the various issues involved in opioid administration. It is recognized that management of chronic non-cancer pain takes place in a wide context of healthcare, involving multiple specialists and multiple techniques. Guidelines cannot be applied to all patients. Consequently, the decision to implement a particular management approach should be based on a comprehensive assessment of the patient's overall health status, disease state, patient preference, and physician training and skill.

1.8 Methodology

A policy committee was convened and included a broad representation of academic and clinical practitioners, representing a variety of practices and geographic areas, all recognized as experts in opioid use and management of patients with chronic non-cancer pain. This committee formalized the essentials of the guidelines. The elements of the guidelines preparation process included literature searches, literature synthesis, consensus evaluations, open forum presentations, formal endorsement by the ASIPP board of directors and peer review (20-40).

Evidence-based medicine is defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (41). It is not "cookbook" medicine, but instead requires an integration of the best external evidence combined with individual clinical expertise and the patient's choice. While an evidence-based approach may seem to enhance the scientific rigor of guideline development, recommendations may not always meet the highest scientific standards (42). The study of pain treatments has been limited due to the subjective nature of pain, especially non-cancer pain, and the effectiveness of interventions (such as the use of opioids) has to be judged relative to non-intervention (39,43-50).

In preparation of these guidelines, it is recognized that at the core of an evidence-based approach to clinical or public health issues is, inevitably, the evidence itself, which needs to be carefully gathered and collated from a systematic literature review of the particular issues. It follow that process by which the strength of scientific evidence is evaluated in the development of evidence-based medicine recommendations and guidelines is crucial. The practice of evidence-based medicine requires the integration of individual clinical expertise with the best available clinical evidence from systematic research.

Systems for grading the strength of a body of evidence are much less uniform and consistent than those for rating study quality (24-40). Consequently, the guideline committee designed levels of evidence from Level I through Level III, adapted from the U.S. Preventive Services Task Force (USPSTF) (26) as shown in Table 1.

Table 1. *Quality of evidence.*

I:	Evidence obtained from at least one properly randomized controlled trial.
II-1:	Evidence obtained from well-designed controlled trials without randomization.
II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III:	Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees.

Adapted from the Agency for Healthcare Research and Quality U.S. Preventive Services Task Force (USPSTF) (Ref. 24)

Recommendations were provided based on methodological quality of supporting evidence, benefit versus risks and burdens, and implications (37) (Table 2).

2.0 Chronic Pain

2.1 Definitions

Acute pain is a vital, protective mechanism that allows us to live in an environment filled with potential dangers. On the other hand, chronic pain serves no such physiologic function, and is itself not a useful symptom. Chronic pain is difficult to define. Consequently, a combination of multiple definitions must be utilized.

- Pain that persists beyond the usual course of an acute disease or a reasonable time for any injury to heal that is associated with chronic pathologic processes that cause continuous pain or pain at intervals for months or years
- Persistent pain that is not amenable to routine pain control methods.

2.2 Prevalence

Any description of the epidemiology of chronic pain starts with its significance as a national public health problem. In a survey of chronic pain in America conducted by the American Pain Society (an advocacy group), 9% of the adult population was shown

Table 2. *Grading recommendations.*

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Adapted from Guyatt et al (37). Grading strength of recommendations and quality of evidence in clinical guidelines. Report from an American College of Chest Physicians task force. *Chest* 2006; 129:174-181.

SPECIAL ARTICLE

Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action

Canabidiol: de um canabinóide inativo a uma droga com amplo espectro de ação

Antonio Waldo Zuardi[1]

Abstract

Objective: *The aim of this review is to describe the historical development of research on cannabidiol.* ***Method:*** *This review was carried out on reports drawn from Medline, Web of Science and SciELO.* ***Discussion:*** *After the elucidation of the chemical structure of cannabidiol in 1963, the initial studies showed that cannabidiol was unable to mimic the effects of Cannabis. In the 1970's the number of publications on cannabidiol reached a first peak, having the research focused mainly on the interaction with delta9-THC and its antiepileptic and sedative effects. The following two decades showed lower degree of interest, and the potential therapeutic properties of cannabidiol investigated were mainly the anxiolytic, antipsychotic and on motor diseases effects. The last five years have shown a remarkable increase in publications on cannabidiol mainly stimulated by the discovery of its anti-inflammatory, anti-oxidative and neuroprotective effects. These studies have suggested a wide range of possible therapeutic effects of cannabidiol on several conditions, including Parkinson's disease, Alzheimer's disease, cerebral ischemia, diabetes, rheumatoid arthritis, other inflammatory diseases, nausea and cancer.* ***Conclusion:*** *In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials.*

Descriptors: *Cannabidiol; Cannabis; Cannabinoids; History; Therapeutic uses*

Resumo

Objetivo: *O objetivo desta revisão é descrever a evolução histórica das pesquisas sobre o canabidiol.* ***Método:*** *Esta revisão foi conduzida utilizando-se bases de dados eletrônicas (Medline, Web of Science e SciELO).* ***Discussão:*** *Após a elucidação de sua estrutura química, em 1963, os estudos iniciais do canabidiol demonstraram que ele não foi capaz de mimetizar os efeitos da maconha. Na década de 70, o número de publicações sobre o canabidiol atingiu um primeiro pico, com as investigações centrando-se principalmente na sua interação com o delta9-THC e nos seus efeitos antiepiléptico e sedativo. As duas décadas seguintes apresentaram um menor nível de interesse e as propriedades terapêuticas potenciais do canabidiol investigadas foram, principalmente, as ansiolíticas, antipsicóticas e seus efeitos sobre as doenças motoras. Os últimos cinco anos têm demonstrado um notável aumento de publicações sobre o canabidiol, principalmente estimulado pela descoberta dos seus efeitos anti-inflamatório, anti-oxidativo e neuroprotetor. Estes estudos têm sugerido uma vasta gama de possíveis efeitos terapêuticos da canabidiol em várias condições, incluindo doença de Parkinson, doença de Alzheimer, isquemia cerebral, diabetes, náusea, câncer, artrite reumatóide e outras doenças inflamatórias.* ***Conclusão:*** *Nos últimos 45 anos, foi possível demonstrar uma vasta gama de efeitos farmacológicos do canabidiol, muitos dos quais são de grande interesse terapêutico, que ainda necessitam ser confirmados por estudos clínicos.*

Descritores: *Canabidiol; Cannabis; Canabinóides; História; Usos terapêuticos*

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Introduction

In the tip of secreting hairs located mainly on female-plant flowers and, in a smaller amount, in the leaves of *cannabis* plant, there are resin glands that have a considerable amount of chemically related active compounds, called cannabinoids. In some varieties of *cannabis* the main cannabinoid is the psychoactive component of the plant, delta9-tetrahydrocannabinol (delta9-THC). *Cannabis* varieties typically bred for fiber are nearly always relatively low in delta9-THC, cannabidiol (CBD) being the predominant cannabinoid in these plants.[1]

Although CBD was isolated from marijuana extract in 1940 by Adams et al.,[2] for almost 25 years no further work has been reported, except for a few early works about its isolation. Only in 1963 its exact chemical structure was elucidated by Mechoulam and Shvo.[3] Over the following few years Mechoulam's group was responsible for the structure and stereochemistry determination of the main cannabinoids, which opened a new research field on pharmacological activity of *cannabis* constituents.[4,5]

The evolution of the number of publications on CBD since 1963, in comparison with publications on *cannabis* in general, is shown in Figure 1. Only a few pharmacological studies on CBD were reported before the early 1970's, showing that CBD had no *cannabis*-like activity.[6] The number of publications increased in this decade and reached a first peak around 1975. In this period, a Brazilian research group led by Carlini, gave an important contribution, especially about the interactions of delta9-THC with other cannabinoids, including CBD.[7] Then, the number of publications declined and remained stabilized until a few years ago. The interest in studies about *cannabis* was renewed in the early 1990's, by the description and cloning of specific receptors for the cannabinoids in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.[8] Afterwards, the number of publications about *cannabis* has been continuously growing, but the reports on CBD remained stable until the early 2000's. In the last five years there has been an explosive increase in publications on CBD, with the confirmation of a plethora of pharmacological effects, many of them with therapeutic potential.

There are some recent and very good reviews on CBD.[9-12] As historical aspects have so far not been yet emphasized, the aim of the present review is to describe the development of this research field which transformed our view about CBD from an inactive cannabinoid to a drug with multiple actions.

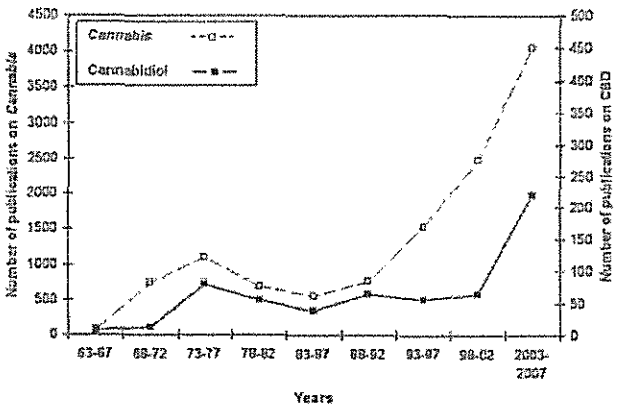

Figure 1 - Number of *cannabis* and cannabidiol-related publications in the last 45 years. The source used was the 'ISI Web of Knowledge' with the keywords: *Cannabis* and cannabidiol.

Inactive cannabinoid that interact with delta9-THC (1970's)

The early pharmacological tests on isolated cannabinoids had evidenced that except for delta9-THC, no other major psychotomimetically active compounds were present in *cannabis*.[13] During this period, several reports attested that CBD was unable to mimic the effects of *cannabis* both in animals[14] and in humans,[15,16] leading to the thought that it was an inactive cannabinoid.

This thought began to change with the observation that the activity in animals of several samples of *cannabis* differed widely, a fact which could not be attributed only to the different delta9-THC contents of the samples.[17,18] It was then hypothesized that other cannabinoids, among them CBD, could be interfering with the delta9-THC effects.

Many interactive studies between CBD and delta9-THC were accomplished by different groups, producing seemingly contradictory results both in animals,[19-21] and in humans.[22-24] Different schedules of drug administration used in these studies may help explain the contradictions. It seems that CBD administered before delta9-THC potentiates the effects of the latter compound. However, concomitant use of both compounds suggests that CBD antagonizes delta9-THC effects.[25-27] This difference could be explained by pharmacokinetic or pharmacodynamic interactions between the two cannabinoids.

CBD has been found to be a potent inhibitor of hepatic drug metabolism.[28,29] Pre-treatment of mice with high doses of CBD causes an increase in delta9-THC level in the brain.[30] Recently, evidence that CBD also inhibits the metabolic hydroxylation of delta9-THC in human volunteers[31] has been obtained. This pharmacokinetic interaction could explain the increased effects of delta9-THC by CBD pretreatment. On the other hand, CBD is not able to change delta9-THC blood level with co-administration of both compounds in rats[32] or humans volunteers.[33] Therefore, it has been suggested that CBD can antagonize delta9-THC effects pharmacodynamically.[34]

Early evidence (1970's) on CBD pharmacological activity

1. Antiepileptic action

The first pharmacological actions of CBD described were the antiepileptic and the sedative ones. In 1973, a Brazilian group reported that CBD was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures,[35,36] which was confirmed by another group one year later.[37] At the end of that decade, the same Brazilian group has tested CBD as a treatment for intractable epilepsy in 16 grand- mal patients. Each patient received, in a double-blind procedure, 200 to 300 mg daily of CBD or placebo for as long as four and a half months. Throughout the experiment, the patients did not stop taking the antiepileptic drugs prescribed before the experiment (which had not eliminated their seizures). Only one of the eight patients getting CBD showed no improvement, while among the patients who received the placebo, 1 improved and 7 remained unchanged.[38] In a less successful study, no significant improvement in seizure frequency was observed among 12 epileptic patients who received 200-300 mg of cannabidiol per day, in addition to standard antiepileptic drugs.[39] No further clinical trials with CBD have been published since then. Therefore, the clinical efficacy of CBD on epilepsy is still uncertain.

2. Sedative action

In the early 1970's, suggestive evidence of a sedative action appeared, based on the observation that CBD reduced ambulation in

rats[40] and, with higher doses, operant behavior in rats and pigeons.[41] Few years later, Monti[42] reported sleep-inducing effects of CBD in rats, with an increase in total sleeping time, increment of slow-wave sleep (SWS) and decrease of SWS latency. In humans with insomnia, high doses of CBD (160 mg) increased sleep duration compared to placebo.[43] Sedative effect was also observed in healthy volunteers with high CBD dose (600 mg).[44] This effect of CBD may be biphasic, since in low doses (15 mg) the cannabinoid appears to have alerting properties in healthy volunteers, as it increases wakefulness during sleep and counteracts the residual sedative activity of 15 mg THC.[45] Previous reports of subjective feelings by healthy volunteers after CBD (1 mg/Kg) showed a significant increase in "clear minded" and "quick- witted" feelings, in contrast with THC (0.5 mg/Kg) that induced an increase in "muzzy"[46] feelings. In agreement with the two last observations, intracerebroventricular administration of CBD in rats during the lights-on period increased wakefulness (W) and decreased rapid eye movement sleep (REMS), probably through increased dopamine release.[47]

CBD effects on anxiety, psychoses and movement disorders (1980's and 1990's)

After the peak of reports on CBD in the 1970's, the next two decades the publication rate remained stabilized, indicating a lower degree of interest on the study of therapeutic actions of CBD. The reports in this field were maintained mainly by Brazilian researchers investigating the anxiolytic and antipsychotic properties of CBD and by a few studies about its effects in motor diseases conducted by Consroe et al.[48,49]

1. Anxiolytic action

In 1974, an interactive study between CBD and THC, *per os*, in healthy volunteers, gave the first clue that CBD could act as an anxiolytic drug.[24] This study showed that CBD (60 mg), added to delta9-THC (30 mg), changed the symptoms induced by delta9-THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects. In 1982, a study with appropriate rating scales confirmed that CBD (1 mg/kg), co-administered with delta9-THC (0.5 mg/kg), significantly reduced anxiety indexes in healthy volunteers.[46]

The anxiolytic properties of CBD have been demonstrated by several pre-clinical studies that employed different paradigms such as the conditioned emotional response,[50] the Vogel conflict test[51] and the elevated plus-maze.[52,53] In the latter study,[53] the effective doses of CBD ranged from 2.5 to 10 mg/kg, and the drug produced an inverted U-shaped dose-response curve, the higher doses being no longer effective. This could explain the negative results obtained with high doses of CBD (above 100 mg/kg) in a previous study employing the Geller-Seifter conflict test.[54] A recent study showed that the anxiolytic effect of CBD in the Vogel test was not mediated by benzodiazepine receptors.[55]

In order to evaluate a possible anxiolytic effect of CBD in humans, a double-blind study was conducted on healthy volunteers submitted to a simulation of the public speaking test. CBD (300 mg, *po*) was compared to ipsapirone (5 mg), diazepam (10 mg) or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated the anxiety induced by the test.[56] The anxiolytic-like effect of CBD in healthy volunteers was also observed in a more recent double-blind study that investigated its effects on regional cerebral blood flow by single-photon emission computed tomography. Because the procedure itself can be interpreted as an anxiogenic situation, it allows the evaluation of anxiolytic drug action. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity.[57] Another study, using functional magnetic resonance imaging (fMRI) to investigate the neurophysiologic basis of the effects of cannabis on human anxiety, showed that CBD affected activation when subjects were processing intensely fearful stimuli, attenuating responses in the amygdala and cingulate cortex. The suppression of the amygdalar response was correlated to the drug effect of reducing fluctuations of skin conductance.[58] Therefore, similar to the data obtained in animal models, results from studies in healthy volunteers strongly suggest an anxiolytic action of CBD.

2. Antipsychotic action

The first evidence that CBD could have antipsychotic effects was obtained in the interactive study of CBD and delta9-THC in healthy volunteers published in 1982.[46] This study demonstrated that CBD could inhibit THC-induced subjective changes that resembled symptoms of psychotic diseases such as: disconnected thought, perceptual disturbance, depersonalization and resistance to communication. In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa, after the use of a variety of cannabis virtually devoid of CBD, showed much higher frequency of acute psychotic episodes than in other countries.[59] These lines of evidence led to several investigations of a possible antipsychotic action of CBD.

As a first step to investigate antipsychotic-like properties of CBD in animal models, the drug was compared to haloperidol in rats.[60] Both drugs reduced the apomorphine-induced stereotyped behavior (such as sniffing and biting), in a dose-related manner. Even though these drugs also increased the plasma level of prolactine, CBD needs higher doses (120 and 240 mg/kg) to show such an effect. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg/kg. These results suggest that CBD may exhibit a profile similar to atypical antipsychotic drugs. Recently, a study tested CBD effects both in dopamine-based and glutamate-based models predictive of antipsychotic activity in mice.[61] In this study CBD was compared to haloperidol and clozapine, an atypical antipsychotic drug. CBD inhibited the hyperlocomotion induced by amphetamine in a dose-related manner, in agreement with the data obtained with another dopamine-based model, and also attenuated the hyperlocomotion induced by ketamine, extending its antipsychotic-like action to a glutamate-based model. As expected, while both haloperidol and clozapine inhibited hyperlocomotion, only haloperidol induced catalepsy within the dose range used. Therefore, similar to clozapine, CBD did not induce catalepsy with doses that inhibited hyperlocomotion. Strengthening these results, CBD reversed the disruption of prepulse inhibition (PPI) of the startle response in mice caused by MK-801, a glutamate receptor antagonist, as did clozapine, further supporting the idea that this compound may act as an atypical antipsychotic drug.[62] Consistent with the behavioral data, both CBD and clozapine, but not haloperidol, induced Fos immunoreactivity (Fos) in the prefrontal cortex, while only haloperidol increased Fos in the dorsal striatum.[63,64]

Even in human models of psychotic symptoms induced in healthy volunteers, the antipsychotic-like activity of CBD can be demonstrated. In the perception of binocular depth inversion, used to evaluate the antipsychotic effects of new drugs,[65] the impairment of

the perception of illusory image induced by nabilone was attenuated by CBD, suggesting an antipsychotic-like effect of this compound.[56] Another model used to evaluate antipsychotic-like activity of drugs in healthy volunteers is the administration of sub-anesthetic doses of ketamine that induce a psychotic reaction mimicking both positive and negative symptoms of schizophrenia.[57] A double-blind crossover procedure using this model was performed to compare the effects of CBD (600 mg) and placebo in nine healthy volunteers.[58] CBD attenuated the effects of ketamine on the depersonalization factor of a dissociative rating scale, further reinforcing the antipsychotic-like properties of CBD.

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In a case study, a schizophrenic patient, who presented serious side effects after treatment with conventional antipsychotics, received oral doses of CBD (reaching 1500 mg/day) for 4 weeks.[59] A significant improvement was observed during CBD treatment, while a worsening was observed when the administration was interrupted. More recently, CBD was administered to three schizophrenic patients who had not responded to typical antipsychotic drugs.[70] A partial improvement was observed in one patient, but only slight or no improvement in the other two, thus suggesting that CBD has little effect in patients resistant to typical antipsychotics. Confirming the suggestion of case-studies, a preliminary report from a 4-week double-blind controlled clinical trial, using an adequate number of patients and comparing the effects of CBD with amisulpride in acute schizophrenic and schizophreniform psychosis, showed that CBD significantly reduced acute psychotic symptoms after 2 and 4 weeks of treatment when compared to baseline. In this trial, CBD did not differ from amisulpride except for a lower incidence of side effects.[71] In conclusion, clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients.

3. Action on movement disorders

The possible therapeutic effect of CBD on movement disorders came from anecdotal accounts and preliminary reports of open trials, in the middle 1980's. CBD (100 to 600 mg/day) had antidystonic effects in humans when administered along with standard medication to five patients with dystonia, in an open study.[48] In Huntington's disease (HD), the effectiveness of CBD was investigated with a small number of patients (four) and a non-blinded design, showing some beneficial effects of CBD.[72] However, the latter finding was not confirmed by a study comparing the effects of oral CBD (10 mg/kg/day for 6 weeks) with placebo under a double-blind, randomized cross-over design. In this study, CBD at an average daily dose of about 700 mg/day was neither symptomatically effective nor toxic in neuroleptic-free patients with HD.[49]

Afterwards, this field of research was apparently abandoned until recently, when CBD's neuroprotective effects began to be reported in animal models of Parkinson's disease.

CBD as a drug with a wide spectrum of action (2000's)

The interest in studies about *cannabis* was renewed in the early 1990's, with the description and cloning of specific receptors for the cannabinoids (CB_1 and CB_2) in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.[73] After that, the number of publications about *cannabis* has been continuously growing, attesting the great interest in research involving the herb. However, the number of studies on CBD has increased only in the last five years (Figure 1), mainly stimulated by discoveries of the anti-inflammatory, anti-oxidative and neuroprotective actions of CBD.

1. Anti-oxidative and neuroprotective actions

In the late 1990's, it was demonstrated that CBD reduced glutamate toxicity mediated by N-methyl-D-aspartate receptors (NMDAr), 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl) propionic acid receptors (AMPA) or kainate receptors. The neuroprotection observed with cannabidiol was not affected by a cannabinoid receptor antagonist, indicating it is cannabinoid-receptor independent.[74] Previous studies had shown that glutamate toxicity may be prevented by antioxidants. In line with this, it was demonstrated that CBD can reduce hydroperoxide-induced oxidative damage as well as or better than other antioxidants. CBD was more protective against glutamate neurotoxicity than either ascorbate or a-tocopherol, indicating that this drug is a potent antioxidant.[74]

The anti-oxidative action of CBD can be responsible for the neuroprotection reported in animal models of Parkinson's disease (PD). Daily administration of CBD during 2 weeks may produce a significant waning in the magnitude of toxic effects caused by a unilateral injection of 6-hydroxydopamine into the medial forebrain bundle,[75] probably due to receptor-independent actions. In this model of PD, CBD led to an up-regulation of mRNA levels of Cu/Zn-superoxide dismutase, a key enzyme in endogenous defense against oxidative stress. The conclusion was that the antioxidant properties of CBD can provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons that occur in PD.[76] This is reinforced by the observation that CBD reduced the striatal atrophy caused by 3-nitropropionic acid, *in vivo*, through mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A_{2A} receptors.[77] The neuroprotective action of CBD in the human basal ganglia was suggested by the strong positive correlation of N-acetylaspartate/total creatine ratio and CBD in the putamen/globus pallidum found in recreational cannabis users. This could reflect an enhancement of neuronal and axonal integrity in these regions by CBD.[78] Considering the relevance of these preclinical data and the possible antipsychotic effect of CBD, a recently study evaluated, for the first time, the efficacy, tolerability and safety of CBD in PD patients with psychotic symptoms.[79] In an open-label pilot study, six consecutive outpatients with the diagnosis of PD and who also had psychosis for at least 3 months, have received a flexible-dose regimen of CBD administration (starting with an oral dose of 150 mg/day) for four weeks, in addition to their usual therapy. The psychotic symptoms significantly decreased along the CBD treatment, and the scale used to follow up the PD course exhibited a significant decrease of the total score. These preliminary data suggest that CBD may have a beneficial action in PD.[79]

The possible neuroprotective actions of CBD highlight the importance of studies on the therapeutic potential of this compound in Alzheimer's disease (AD). AD is widely associated with oxidative stress due in part, to the membrane action of beta-amyloid peptide (beta-A) aggregates. A marked reduction in the cell survival was observed following exposure of cultured rat pheochromocytoma PC12 cells to beta-A peptide. Treatment of the cells with CBD prior to beta-A exposure significantly elevated the cell survival, probably by a combination of neuroprotective, anti-oxidative and anti-apoptotic actions against beta-A toxicity. In addition, CBD inhibited caspase 3 generation from its inactive precursor, pro-caspase 3, an effect that is involved in the signaling pathway for this neuroprotection.[80] In the search for the molecular mechanism of this CBD-induced

neuroprotective action it was reported that CBD inhibits hyperphosphorylation of tau protein in beta-A-stimulated PC12 neuronal cells, which is one of the most representative hallmarks of AD.[81] A possible anti-inflammatory action may be involved in this CBD effect, since CBD inhibited both nitrite production and nitric oxide synthase (iNOS) protein expression induced by beta-A.[82] These results of *in vitro* studies were confirmed *in vivo* with a mouse model of AD-related neuroinflammation. Mice were inoculated with human beta-A into the right dorsal hippocampus, and treated daily with vehicle or CBD (2.5 or 10 mg kg, i.p.) for 7 days. In contrast to vehicle, CBD dose-dependent significantly inhibited mRNA for glial fibrillary acidic protein and the protein expression in beta-A injected animals. Moreover, under the same experimental conditions, CBD impaired iNOS and IL-1beta protein expression, and the related NO and IL-1beta release.[83] The possibility of CBD inhibiting beta-A-induced neurodegeneration is very promising to AD prevention.

Recently it has been suggested that CBD may protect neurons against the multiple molecular and cellular factors involved in the different steps of the neurodegenerative process, which takes place during prion infection.[84] Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation in the CNS of the protease-resistant prion protein, a structurally misfolded isoform of its physiological counterpart.[84]

2. Anti-inflammatory action

In 2000, a few previous reports showing that CBD can modulate tumor necrosis factor *in vitro* and suppress chemokine production by a human B cell,[85-87] motivated the study of CBD as a therapeutic agent in collagen-induced arthritis, a model for rheumatoid arthritis.[88] This model is based on immunizing mice with type-II collagen. CBD, administered i.p. or orally, has blocked the progression of arthritis. Dose-dependency was shown by a bell-shaped curve, with an optimal effect at 5 mg/kg per day (i.p.), or at 25 mg/kg per day (orally). In addition, CBD has suppressed T cell responses and has decreased the release of bioactive tumor necrosis factor (TNF) from synovial cells isolated from arthritic knee joints of treated mice. Data of this study suggest that the antiarthritic effect of CBD is due to a combination of immunosuppressive and anti-inflammatory actions.[10,12] A CBD anti-inflammatory effect was observed in acute inflammation induced by intraplantar injection of 0.1 ml carrageenan in rats.[89] Oral CBD (5-40 mg/kg) once a day for 3 days after the onset of acute inflammation had a beneficial action on edema and hyperalgesia. CBD also proved effective in chronic neuropathic (sciatic nerve chronic constriction) painful states in rats, reducing hyperalgesia to mechanical stimuli. This effect was prevented by the vanilloid antagonist capsazepine, but not by cannabinoid receptor antagonists.[90] In these models of inflammation, decreases in prostaglandin E2 (PGE2) plasma levels, tissue cyclooxygenase (COX) activity and production of nitric oxide (NO)[89,90] have been observed. The suppressive effects of CBD on cellular immune responses and on the production of pro-inflammatory mediators may indicate its usefulness in several inflammatory diseases.

3. Action on ischemia

The anti-oxidative and anti-inflammatory properties of CBD have led to the research of its possible activity in preventing damage caused by cerebral ischemia. CBD (1.25-20 mg/kg) was administered to freely-moving gerbils 5 min after bilateral carotid-artery occlusion for 10 minutes. Seven days after the ischemia, CBD antagonized electroencephalographic flattening, showing a dose-dependent bell-shaped curve. The best neuroprotective effect was observed at 5 mg/kg. Histological examination showed the complete survival of CA1 neurons in CBD-treated gerbils.[91] A similar effect has been reported by another research group in mice, after middle cerebral artery occlusion; the neuroprotective action of CBD being unaffected by CB_1 receptor blockade.[92] The same research group has verified that this effect was inhibited by WAY100135, a serotonin 5-hydroxytriptamine 1A (5-HT_{1A}) receptor antagonist, but not by capsazepine, a vanilloid receptor antagonist, suggesting that the neuroprotective effect of CBD may be due to the increase in cerebral blood flow mediated by the serotonergic 5-HT_{1A} receptor.[93] Experimental evidence has suggested that beyond this action on the 5-HT_{1A} receptor, the protective effect of CBD on ischemic injury is also secondary to its anti-inflammatory action.[94] In another study, the same research group reported that, while repeated treatment with delta9-THC leads to the development of tolerance for this neuroprotective effect, this phenomenon is not observed with CBD.[95]

CBD has been studied for ischemic heart diseases in rats.[96] The left anterior descending coronary artery was transiently obstructed for 30 min, and the rats were treated for 7 days with CBD (5 mg/kg, ip) or vehicle. Cardiac function was studied by echocardiography and showed preservation of shortening fraction in CBD-treated animals. Infarct size was reduced by 66% in CBD-treated animals and this effect was associated with reduction of myocardial inflammation and reduction of IL-6 levels. In isolated hearts, no significant difference was detected between rats that received CBD or vehicle regarding: infarct size, left ventricular developed pressures during ischemia and reperfusion, or coronary flow. This study shows that CBD induces a substantial cardioprotective effect, but only *in vivo*.

4. Action on diabetes

The potent anti-inflammatory effect of CBD, with reduction of cytokines production (IFN-γ and TNF-α) and inhibition of T cell proliferation observed in experimental arthritis,[88] led to investigation of the possible CBD effects on others autoimmune diseases.[12] Type 1 diabetes mellitus (insulin-dependent) is an autoimmune disease that results in the destruction of insulin-producing pancreatic β cells. The initial lesion of insulin-dependent diabetes mellitus is an inflammation of the islands of Langerhans, during which leukocytes, lymphocytes in particular, surround and infiltrate the islets. That way Mechoulam's group investigated CBD action on non-obese diabetic (NOD) mice. They found that CBD treatment of NOD mice before the development of the disease reduced its incidence from 86% in the non-treated control mice to 30% in CBD-treated mice. CBD treatment also resulted in significant reduction of plasma levels of the pro-inflammatory cytokines, IFN-γ and TNF-α. Histological examination of the pancreatic islets of CBD-treated mice revealed significant reduction of the inflammation.[97] It was also observed that administration of CBD to 11-14 week old female NOD mice, which were either in a latent diabetes stage or had initial symptoms of diabetes, ameliorated the manifestations of the disease. In addition, the level of the pro-inflammatory cytokine IL-12 produced by splenocytes was significantly reduced, whereas the level of the anti-inflammatory IL-10 was significantly elevated after CBD treatment.[98] This data have suggested that CBD can possibly be used as a therapeutic agent for the treatment of type 1 diabetes.

CBD has also been proven useful for possible complications of diabetes. The majority of diabetic complications are associated with pathophysiological alterations in the vasculature. Microvascular complications involve retinopathy and nephropathy while the atherosclerosis is the most common macrovascular complication of diabetes. The protective effects of CBD were studied in experimental diabetes induced by streptozotocin in rats. CBD treatment prevented retinal cell death and vascular hyperpermeability in the diabetic retina. In addition, it significantly reduced oxidative stress, decreased the levels of TNF-α, vascular endothelial growth factor, and intercellular adhesion-molecule.[99] It has also been suggested that CBD has significant therapeutic benefits against other diabetic complications and atherosclerosis, since it attenuated several effects of high glucose, including the disruption of the endothelial function.[100]

5. Antiemetic action

The treatment of nausea and vomiting associated with chemotherapy was one of the first therapeutic uses of cannabis and cannabinoids that has been evaluated with clinical trials. In the mid 1970's, a clinical trial indicated that delta9-THC was effective as an anti-nausea agent in patients receiving cancer chemotherapy.[101] In 1990, a survey of the members of the American Society of Clinical Oncology found that more than 44% of the respondents reported that they had already recommended the use of marijuana for the control of emesis to at least one cancer chemotherapy patient.[102]

Although the anti-emetic action has been associated to delta9-THC, many users claim that marijuana suppresses nausea more effectively than oral delta9-THC.[103] These observations led a Canadian group to investigate whether CBD can suppress nausea in the conditioned rejection model in rats. The association between a flavor and an emetic drug results in altered affective reactions, called conditioned rejection reactions, which reflect nausea.[19] In this model, rats were injected with a low dose (5 mg/kg i.p.) of CBD, a synthetic dimethylheptyl homolog of CBD, or vehicle 30 min prior to a pairing of saccharin solution and lithium chloride (20 ml/kg of 0.15 M LiCl) or saline. The rejection reactions (gapes, chin rubs and paw treads) that were elicited by lithium chloride and by a flavor paired with lithium chloride were suppressed by CBD and its synthetic dimethylheptyl homolog.[104] Since rats are incapable of vomiting, a better model for vomiting was found with a mouse species *(Suncus murinus)*, which both vomits and expresses nausea.[12] These animals were injected with vehicle or one of two cannabinoids, THC (1-20 mg/kg) or CBD (2.5-40 mg/kg), 10 min prior to an injection of LiCl (390 mg/kg of 0.15 M) and were then observed for 45 min. delta9-THC produced a dose-dependent suppression of Li-induced vomiting while CBD produced a biphasic effect, having lower doses produced suppression and higher doses produced enhancement of Li-induced vomiting. The suppression of Li-induced vomiting by delta9-THC, but not by CBD, was reversed by SR-141716, a CB_1 antagonist, suggesting that both cannabinoids are effective treatments for Li-induced vomiting, however, only delta9-THC acts through the CB_1 receptor.[105] CBD was effective also in the conditioned retching reaction, which is a model of anticipatory nausea. Following three pairings of a novel distinctive contextual cue with the emetic effects of an injection of lithium chloride, the context acquired the potential to elicit conditioned retching in the absence of the toxin. The expression of this conditioned retching reaction was completely suppressed by CBD and delta9-THC, but not by ondansetron, a 5-HT_3 antagonist that interferes with acute vomiting in this species.[106] A similar effect of CBD on anticipatory nausea was observed with a rat model of nausea (conditioned gaping).[107] These results support anecdotal claims that marijuana may suppress the expression of anticipatory nausea experienced by chemotherapy patients, resistant to current anti-nausea treatments.

6. Anticancer action

In the mid 1970's, several cannabinoids, including CBD, were studied in cancer cells and the results observed with CBD were not promising. However, these experiments were performed with extremely high doses (e.g., 200 mg/kg) and it is unlikely that these observations are relevant to the usual doses of CBD.[12]

In 2000, the interest in CBD as a potential anticancer drug was renewed with an investigation of its effect on glioma cells. In this study, CBD produced a modest reduction in the cell viability of C6 rat glioma cells, only evident after 6 days of incubation with the drug and only in a serum-free condition.[108] A further study has demonstrated that CBD, *in vitro*, caused a concentration-related inhibition of the human glioma cell viability that was already evident 24 h after the CBD exposure and significantly inhibited the growth of subcutaneously implanted human glioma cells in nude mice. The authors also showed for the first time that the antiproliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and single-strand DNA staining, which was not reverted by cannabinoid and vanilloid receptor antagonists.[109] CBD also caused apoptosis in human myeloblastic leukemia cells.[110] In addition, CBD inhibits the migration of U87 human glioma cells *in vitro* and this effect was also not antagonized by either selective CB_1 or CB_2 receptor antagonists.[111] A study of the effect of different cannabinoids on eight tumor cell lines, *in vitro*, has clearly indicated that, of the five natural compounds tested, CBD was the most potent inhibitor of cancer cell growth. In this study, two different tumor cell lines transplanted to hairless mice were half as big as those of the untreated group, and both breast- and lung-cancer cells injected to paws showed approximately three times less metastatic invasion.[112] An inhibitor of basic helix-loop-helix transcription factors (Id1) has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. CBD could down-regulate the Id-1 expression in aggressive human breast cancer cells, and the concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells.[113]

The precise mechanisms underlying CBD effects on apoptosis and tumor growth are not clear, and have recently been discussed in a review by Mechoulam.[12]

CBD: a drug with multiple mechanisms of action

The plethora of CBD effects described above can be explained by its multiple mechanisms of action. The description and cloning of specific receptors for the cannabinoids in the nervous system have been a great contribution to the understanding of the mechanism of actions of cannabinoids. However, in contrast to delta9-THC, CBD has little affinity to CB_1 and CB_2 receptors.[114]

1. Actions on the cannabinoid system

In spite of its low affinity for CB_1 and CB_2 receptors, experimental evidence has shown that CBD is capable of antagonizing $CB1_1$/CB_2 receptor agonists at reasonably low concentrations.[115] This unexpected effect of CBD raises the possibility that this antagonism is non-competitive in nature, a hypothesis that has been discussed

by Pertwee.[116] Recently, the cloning and protein sequence of the human, mouse and rat new cannabinoid receptor (GPR55) that can be activated by the established CB_1/CB_2 receptor agonists, such as delta9-THC and endogenous cannabinoids, has been described. The activation of the GPR55 receptor is antagonized by CBD at a concentration that is below any concentration at which it displaces agonists from CB_1 or CB_2 receptors.[117] Other actions of CBD on the cannabinoid system are the blockade of anandamide uptake and the inhibition of its enzymatic hydrolysis.[118]

2. Action on the vanilloid receptor type 1

CBD stimulated vanilloid receptors (VR1) with EC_{50} = 3.2 ± 3.5 mM and with a maximal effect similar in efficacy to that of capsaicin, the natural agonists of this receptor.[118] Although VR1 is involved in inflammatory hyperalgesia, the stimulation of this receptor by capsaicin and some of its analogues leads to rapid desensitization, with subsequent paradoxical analgesic and anti-inflammatory effects. CBD desensitized VR1 to the action of capsaicin, thus opening the possibility that this cannabinoid exerts an anti-inflammatory action in part by desensitization of sensory nociceptors.[118]

3. Action on the5-HT_{1A} receptor

CBD displaces the agonist [3H]8-OHDPAT from the cloned human 5-HT_{1A} receptor in a concentration-dependent manner. In signal-transduction studies, CBD acts as an agonist at the human 5-HT_{1A} receptor.[119] This CBD action is probably involved in the protective effect of CBD on ischemia[93] and in its anxiolytic-like effects.[120]

4. Action on adenosine signaling

CBD decreases the uptake of [3H] adenosine in both murine microglia and macrophages, and binding studies show that CBD binds to the equilibrative nucleoside transporter.[121] The enhancement of adenosine signaling through inhibition of its uptake can provide a non-cannabinoid receptor mechanism by which CBD can decrease inflammation.

5. Anti-oxidant action

As mentioned above, CBD prevents hydroperoxide (H_2O_2)-induced oxidative damage equally well, or better than ascorbate (vitamin C) or tocopherol (vitamin E).[74] This action may be related to the neuroprotective effect of CBD.

6. Immunosuppressive and anti-inflammatory actions

The effects of CBD on pro-inflammatory cytokines and related compounds as well as its immunosuppressive effect have been reviewed above.

Conclusion

In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials. It is important to highlight that many effects of CBD draw a bell-shaped dose-response curve, suggesting that the dose is a pivotal factor in CBD research. The wide range of CBD effects can be explained by the multiple mechanisms through which CBD acts, although further research is needed to clarify the precise mechanisms that underlie some of the potentially beneficial effects of CBD.

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speakear's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Antonio W. Zuardi	FMRP-USP	CNPq FAPESP	—	—	—	—	—

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.
For more information, see Instructions for authors.

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Review

Cannabinoids in medicine: A review of their therapeutic potential

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Abstract

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded.

Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

Keywords: Cannabinoids; Cannabis; Therapeutic potential; Controlled clinical trials; Efficacy; Safety

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1. Introduction

Originating from Central Asia, cannabis is one of the oldest psychotropic drugs known to humanity. The beginnings of its use by humans are difficult to trace, because it was cultivated and consumed long before the appearance of writing. According to archeological discoveries, it has been known in China at least since the Neolithic period, around 4000 BC (McKim, 2000).

There are several species of cannabis. The most relevant are *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. *Cannabis sativa*, the largest variety, grows in both tropical and temperate climates. The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to the dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant (Ben Amar and Léonard, 2002).

The Emperor of China, Shen Nung, also the discoverer of tea and ephedrine, is considered to be the first to have described the properties and therapeutic uses of cannabis in his compendium of Chinese medicinal herbs written in 2737 BC (Li, 1974). Soon afterwards, the plant was cultivated for its fibre, seeds, recreational consumption and use in medicine. It then spread to India from China (Mechoulam, 1986).

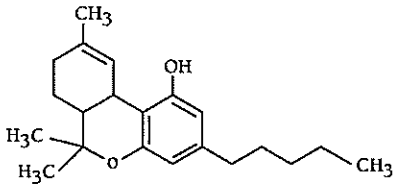
In 1839, William O'Shaughnessy, a British physician and surgeon working in India, discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The publication of his observations quickly led to the expansion of the medical use of cannabis (O'Shaugnessy, 1838–1840). It was even prescribed to Queen Victoria for relief of dysmenorrhea (Baker et al., 2003).

In 1854, cannabis is listed in the United States Dispensatory (Robson, 2001). It is sold freely in pharmacies of Western countries. It would be available in the British Pharmacopoeia in extract and tincture form for over 100 years (Iversen, 2000).

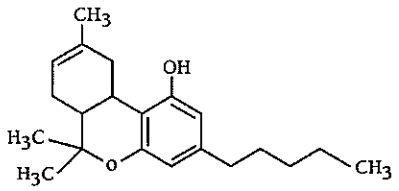
However, after prohibition of alcohol was lifted, the American authorities condemned the use of cannabis, making it responsible for insanity, moral and intellectual deterioration, violence and various crimes. Thus, in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of the American Medical Association, the U.S. Government introduced the *Marihuana Tax Act*: a tax of $1 per ounce was collected when marijuana was used for medical purposes and $100 per ounce when it was used for unapproved purposes (Solomon, 1968; Carter et al., 2004). In 1942, cannabis was removed from the United States Pharmacopoeia, thus losing its therapeutic legitimacy (Fankhauser, 2002).

Great Britain and most European countries banned cannabis by adopting the 1971 Convention on Psychotropic Substances instituted by the United Nations.

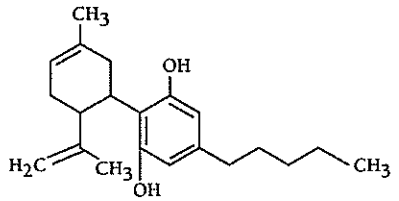
Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the name cannabinoids (Ben Amar, 2004). The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol (Δ^8THC), cannabinol (CBN), cannabidiol (CBD), cannabicyclol (CBL), cannabichromene (CBC) and cannabigerol (CBG), but they are present in small quantities and have no significant psychotropic effects compared to THC (Smith, 1998; McKim, 2000). However, they may have an impact on the product's overall effect (Ashton, 2001). Cannabinoids exert their actions by binding to specific receptors: the CB_1 cannabinoid receptors, discovered by Devane et al. (1988), then cloned by Matsuda et al. (1990) and the CB_2 cannabinoid receptors, identified by Munro et al. (1993). Both cannabinoid receptors are part of the G-protein coupled class and their activation results in inhibition of adenylate cyclase activity. The identification of agonists (anandamide and 2-arachidonylglycerol, the most studied endocannabinoids, participate in the regulation of neurotransmission) and antagonists of these receptors has stimulated interest in the medical uses of cannabis (Baker et al., 2003; Iversen, 2003; Di Marzo et al., 2004).



Δ^9- tetrahydrocannabinol (THC)



Δ^8- tetrahydrocannabinol



Cannabidiol (CBD)

Despite its illegality, patients have continued to obtain cannabis on the black market for self-medication. In 1978, in response to the success of a lawsuit filed by a glaucoma patient (Robert Randall) who had begun treating himself by smoking marijuana after losing a substantial part of his vision, the U.S. Government created a compassionate program for medical marijuana: 20 people suffering from debilitating diseases legally received marijuana cigarettes from the National Institute on Drug Abuse (NIDA), after approval by the Food and Drug Administration (FDA). This program was closed to new candidates in 1991 by President Bush, but still recently seven people continued to receive their marijuana (Mirken, 2004).

In Canada, 14 years after the 1988 arrest of Terrance Parker (an Ontario patient who had discovered that marijuana con-

sumption relieved his epileptic attacks, contrary to conventional drugs) and 1 year after the Ontario Court of Appeal ruled that discretionary regulation of marijuana use for medical purposes was contrary to the principles of the Canadian Charter of Rights and Freedoms, the Government of Canada decided to draft new regulations (Hoey, 2001). Thus, since July 30, 2001, the *Marihuana Medical Access Regulations* (MMAR) allow Canadian patients suffering from a serious disease to be eligible for therapeutic marijuana consumption. As of April 2005, 821 people were thus authorized to possess marijuana for medical purposes and 363 physicians had supported a request for authorization of possession (Health Canada, 2005).

The therapeutic applications of cannabis and its derivatives have been studied by various world bodies, including the Scientific Committee of the House of Lords in Great Britain (1998), the Institute of Medicine in the United States (1999) and the Senate Special Committee on Illegal Drugs in Canada (Nolin et al., 2002). Since 2003, medicinal cannabis, in standard cannabinoid concentrations, is sold in pharmacies in the Netherlands by medical prescription (Gorter et al., 2005). It is presently available in two dosages: cannabis flos, variety Bedrocan, containing 18% dronabinol and 0.8% cannabidiol and cannabis flos, variety Bedrobinol, containing 13% dronabinol and 0.2% cannabidiol (Office of Medicinal Cannabis, 2005). Various Western countries have authorized and conducted clinical trials on cannabis and its derivatives. Thus, for example, since 1999, Health Canada, in collaboration with the Canadian Institutes of Health Research, has established a Medical Marihuana Research Program (Health Canada/CIHR, 1999).

To date, there are a multitude of anecdotal reports and a certain number of clinical trials evaluating the therapeutic applications of cannabis and its derivatives. This review reports on the most current data available on the therapeutic potential of cannabinoids.

2. Methodology

A systematic search was performed in Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained. Thus, open-label studies were excluded.

The list of references of all the relevant articles was also studied to include all reports and reviews related to the subject. The research included the works and data available in English, French and Spanish.

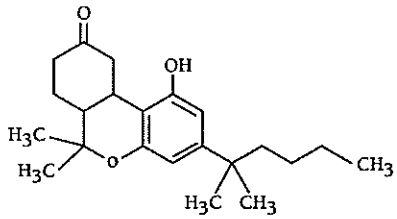
For each clinical study, the country where the project was held, the number of patients assessed, the type of study and comparisons made, the products and the dosages used, their efficacy and their adverse effects were identified.

3. Results

The meta-analysis identified 10 pathologies in which controlled studies on cannabinoids have been published: nausea and vomiting associated with cancer chemotherapy, loss of appetite, pain, multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy, glaucoma, Parkinson disease and dystonia.

3.1. Antiemetic effect

Cancer chemotherapy frequently causes nausea and vomiting which vary in intensity, but which can sometimes be severe and prolonged. In the 1970s and 1980s, the most widely used antiemetics were prochlorperazine, metoclopramide, chlorpromazine, domperidone, thiethylperazine and haloperidol. During this same period, various controlled studies evaluating the antiemetic effects of nabilone and dronabinol described the efficacy of these two cannabinoids (Table 1). Nabilone is a synthetic analog of THC and dronabinol is synthetic THC. The two substances were administered orally in clinical trials.



Nabilone (Cesamet®)

In the 15 controlled studies in which nabilone was compared to a placebo or an antiemetic drug, a total of 600 patients suffering from various types of cancers received this cannabinoid. Nabilone turned out to be significantly superior to prochlorperazine, domperidone and alizapride for treating nausea and vomiting associated with cancer chemotherapy. On the other hand, the patients clearly favoured nabilone for continuous use. The results led Health Canada to approve the marketing of this product. Marketed under the name Cesamet®, nabilone has been available in Canada since 1982. It is presented in the form of 1 mg pulvules. The recommended dosage is 2–6 mg per day (CPA, 2005).

With dronabinol, 14 controlled studies involving a total of 681 patients suffering from various types of cancers demonstrated that this cannabinoid exhibits an antiemetic effect equivalent to or significantly greater than chlorpromazine and equivalent to metoclopramide, thiethylperazine and haloperidol. All of these data led to the approval and marketing of dronabinol in the United States in 1985 and in Canada in 1995. Available under the name Marinol®, it is presented in the form of capsules of 2.5, 5 and 10 mg of THC. The recommended dosage as an antiemetic for nausea and vomiting induced by cancer chemotherapy is 5–15 mg/m^2/dose, without exceeding 4–6 doses per day (CPA, 2005).

Nonetheless, the efficacy of nabilone and dronabinol as antiemetic agents is eclipsed by the high and sometimes severe incidence of their undesirable reactions. On the other hand, their interest has declined considerably since the advent of

Table 1
Controlled studies evaluating the antiemetic effects of cannabinoids in patients receiving cancer chemotherapy

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Sallan et al. (1975)	United States	20 adults with various tumors (ages: 18–76)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 15 mg or 10 mg/m^2 × 3 times	Antiemetic effect of THC significantly superior to placebo	Drowsiness in 2/3 of the patients; euphoria in 13 patients
Chang et al. (1979)	United States	15 patients with osteogenic sarcoma (ages: 15–49)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m^2 × 5 times or smoked: one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	Oral THC alone or the combination of oral and smoked THC had an antiemetic effect significantly superior to placebo	Sedation in 80% of the patients
Frytak et al. (1979)	United States	116 adults with gastrointestinal tumors (median age: 61 years)	Randomized, double-blind, placebo-controlled, parallel groups	Oral THC: 15 mg × 3 times: 38 patients; oral prochlorperazine 10 mg × 3 times: 41 patients; placebo: 37 patients	Antiemetic effect equivalent with THC and prochlorperazine and superior to placebo	More frequent and more severe with THC than with prochlorperazine; 12 patients receiving THC and 1 patient receiving prochlorperazine dropped out of the study due to intolerable central nervous system toxicity
Kluin-Neleman et al. (1979)	The Netherlands	11 adults with Hodgkin or non-Hodgkin lymphoma (ages: 21–53)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m^2 × 3 times	Antiemetic effect of THC significantly superior to placebo	Dizziness (82%), hallucinations (45%), euphoria (36%), drowsiness (36%), derealization (18%), concentration disorders (18%); some severe effects of THC resulted in stoppage of the clinical trial
Herman et al. (1979)	United States	113 patients with various tumors (ages: 15–74)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 3 or 4 times; oral prochlorperazine: 10 mg × 3 or 4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine; the patients clearly favoured nabilone for continuous use	Drowsiness, dry mouth and dizziness observed with both products but twice as frequent and often more severe with nabilone; four patients taking nabilone exhibited undesirable effects which required medical attention: hallucinations in three patients and hypotension in one patient; euphoria associated with nabilone was infrequent (16% of cases) and mild

Table 1 (*Continued*)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Orr et al. (1980)	United States	55 adults with various tumors (ages: 22–71)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 7 mg/m^2 × 4 times; oral prochlorperazine: 7 mg/m^2 × 4 times	Antiemetic effect of THC significantly superior to prochlorperazine; the antiemetic effect of prochlorperazine was not statistically better than that of placebo	THC: euphoria (82%), sedation (28%), transient loss of emotional or physical control (21%); prochlorperazine: sedation (26%), dizziness (22%), dry mouth (11%)
Sallan et al. (1980)	United States	73 patients with various tumors (ages: 9–70)	Randomized, double-blind, crossover	Oral THC: 15 mg or 10 mg/m^2 × 3 times; oral prochlorperazine: 10 mg × 3 times	Antiemetic effect of THC significantly superior to prochlorperazine; most patients preferred THC to prochlorperazine; increase in food intake more frequent with THC	Euphoria with THC frequent but well tolerated
Colls et al. (1980)	New Zealand	35 adults with solid tumors	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 12 mg/m^2 × 3 times; oral thiethylperazine: 6.6 mg/m^2 × 3 times; metoclopramide IV: 4.5 mg/m^2 × 1 time	Antiemetic effect equivalent with all three products	Adverse effects, primarily of a neuropsychiatric nature, more frequent and severe with THC than with thiethylperazine or metoclopramide
Steele et al. (1980)	United States	37 adults with various tumors (ages: 19–65)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 2 times; oral prochlorperazine: 10 mg × 2 times	Antiemetic effect of nabilone superior to prochlorperazine	Nabilone: drowsiness (47%), dizziness (36%), dry mouth (25%), euphoria (19%), postural hypotension (17%). These side effects were severe enough to prohibit or modify the use of nabilone in 25% of patients; prochlorperazine: drowsiness (35%), dizziness (9%), dry mouth (5%). These side effects were mild
Chang et al. (1981)	United States	8 patients with various tumors (ages: 17–58)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 mg/m^2 × 5 times or smoked: one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	No antiemetic effect of THC in this group of patients receiving cyclophosphamide or doxorubicin	Euphoria (75%) and short lasting episodes of tachycardia
Neidhart et al. (1981)	United States	36 patients with various tumors (median age: 45 years)	Randomized, double-blind, crossover	Oral THC: 10 mg × (4–8) times; oral haloperidol: 2 mg × (4–8) times	Antiemetic effect equivalent with THC and haloperidol	THC: toxicity in 94% of the patients. The most frequent manifestations were drowsiness (58%), feeling faint (55%), euphoria (40%), spasms or tremors (15%). Toxicity interfered with function in 25% of the cases; haloperidol: toxicity in 79% of the patients. The most frequent manifestations were drowsiness (36%), euphoria (30%) and spasms or tremors (18%). Toxicity interfered with function in 6% of the cases

Table I (*Continued*)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Einhorn et al. (1981)	United States	80 patients with various tumors (ages: 15–74)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 4 times; oral prochlorperazine: 10 mg × 4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine; 75% of patients preferred nabilone for continuous use	Hypotension, euphoria, drowsiness and lethargy more pronounced with nabilone
Ungerleider et al. (1982)	United States	172 adults with various tumors (ages: 18–82)	Randomized, double-blind, crossover	Oral THC: 7.5–12.5 mg × 4 times; oral prochlorperazine: 10 mg × 4 times	Antiemetic effect equivalent with THC and prochlorperazine	Drowsiness, dizziness, concentration disorders, spatial-time distortions, euphoria, loss of activity and reduction of social interactions more frequent with THC than with prochlorperazine
Johansson et al. (1982)	Finland	18 adults with various tumors (ages: 18–70)	Randomized, double-blind, crossover	Oral nabilone: 2 mg b.i.d.; oral prochlorperazine: 10 mg b.i.d.	Antiemetic effect of nabilone significantly superior to prochlorperazine; 72% of patients preferred nabilone for continuous use	More frequent and more severe with nabilone than with prochlorperazine. Main side effects: nabilone: postural hypotension (42%), dizziness (23%), mood disorders (8%); prochlorperazine: headaches (13%), postural hypotension (9%), dizziness (9%)
Wada et al. (1982)	United States	84 adults with various tumors (ages: 18–81)	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (40%), drowsiness (34%), dry mouth (28%), euphoria (25%), dysphoria (10%); generally mild or moderate except in 11 patients who reported severe reactions which led 8 of them to terminate the study
Jones et al. (1982)	United States	24 adults with various tumors	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (65%), drowsiness (51%), dry mouth (31%), sleep disorders (14%); 11 patients dropped out of the study due to side effects caused by nabilone
Levitt (1982)	Canada	36 patients with various tumors (ages: 17–78)	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 2 mg × 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: vertigo (67%), drowsiness (61%), depersonalization (35%) dry mouth (24%), disorientation (16%); five patients dropped out of the study due to side effects caused by nabilone

Table 1 (*Continued*)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Dalzell et al. (1986)	Great Britain	18 patients with various tumors (ages: 10 months to 17 years)	Randomized, double-blind, crossover	Oral nabilone: 1–3 mg; oral domperidone: 15–45 mg	Antiemetic effect of nabilone significantly superior to domperidone; most patients or their parents preferred nabilone for continuous use	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (55%), dizziness (36%), mood changes (14%); domperidone: drowsiness (27%), dizziness (5%), mood changes (5%)
Pomeroy et al. (1986)	Ireland	38 adults with various tumors (ages: 21–66)	Randomized, double-blind, parallel groups	Oral nabilone: 1 mg × 3 times: 19 patients; oral domperidone: 20 mg × 3 times: 19 patients	Antiemetic effect of nabilone significantly superior to domperidone	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (58%), dizziness (58%), dry mouth (53%), postural hypotension (21%), euphoria (11%), headaches (11%), lightheadedness (11%); domperidone: drowsiness (47%), dry mouth (42%), dizziness (21%), headaches (16%)
Niederle et al. (1986)	Germany	20 adults with testicular cancer (ages: 19–45)	Randomized, double-blind, crossover	Oral nabilone: 2 mg × 2 times; oral alizapride: 150 mg × 3 times	Antiemetic effect of nabilone significantly superior to alizapride; 50% of the patients preferred nabilone, 35% preferred alizapride and 15% expressed no preference	More frequent with nabilone than with alizapride. Main side effects: nabilone: drowsiness (80%), hypotension or tachycardia (70%), dry mouth (65%), apathy (15%), euphoria (10%), decreased concentration (10%); alizapride: drowsiness (20%), extrapyramidal effects (20%), headaches (10%)
Crawford and Buckman (1986)	Great Britain	32 patients with ovarian cancer or germ cell tumors	Randomized, double-blind, crossover	Oral nabilone: 1 mg × 5 times; metoclopramide IV: 1 mg/kg × 5 times	Antiemetic effect equivalent but insufficient with nabilone and metoclopramide	Main side effect of nabilone: drowsiness; main side effect of metoclopramide: diarrhea
Chan et al. (1987)	Canada	30 patients with various tumors (ages: 3.5–17.8)	Randomized, double-blind, crossover	Oral nabilone: 1–4 mg; oral prochlorperazine: 5–20 mg	Antiemetic effect of nabilone significantly superior to prochlorperazine; 66% of the patients preferred nabilone, 17% prefered prochlorperazine and 17% expressed no preference; lower doses of nabilone had equivalent efficacy and did not induce major side effects	More frequent with nabilone than with prochlorperazine but generally well tolerated. Main side effects: nabilone: drowsiness (67%), dizziness (50%), mood disorders (14%); prochlorperazine: drowsiness (17%), mood disorders (11%)
McCabe et al. (1988)	United States	36 adults with various tumors (ages: 18–69)	Randomized, crossover	Oral THC: 15 mg/m^2 × 7 times; oral prochlorperazine: 10 mg × 7 times	Antiemetic effect of THC significantly superior to prochlorperazine	Frequent but transient dysphoria with THC
Lane et al. (1991)	United States	54 adults with various tumors (ages: 20–68)	Randomized, double-blind, parallel groups	Oral THC: 10 mg × 4 times: 17 patients; oral prochlorperazine: 10 mg × 4 times: 20 patients; oral THC (10 mg × 4 times) + oral prochlorperazine (10 mg × 4 times):17 patients	Antiemetic effect of THC significantly superior to prochlorperazine; the combination of THC and prochlorperazine was significantly more effective as an antiemetic than monotherapy	Adverse reactions, essentially related to the CNS, were more frequent with THC than with prochlorperazine; bitherapy reduced the frequency of dysphoric symptoms observed with THC alone

Reviews on cannabis and emesis: British Medical Association (1997; pp. 21–27), Tramer et al. (2001) and Bagshaw and Hagen (2002).

5-HT_3 receptor antagonists such as dolasetron, granisetron, ondansetron, palonosetron and tropisetron. These agents are more potent, do not exhibit significant psychotropic effects and can be administered intravenously (Iversen, 2000; Robson, 2001; Söderpalm et al., 2001; Jordan et al., 2005).

Levonantradol, a synthetic cannabinoid administered intramuscularly, has also proved its antiemetic efficacy in a controlled study. In 108 patients suffering from various tumors, it turned out to be significantly superior to chlorpromazine to relieve nausea and vomiting related to antineoplasic chemotherapy. However, its adverse central effects limit its utility (Hutcheon et al., 1983; British Medical Association, 1997).

Only three controlled studies have evaluated the efficacy of smoked marijuana to alleviate nausea and vomiting accompanying cancer chemotherapy (Chang et al., 1979, 1981; Levitt et al., 1984; Table 1): the first two used smoked marijuana which substituted oral THC, only in case of failure with dronabinol (Chang et al., 1979, 1981), the third compared smoked marijuana to oral THC (Levitt et al., 1984). In this third case, during a randomized, double-blind, crossover, placebo-controlled clinical trial, conducted in Canada on 20 adults suffering from various tumors and receiving cancer chemotherapy, Levitt et al. (1984) evaluated the antiemetic effects of smoked marijuana and oral THC (Table 1). The treatments only turned out to be effective in 25% of the patients. While questioning the 20 subjects, 35% preferred oral dronabinol, 20% preferred smoked marijuana and 45% did not express a preference. In addition, seven individuals experienced distortions of time perception or hallucinations: four with oral THC alone, two with smoked marijuana alone and one with both substances.

Despite the existence of many clinical trials with cannabinoids against nausea and vomiting associated with cancer chemotherapy, none have compared their efficacy against newer generation agents such as the 5-HT_3 receptor antagonists and the more recent neurokinin-1-receptor-antagonists (Jordan et al., 2005).

3.2. Appetite stimulation

Anorexia (loss of appetite) and a progressive weight loss are observed in patients suffering from advanced stages of cancer or HIV infection. In the case of AIDS, cachexia (extreme weight loss) may be accompanied by chronic diarrhea and weakness (Iversen, 2000).

Two controlled studies have demonstrated that oral THC stimulates appetite and helps retard chronic weight loss in adults suffering from various advanced cancers (Table 2). On the other hand, a clinical trial conducted on 139 patients suffering from AIDS and a weight loss of 2.3 kg or more illustrated that, compared to placebo, oral THC induced a marked, statistically significant stimulation of appetite after 4–6 weeks of treatment. THC tended to stabilize weight, while patients on placebo continued to lose weight. This effect persisted in the subjects who continued to receive dronabinol after the end of the study (Beal et al., 1995).

In a randomized, double-blind, parallel-group clinical trial of 469 individuals suffering from advanced cancer accompanied by weight loss of 2.3 kg or more in the past 2 months and/or a daily intake of less than 20 calories/kg of body weight, Jatoi et al. (2002) compared the effects of oral THC at a 2.5 mg b.i.d. dose (152 patients), oral megestrol, a synthetically derived progesterone, at a 800 mg/day dose (159 patients) and the association of the two products at the aforesaid dosages (158 patients) on the anorexia of these subjects. The authors found that at these doses, megestrol alone stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC alone stimulated appetite in 49% of the patients and produced a weight gain in 3% of the patients. These two differences were statistically significant. Moreover, the combined therapy did not confer additional benefits. The toxicity of these two substances was comparable, except for an increased incidence of impotence in men receiving megestrol (Table 2). This study was criticized for the use of a low dosage of dronabinol (Roncoroni, 2003).

Indeed, a recent study conducted in the United States on 67 HIV-infected adults using a higher dosage of oral THC (2.5 mg t.i.d.) made it possible to obtain more interesting results (Abrams et al., 2003). Comparing smoked marijuana (one to three cigarettes per day containing 3.95% THC), oral THC and placebo, the clinical trial illustrated that after 21 days of treatment, smoked THC and oral THC induced a statistically greater weight gain than placebo (Table 2). The study also showed that during the treatment period, THC administered by intrapulmonary or oral routes did not affect neither the viral load nor the number of $CD4^+$ and $CD8^+$ lymphocytes. Moreover, the two forms of THC did not interfere with the protease inhibitors (indinavir or nelfinavir) taken by the patients (Abrams et al., 2003).

Health Canada has approved oral THC (Marinol®) as an appetite stimulant for the treatment of anorexia and weight loss associated with AIDS. This synthetic THC or dronabinol (Marinol®) is available in the form of 2.5, 5 and 10 mg THC capsules. The recommended dosage for this therapeutic indication is 2.5–20 mg per day (CPA, 2005).

3.3. Analgesia

Several cannabinoids proved to be effective analgesics in acute and chronic pain animal models (Segal, 1986; Consroe and Sandyk, 1992; Iversen, 2000; Duran et al., 2004). The literature review identified 14 controlled studies (Table 3) evaluating the effects of cannabinoids on human beings suffering from acute pain (postoperative or experimental pain) or chronic pain (cancerous, neuropathic or of various origins). The substances analyzed were oral THC in capsules (four studies) or in extract form (one study), THC in sublingual spray (two studies), intravenous THC (one study), cannabidiol in sublingual spray (two studies) and the following synthetic analogs: oral benzopyranoperidine (three studies), oral CT-3 (one study) and intramuscular levonantradol (one study).

Two controlled studies performed on a total of 46 patients demonstrated the analgesic efficacy of oral THC in 10, 15 and 20 mg doses on their cancerous pains. However, drowsiness and confusion were frequent (Noyes et al., 1975a,b). In contrast, oral THC at the 5 mg dosage did not show an analgesic effect

Table 2
Controlled studies evaluating the appetite stimulant effects of cannabinoids in cancer or HIV/AIDS patients

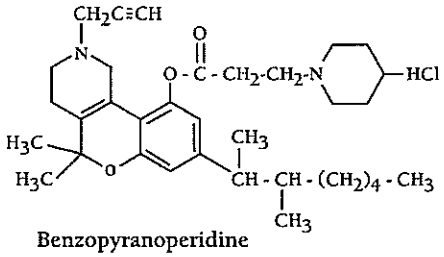
Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Regelson et al. (1976)	United States	54 adults with advanced cancer (ages: 21–73)	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 0.1 mg/kg t.i.d., i.e. 5–22.5 mg/day	THC stimulated appetite and helped retard chronic weight loss associated with cancer: on THC: total weight gain of 1.25 lb; on placebo: total weight loss of 21.25 lbs	The side effects limiting the use of THC in 25% of the patients were dizziness, confusion, drowsiness and dissociation
Struwe et al. (1993)	United States	12 men with symptomatic HIV infection and weight loss of 2.3 kg or more	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5 mg b.i.d.	THC stimulated appetite but the weight variation observed on THC and on placebo was statistically insignificant: on THC: median weight gain of 0.5 kg; on placebo: median weight loss of 0.7 kg	Two patients exhibited sedation and mood disorders and withdrew from the study
Beal et al. (1995)	United States	139 patients with AIDS and weight loss of 2.3 kg or more	Randomized, double-blind, parallel groups, placebo-controlled	Oral THC: 2.5 mg b.i.d.: 72 patients; placebo: 67 patients	THC induced a marked, statistically significant stimulation of appetite. It tended to stabilize weight, while patients on placebo continued to lose weight	Generally minor or moderate. Main side effects: euphoria (12,5%), dizziness (7%), confusion (7%), drowsiness (6%)
Jatoi et al. (2002)	United States	469 adults with advanced cancers, weight loss of 2.3 kg or more over the past 2 months and/or intake of less than 20 calories/kg/day	Randomized, double-blind, parallel groups	Oral THC: 2.5 mg b.i.d.: 152 patients; oral megestrol (synthetically derived progesterone): 800 mg die: 159 patients; oral THC: 2.5 mg b.i.d. + oral megestrol 800 mg die: 158 patients	In monotherapy, megestrol stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC stimulated appetite in 49% of the patients and caused a weight gain in 3% of the patients. These two differences were statistically significant; combined therapy did not confer additional benefits	Main side effects: THC: drowsiness (36%), confusion (24%), loss of coordination (15%); megestrol: drowsiness (33%), confusion (21%), male impotence (18%), fluid retention (18%), loss of coordination (16%); THC + megestrol: drowsiness (39%), confusion (21%), loss of coordination (18%), male impotence (14%), fluid retention (13%)
Abrams et al. (2003)	United States	67 adults with HIV infection	Randomized, double-blind for oral THC or placebo, parallel groups, placebo-controlled	Smoked THC: one to three marijuana cigarettes per day containing 3.95% THC $n=21$ patients; oral THC: 2.5 mg t.i.d. $n=25$ patients; placebo: $n=21$ patients	Weight gain equivalent with smoked THC and oral THC and statistically superior to placebo after 21 days of treatment: smoked THC group: average weight gain of 3.0 kg; oral THC group: average weight gain of 3.2 kg; placebo group: average weight gain of 1.1 kg; smoked THC and oral THC did not affect the viral load nor the number of $CD4^+$ and $CD8^+$ lymphocytes for the duration of treatment; smoked THC and oral THC did not interfere with the protease inhibitors taken by the patients (indinavir or nelfinavir)	Generally well tolerated; one patient in the smoked THC group dropped out of the study due to grade 2 neuropsychiatric troubles; two patients in the oral THC group dropped out of the study due to side effects: grade 2 paranoia (one patient), persistent headache and nausea (one patient)

Reviews on cannabis and anorexia: British Medical Association (1997; pp. 45–49), Iversen (2000; pp. 147–155) and Bagshaw and Hagen (2002).

on postoperative pain in 40 women who had undergone elective abdominal hysterectomy (Buggy et al., 2003), nor did oral THC at a 20 mg dose manifest antinociceptive properties in 12 healthy subjects under experimental pain conditions (Naef et al., 2003).

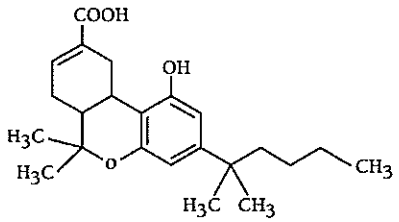
In two recent studies conducted on 34 subjects suffering from chronic pain (Notcutt et al., 2004) and 48 patients exhibiting central neuropathic pain (Berman et al., 2004), THC in sublingual spray (2.5 or 2.7 mg, respectively), whether alone or combined to cannabidiol in sublingual spray (2.5 mg), exhibited pain relief and improvement in sleep quality (Berman et al., 2004; Notcutt et al., 2004), while cannabidiol alone, in this same sublingual spray format, turned out to be ineffective (Notcutt et al., 2004). Nor did oral cannabidiol show an analgesic effect in 10 patients suffering from chronic neuropathic pain (Lindstrom et al., 1987). Intravenous THC in 0.22 and 0.44 mg/kg doses also appeared to be ineffective in treatment of postoperative pain in 10 healthy volunteers undergoing molar extractions (Raft et al., 1977).

On the other hand, benzopyranoperidine, a synthetic nitrogen analog of THC, administered orally in the 4 mg dose, manifested an analgesic effect in a total of 45 patients suffering from cancerous pains (Staquet et al., 1978). Nonetheless, the beneficial effect of benzopyranoperidine was absent in a group of 35 subjects suffering from chronic pain (Jochimsen et al., 1978). The major undesirable effect of benzopyranoperidine was drowsiness.



Benzopyranoperidine

Furthermore, oral CT-3 (ajulemic acid), a synthetic analog of 11-hydroxy-THC, showed analgesic efficacy in a study of 21 patients suffering from chronic neuropathic pain, without exhibiting major adverse effects (Karst et al., 2003).



Ajulemic acid (CT-3)

Finally, levonantradol, a synthetic cannabinoid administered intramuscularly in 1.5, 2, 2.5 and 3 mg doses to 56 patients suffering from postoperative pain, manifested significant analgesic efficacy in the four dosages used. Analgesia persisted for more than 6 h with the 2.5 and 3 mg doses of levonantradol. Drowsiness was frequent but few other psychoactive effects were reported (Jain et al., 1981).

Recently, after completion of this review, Blake et al. (2005) published a study on the efficacy and the safety of a mixture of 2.7 mg THC and 2.5 mg CBD delivered via an oromucosal spray (Sativex®) and used against pain caused by rheumatoid arthritis. In a randomized, double-blind, parallel groups, placebo-controlled trial, the authors compared Sativex® ($n = 31$) to a placebo ($n = 27$) over 5 weeks of treatment. They concluded that Sativex® produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and disease activity. There was no effect on morning stiffness, although baselines scores were low. The cannabis-based medicine (CBM) had mild or moderate side effects in the large majority of patients and none of them had to withdraw from the study due to adverse reactions in the CBM group (Blake et al., 2005).

3.4. Multiple sclerosis

Multiple sclerosis is a neurodegenerative disease which is accompanied by spasticity (muscle rigidity), painful muscle cramps, chronic pain in the extremities, tingling and prickling of the fingers of the hands and feet, as well as ataxia, tremors and vesical and intestinal dysfunctions (Petro, 1997; Smith, 1998; Iversen, 2000). Current symptomatic therapies for this demyelinating pathology of the central nervous system are in some cases ineffective and may present a risk of serious adverse effects. This has led some patients to self-medicate with cannabis, which anecdotal reports suggest may be beneficial to control some symptoms such as spasticity, tremor, pain and bladder dysfunction (Croxford and Miller, 2004).

Thirteen controlled studies evaluated the effects of cannabinoids on this pathology. The preparations studied were smoked marijuana and hashish, oral THC in capsule form, oral extracts of *Cannabis sativa* administered in capsules or sublingual spray and containing THC, cannabidiol or a combination of the two, and oral nabilone.

The results of these clinical trials are mixed: in some cases only, patients reported an improvement in spasticity, muscle spasms, pain, sleep quality, tremors and their general condition (Table 4). The most reliable conclusions on the efficacy and innoxiousness of cannabinoids in the treatment of multiple sclerosis should be taken from two clinical trials recently conducted in Great Britain and covering the largest population samples (Zajicek et al., 2003; Wade et al., 2004).

Thus, in a randomized, double-blind, parallel group trial (the CAMS study), evaluating a total of 630 patients suffering from multiple sclerosis, 206 individuals received oral THC in capsules, 211 subjects consumed an oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannabinoids per capsule and 213 persons took a placebo (Zajicek et al., 2003). The total duration of the study was 14 weeks. The authors reported the absence of beneficial effects of cannabinoids on spasticity, estimated by means of the Ashworth scale, while noting after the fact the limitations of this scale in measuring the highly complex symptoms of spasticity. However, they observed an objective improvement in mobility with oral THC and a subjective improvement in spasticity, muscle spasms, pain, sleep quality and general condition, as well as a decrease in hospitalizations for relapses with the two types of cannabinoids. The reported adverse effects were generally mild and well tolerated (Zajicek et al., 2003). Recent data from the CAMS study provide a longer term information on the efficacy

Table 3
Controlled studies evaluating the analgesic effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Noyes et al. (1975a)	United States	36 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 10 and 20 mg (capsules); oral codeine: 60 and 120 mg	Pain relief equivalent with 10 mg of THC and 60 mg of codeine, as well as with 20 mg of THC and 120 mg of codeine	THC, 10 mg: well tolerated; THC, 20 mg: drowsiness, dizziness, ataxia, confusion and frequent mental disorders
Noyes et al. (1975b)	United States	10 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5, 10, 15 and 20 mg (capsules)	Pain relief with the 15 and 20 mg doses	Frequent drowsiness and confusion
Raft et al. (1977)	United States	10 healthy volunteers undergoing dental extractions (4 molars for each patient)	Randomized, double-blind, crossover, placebo-controlled	THC IV: 0.22 and 0.44 mg/kg; diazepam IV: 0.157 mg/kg	No analgesic effect of THC on postoperative pain	0.22 mg/kg dose of THC: euphoria/dysphoria; 0.44 mg/kg dose of THC: anxiety
Staquet et al. (1978)	Belgium, United States	30 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine in 4 mg capsules (synthetic analog of THC); oral codeine (50 mg capsules)	Equivalent pain relief with benzopyranoperidine and codeine and superior to placebo	Drowsiness in 40% of the patients treated with benzopyranoperidine and in 44% of the patients treated with codeine
Staquet et al. (1978)	Belgium, United States	15 patients with cancer pain	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine in 4 mg capsules (synthetic analog of THC); oral secobarbital (50 mg capsules)	Superior pain relief with benzopyranoperidine compared to secobarbital and placebo; secobarbital did not exhibit analgesic properties	Drowsiness in 40% of the patients treated with benzopyranoperidine and in 33% of the patients treated with secobarbital
Jochimsen et al. (1978)	United States	35 patients with chronic pain due to malignancies	Randomized, double-blind, crossover, placebo-controlled	Oral benzopyranoperidine: 2 and 4 mg (synthetic analog of THC); oral codeine: 60 and 120 mg	No analgesic effect of benzopyranoperidine	Sedation equivalent with benzopyranoperidine and codeine
Jain et al. (1981)	United States	56 patients with postoperative or trauma pain	Randomized, double-blind, parallel groups, placebo-controlled	Levonantradol IM 1.5; 2; 2.5 and 3 mg (synthetic cannabinoid): 1.5 mg, 10 patients; 2 mg, 10 patients; 2.5 mg, 10 patients; 3 mg, 10 patients; placebo, 16 patients	Pain relief with the four doses; analgesia persisted for more than 6 h with the 2.5 and 3 mg doses	Frequent drowsiness (18 patients on levonantradol)
Lindstrom et al. (1987)	Sweden	10 patients with chronic neuropathic pain	Randomized, double-blind, crossover, placebo-controlled	Oral cannabidiol: 450 mg/day in three split doses for 1 week	No analgesic effect of cannabidiol	Sedation in seven patients
Holdcroft et al. (1997)	Great Britain	1 patient with severe chronic gastrointestinal pain (Mediterranean fever)	Double-blind, crossover, placebo-controlled	Oral cannabis extract containing 10 mg of THC × 5 times/day for 3 weeks	Statistically significant reduction in morphine consumption with THC intake	Nausea and vomiting
Karst et al. (2003)	Germany	21 patients with chronic neuropathic pain	Randomized, double-blind, crossover, placebo-controlled	Oral CT-3 (10 mg capsules): 40 mg/day for the first 4 days followed by 80 mg/day for the next 3 days (synthetic analog of 11-hydroxy-THC)	CT-3 in both doses was more effective than placebo in relieving pain, with greater pain-reducing effects at 3 h after intake than at 8 h	No major adverse effects

Table 3 (*Continued*)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Buggy et al. (2003)	Great Britain	40 women with postoperative pain (hysterectomy)	Randomized, double-blind, parallel groups, placebo-controlled	Oral THC: 5 mg: 20 patients; placebo: 20 patients	No analgesic effect of THC on postoperative pain	Increased awareness of surroundings
Naef et al. (2003)	Switzerland	12 healthy cannabis–naïve volunteers under experimental pain conditions (heat, cold, pressure, single and repeated transcutaneous electrical stimulation)	Randomized, double-blind, crossover, placebo-controlled	THC: 20 mg (capsules); morphine: 30 mg (capsules); THC: 20 mg + morphine 30 mg (capsules). The three regimens were administered as single oral doses	THC did not significantly reduce pain in any test compared to placebo; in the cold and heat tests, THC even produced hyperalgesia which is completely neutralized by THC–morphine; THC–morphine had a slight additive analgesic effect in the electrical stimulation test; THC–morphine had no analgesic effect in the pressure test	Sleepiness (12), dry mouth (12), vertigo (11), altered perception (10), euphoria (9), confusion (7) and strange thoughts (7) are common but usually mild
Notcutt et al. (2004)	Great Britain	34 patients with chronic pain	Randomized, double-blind, crossover, placebo-controlled	THC: 2.5 mg in sublingual spray for 4 weeks; cannabidiol (CBD) 2.5 mg in sublingual spray for 4 weeks; THC: 2.5 mg + CBD 2.5 mg in sublingual spray for 4 weeks	Pain relief and improvement of sleep quality with THC alone and the THC–CBD combination; CBD alone ineffective	Dry mouth, drowsiness, euphoria/dysphoria, dizziness
Berman et al. (2004)	Great Britain	48 patients with central neuropathic pain associated with brachial plexus root avulsion	Randomized, double-blind, crossover, placebo-controlled	THC: 2.7 mg in sublingual spray or THC: 2.7 mg + CBD 2.5 mg in sublingual spray for three periods of 2 weeks	Statistically significant decrease in pain and statistically significant improvement in sleep quality with THC alone and the THC-CBD combination	Three patients dropped out of the study, including two due to adverse effects of THC; side effects generally mild to moderate in the other patients

Reviews on cannabis and pain: British Medical Association (1997; pp. 39–45), Campbell et al. (2001) and Beaulieu and Ware (2004).

and safety of cannabinoids in multiple sclerosis. During a 1-year follow-up of this trial, in which 502 (80%) of the initial 630 patients decided to continue the study, overall objective improvements of both spasticity (illustrated by a small benefit in the Ashworth scale) and general disability indices were observed. These improvements were objectively confined to patients taking THC alone, although patients reported beneficial effects with both THC alone (Marinol®) and the combination of THC and CBD (Cannador®). Indeed, subjectively, rating scales showed highly significant favourable effects on spasticity, spams, pain, tiredness and sleep with both Marinol® and Cannador®. Overall, no major safety concerns were observed and minor adverse events were reported by 109 patients on THC, 125 on cannabis extract and 127 on placebo (Zajicek et al., 2005).

In another randomized, double-blind, parallel groups, placebo-controlled study, conducted on 160 subjects suffering from multiple sclerosis, Wade et al. (2004) evaluated the effects of a cannabis extract containing almost equal quantities of THC (2.7 mg) and cannabidiol (2.5 mg) administered in sublingual spray at 2.5–120 mg per day doses of each constituent for a period of 6 weeks. In terms of efficacy, this preparation (Sativex®) exhibited the following properties:

- a statistically significant reduction in spasticity with the cannabis extract compared to placebo, evaluated by means of the VAS scores (objective evaluation);
- a statistically significant subjective improvement in sleep quality with the cannabis extract compared to placebo;
- a statistically insignificant objective improvement in mobility and vesical dysfunction with the cannabis extract compared to placebo.

In terms of toxicity, the undesirable effects observed were generally mild and well tolerated (Wade et al., 2004).

A recent report, published after July 1, 2005, confirmed some of the beneficial effects of Sativex® in multiple sclerosis (Rog et al., 2005). During a randomized, double-blind, parallel groups, placebo-controlled trial, conducted in Great Britain and which

Table 4
Controlled studies evaluating the effects of cannabinoids on multiple sclerosis in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Petro and Ellenberger (1981)	United States	9	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5 or 10 mg; single dose	Significant decrease in spasticity in four patients with both doses of THC (objective evaluation)	Minimal
Clifford (1983)	United States	8	Single blind, placebo	Oral THC: 5 mg/6 h; maximum three doses	Objective improvement in tremors and motor coordination in two patients; subjective improvement in tremors and well-being in five patients	Euphoria in all patients with the highest dose used; dysphoria in two patients
Ungerleider et al. (1987)	United States	13	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5–15 mg/day for 5 days	Subjective improvement in spasticity from the 7.5 mg dose; 2.5 and 5 mg doses ineffective	Frequent from the 7.5 mg dose
Greenberg et al. (1994)	United States	10	Randomized, double-blind, parallel groups, placebo-controlled; control group of 10 healthy volunteers	One marijuana cigarette smoked over 10 min (1.54% THC)	Subjective feeling of clinical improvement in some patients; impairment of posture and balance in the 10 patients with multiple sclerosis	Euphoria in all patients smoking marijuana
Martyn et al. (1995)	Great Britain	1	Double-blind, crossover, placebo-controlled	Oral nabilone 1 mg/2 days for two periods of 4 weeks	Significant improvement in muscle spasms, pain, general health status and frequency of nocturia (objective evaluation)	Minor sedation
Killestein et al. (2002)	The Netherlands	16	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5 mg capsules b.i.d. or 5 mg b.i.d. for 4 weeks; oral *Cannabis sativa* extract in capsules providing 2.5 mg b.i.d. or 5 mg b.i.d. of THC with 20–30% CBD and <5% other cannabinoids, for 4 weeks	No benefits on spasticity; treatment with THC or plant extract worsened the patients' global impression	More frequent with the cannabis extract but tolerated
Wade et al. (2003)	Great Britain	18	Randomized, double-blind, crossover, placebo-controlled	*Cannabis sativa* extract containing THC (2.5 mg), CBD (2.5 mg) or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray in doses of 2.5–120 mg/day for four periods of 2 weeks	Statistically significant reduction in spasticity, muscle spasms and pain with THC compared to the placebo (objective evaluation with the VAS scores); statistically significant reduction in pain with CBD compared to placebo; statistically significant reduction in muscle spasms and statistically significant improvement in sleep quality with the THC–CBD combination compared to placebo	Four patients dropped out of the study due to non-tolerated side effects
Zajicek et al. (2003)	Great Britain	630	Randomized, double-blind, parallel groups, placebo-controlled, oral THC: 206 patients; oral cannabis extract: 211 patients; placebo: 213 patients	Oral THC in capsules or oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannabinoids per capsule. Maximum dose: 25 mg of THC/day; duration: 14 weeks	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale (the authors note the limitations of this scale in measuring the highly complex symptoms of spasticity); objective improvement in mobility with oral THC; subjective improvement in muscle spasms, pain, sleep quality and general condition with both types of cannabinoids; decrease in hospitalizations for relapses with both types of cannabinoids	Generally mild and well tolerated

Table 4 (*Continued*)

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Fox et al. (2004)	Great Britain	14	Randomized, double-blind, crossover, placebo-controlled	Oral extracts of *Cannabis sativa* containing 2.5 mg THC per capsule; dose: 5–10 mg of THC b.i.d.; duration: 14 days	No beneficial effects on tremors	Generally mild and well tolerated
Vaney et al. (2004)	Switzerland	50	Randomized, double-blind, crossover, placebo-controlled	Oral extracts of *Cannabis sativa* containing 2.5 mg of THC and 0.9 mg of CBD per capsule; dose: 15–30 mg of THC/day; duration: 14 days	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale; reduction in spasm frequency; improvement in mobility and sleep quality; significant improvement in the patients' general condition	Generally mild and well tolerated
Wade et al. (2004)	Great Britain	160	Randomized, double-blind, parallel groups, placebo	Cannabis extract containing almost equal quantities of THC (2.7 mg) and CBD (2.5 mg) administered in sublingual spray at 2.5-120 mg/day doses of each constituent for 6 weeks (Sativex®); cannabis extracts: 80 patients; placebo: 80 patients	Statistically significant reduction in spasticity with the cannabis extract compared to placebo, evaluated by the VAS scores (objective evaluation); statistically significant subjective improvement in sleep quality with the cannabis extract compared to placebo; statistically insignificant objective improvement in mobility and vesical dysfunction with the cannabis extract compared to placebo	Generally mild and well tolerated
Svendsen et al. (2004)	Denmark	24	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 2.5–10 mg per day for 18–21 days	Statistically significant decrease in central pain with oral THC compared to placebo	Central and musculoskeletal side effects which required a reduction of the THC dose in four patients

Reviews on cannabis and multiple sclerosis: British Medical Association (1997; pp. 27–39), Pertwee (2002), Beard et al. (2003), Killestein et al. (2004), Croxford and Miller (2004), Smith (2004) and Pryce and Baker (2005).

lasted 4 weeks, patients received either a mixture of 2.7 mg THC and 2.5 mg CBD administered by oromucosal spray ($n=32$) or a placebo ($n=32$). The authors showed that the cannabis-based medicine (CBD) was statistically superior to placebo in reducing the mean intensity of pain and sleep disturbance. They noted that CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness ($n=18$ for CBM; $n=5$ for placebo), dry mouth ($n=4$ for CBM; $n=0$ for placebo) and somnolence ($n=3$ for CBM; $n=0$ for placebo). Cognitive adverse reactions were limited to long-term memory storage (Rog et al., 2005).

3.5. Spinal cord injuries

People suffering from spinal cord injuries often exhibit symptoms similar to those of multiple sclerosis, including spasticity, painful muscle spasms and urinary incontinence (British Medical Association, 1997). The available data on cannabinoids for this therapeutic application are limited because they concern a very small number of subjects.

Three controlled studies, one on five patients (Hanigan et al., 1986), the second on one patient (Maurer et al., 1990), and the third on four patients (Wade et al., 2003), are reported in the literature (Table 5). These studies observed that oral THC or *Cannabis sativa* extracts containing THC, cannabidiol or a combination of the two, administered in sublingual spray, may, in some patients, lead to an improvement in spasticity, muscle spasms, pain, vesical dysfunction and sleep quality.

3.6. Gilles de la Tourette's syndrome

Gilles de la Tourette's syndrome is a neurobehavioral dysfunction characterized by motor and verbal tics, as well as a spectrum of behavioral and cognitive disorders. A team of German researchers was particularly interested in the effects of cannabinoids on patients suffering from this problem. In two randomized, double-blind, placebo-controlled studies, one crossover (12 patients), the other with parallel groups (24 initial patients, 7 of whom received oral THC and completed the study), Müller-Vahl et al. (2002a, 2003a) showed that oral THC

Table 5
Controlled studies evaluating the effects of cannabinoids on spinal cord injuries in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Hanigan et al. (1986)	United States	5	Double-blind, crossover, placebo-controlled	Oral THC: 35 mg/day over a period of 20 days	Objective and significant decrease in spasticity in two patients; no objective improvement in spasticity in two other patients	One patient withdrew from the study due to psychological side effects
Maurer et al. (1990)	Switzerland	1	Double-blind, crossover, placebo-controlled	Oral THC 5 mg; oral codeine 50 mg; placebo administered 18 times over 5 months	Pain relief, reduced vesical dysfunction and improvement in sleep quality equivalent with THC and codeine and superior to placebo; decrease in spasticity noted only with THC	None
Wade et al. (2003)	Great Britain	4	Randomized, double-blind, crossover, placebo-controlled	*Cannabis sativa* extracts containing THC (2.5 mg), CBD (2.5 mg) or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray at 2.5–120 mg/day doses for four periods of 2 weeks	Statistically significant decrease in spasticity, muscle spasms and pain with THC compared to placebo (objective evaluation with the VAS scores); statistically significant reduction in pain with CBD compared to placebo; statistically significant reduction in muscle spasms and statistically significant improvement in sleep quality with the THC–CBD combination compared to placebo	Generally mild and well tolerated

Reviews on cannabis and spinal cord injuries: British Medical Association (1997; pp. 27–39) and Consroe (1999).

reduced tics compared to placebo. There were no major undesirable effects in most of the patients (Table 6).

During their latest clinical trial, the researchers also reported that THC did not impair neuropsychological performances: treatment with up to 10 mg oral THC over a 6-week period and immediately as well as 5–6 weeks after withdrawal of THC use had no detrimental effects on learning, interference, recall and recognition of word lists, immediate visual memory and divided attention. To the contrary, the authors even found a trend towards a significant improvement during and after therapy while evaluating immediate verbal memory span. They concluded that treatment with oral THC in patients suffering from Tourette's syndrome did not impair their cognitive function and might even improve it (Müller-Vahl et al., 2003b; Müller-Vahl, 2003).

3.7. Epilepsy

Epilepsy affects about 1% of the world's population. It is estimated that 20–30% of epileptics are not adequately controlled with conventional drugs (Robson, 2001). Cannabidiol appeared

Table 6
Controlled studies evaluating the effects of cannabinoids on Tourette's syndrome in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Müller-Vahl et al. (2002a)	Germany	12 patients	Randomized, double-blind, crossover, placebo-controlled	Oral THC: 5, 7.5 or 10 mg in a single dose	Significant decrease in tics with THC compared to placebo; significant improvement in obsessive-compulsive behavior with THC compared to placebo	No serious adverse effects; five patients experienced mild transient adverse reactions on the nervous system
Müller-Vahl et al. (2003a)	Germany	24 patients (7 patients dropped out or were excluded)	Randomized, double-blind, parallel groups, placebo-controlled; THC: 7 patients; Placebo: 10 patients	Oral THC up to 10 mg/day for 6 weeks	Decrease in tics with THC compared to placebo; THC reached efficacy after about 3 weeks of treatment; this efficacy persisted or increased after more than 4 weeks up to the end of the study (6 weeks)	THC did not impair cognitive functions; no major adverse effects in most patients; one patient dropped out of the study due to side effects such as anxiety and agitation

Reviews on cannabis and Tourette's syndrome: Müller-Vahl et al. (2002b) and Müller-Vahl (2003).

Table 7
Controlled study evaluating the anticonvulsant effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Cunha et al. (1980)	Brazil	15 patients with generalized epilepsy inadequately controlled by standard drugs (ages: 14–49)	Randomized, double-blind, parallel groups, placebo-controlled	Oral cannabidiol 200–300 mg/day for 8–18 weeks; $n = 8$ patients; placebo: seven patients	Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement	Drowsiness reported by four patients on cannabidiol

Reviews on cannabis and epilepsy: British Medical Association (1997; pp. 49–53) and Iversen (2000; pp. 169–171).

to be the most promising cannabinoid in the animal studies. It had a powerful anticonvulsant activity and minimal neurotoxicity (Mechoulam, 1986).

Several anecdotal reports (including the case of Terrance Parker, at the origin of the amendments to the Canadian regulations) suggest that cannabis has anticonvulsant properties and would be effective in treating partial epilepsies and generalized tonicoclonic seizures, still known as grand mal. They are based, among other factors, on the fact that in individuals who smoke marijuana to treat their epilepsy, stopping use of cannabis precipitates the reemergence of convulsive seizures, while resuming consumption of this psychotropic drug controls epilepsy; these results are reproducible (Consroe et al., 1975; Ellison et al., 1990; Grinspoon and Bakalar, 1997; Gurley et al., 1998).

However, only one controlled clinical study exists for this therapeutic application (Cunha et al., 1980). Fifteen patients suffering from secondary generalized epilepsy inadequately controlled by standard drugs, while continuing to take their regular therapy, were subjected to a randomized, double-blind, parallel group study: eight patients received, in addition, oral cannabidiol at 200–300 mg per day for 8–18 weeks and the other seven individuals had their regimen augmented with a placebo. Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement. In the group also receiving the placebo, the condition of six out of seven patients remained unchanged. Drowsiness was reported by four patients on cannabidiol (Table 7).

These results were not confirmed by other controlled clinical studies.

3.8. Glaucoma

Glaucoma is an eye affliction characterized by an increase in intraocular pressure. It can lead to blindness if it is not treated effectively. Several anecdotal reports observe that cannabis has the power to reduce the fluid pressure within the eye (Hepler et al., 1976; Green, 1984; Grinspoon and Bakalar, 1997). Nonetheless, only two controlled studies evaluating the effects of THC on glaucoma patients are reported in the literature (Table 8).

In a randomized, double-blind, crossover, placebo-controlled clinical trial, Merritt et al. (1980) administered one marijuana cigarette containing 2% THC to 18 adults suffering from glaucoma. Marijuana then induced a significant reduction in intraocular pressure but exhibited the following main adverse effects: various sensory alterations (100% of the cases), tachycardia and palpitations (44% of the cases) and postural hypotension (28%).

In another randomized, double-blind, parallel group study against placebo, conducted 1 year later, Merritt et al. (1981) instilled eye drops containing 0.01, 0.05 or 0.1% THC in eight individuals suffering from glaucoma and hypertension (one eye received THC and the other one placebo). They then observed a

Table 8
Controlled studies evaluating the anti-glaucoma effects of cannabinoids in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Merritt et al. (1980)	United States	18 adults with glaucoma (ages: 28–71)	Randomized, double-blind, crossover, placebo-controlled	One marijuana cigarette containing 2% THC	Significant reduction in intraocular pressure	Main side effects: various sensory alterations (100%), tachycardia and palpitations (44%), postural hypotension (28%)
Merritt et al. (1981)	United States	8 patients with glaucoma and hypertension (average age: 65)	Randomized, double-blind, parallel groups, placebo-controlled	Eye drops containing 0.01% (two patients), 0.05% (three patients) or 0.1% (three patients) THC	Significant reduction in intraocular pressure with 0.05% and 0.1% topical solutions of THC; no effect with the 0.01% topical solution of THC	Mild hypotension with the 0.1% topical solution of THC; no psychotropic effects with the 3 THC concentrations administered topically

Reviews on cannabis and glaucoma: British Medical Association (1997; pp. 53–59), Iversen (2000; pp. 164–169) and Järvinen et al. (2002).

Table 9
Controlled studies evaluating the effects of cannabinoids on Parkinson disease in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Sieradzan et al. (2001)	United Kingdom	7	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 0.03 mg/kg in two split doses 12 and 1 h before levodopa administration	Nabilone had no antiparkinsonian effect per se; nabilone had no effect on the antiparkinsonian action of levodopa; significant reduction in total levodopa-induced dyskinesia with nabilone compared to placebo	Two patients withdrew from the study, one because of vertigo, the other one due to postural hypotension; five patients experienced transient side effects of mild sedation, "floating sensation", dizziness, hyperacusis, partial disorientation and formed visual hallucinations
Carroll et al. (2004)	United Kingdom	19	Randomized, double-blind, crossover, placebo-controlled	*Cannabis sativa* extract containing 2.5 mg THC and 1.25 mg CBD per capsule in a 4-week dose escalation study; maximum dose: 0.25 mg/kg of THC per day	The cannabis extract had no pro- or antiparkinsonian effect; the cannabis extract had no effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures	No serious adverse events reported; main side effects: drowsiness/lethargy (nine patients), dry mouth (four patients), detachment (four patients). All adverse effects were improved by dose reduction

significant reduction in intraocular pressure with 0.05 and 0.1% topical solutions of THC. The 0.1% topical solution of THC induced a mild hypotension but no psychotropic effects were observed with the three locally administered THC concentrations.

Even though these results are interesting, the use of cannabis against glaucoma is unsatisfactory, because its beneficial effects are limited by its short-term action (a few hours), by the incidence of undesirable central and peripheral reactions, especially noticeable in the elderly, and by the possibility of using other more effective and less toxic drugs (Hartel, 1999; Institute of Medicine, 1999).

3.9. Parkinson disease

Two controlled clinical trials have evaluated the antiparkinsonian action of cannabinoids as well as their effect on levodopa-induced dyskinesia (Table 9).

In a randomized, double-blind, crossover, placebo-controlled study ($n = 7$), conducted in the United Kingdom, Sieradzan et al. (2001) noted that oral nabilone had no antiparkinsonian action per se when assessed in the practically defined off state and it did not have an influence on the antiparkinsonian effect of levodopa. However, nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo.

In another trial of similar design, performed also in the United Kingdom on 19 patients suffering from Parkinson disease and levodopa-induced dyskinesia, Carroll et al. (2004) showed that the oral administration of a cannabis extract (2.5 mg of THC and 1.25 mg of cannabidiol per capsule) resulted in no objective or subjective improvement in parkinsonism or dyskinesias.

3.10. Dystonia

In a randomized, double-blind, crossover, placebo-controlled trial carried on 15 patients afflicted with generalized and segmental primary dystonia, oral nabilone did not show a significant reduction in total dystonia movement scale score compared to placebo (Table 10). The authors stated that lack of effect of nabilone might have reflected the insufficient dose employed (Fox et al., 2002).

Table 10
Controlled study evaluating the effects of one cannabinoid on dystonia in humans

Study	Country	Number of patients affected	Type of study	Product and dosage	Efficacy	Adverse effects
Fox et al. (2002)	United Kingdom	15 patients with generalized and segmental primary dystonia	Randomized, double-blind, crossover, placebo-controlled	Oral nabilone: 0.03 mg/kg in a single dose	No significant reduction in dystonia with nabilone compared to placebo	Two patients experienced sedation and postural hypotension

Further research will be necessary to determine the impact of cannabinoids in the management of different forms of dystonia.

4. Discussion

The summary of the clinical trials conducted with nabilone and dronabinol reveals that these two cannabinoids have a significant antiemetic efficacy, generally equivalent or superior to that of first-generation antiemetic drugs to relieve nausea and vomiting associated with cancer chemotherapy. Unfortunately, this interest has largely faded since the marketing of new, more potent and less toxic antiemetic drugs. Thus, the existing oral formulations are not recommended as first-line antiemetics.

Nonetheless, cannabinoids could be useful in the 10–20% of cancer patients whose nausea and vomiting are not well controlled by serotonin antagonists or by the more recent neurokinin-1-receptor-antagonists (Jordan et al., 2005). Clinical trials should thus be envisioned to compare the antiemetic effects of cannabinoids to those agents and evaluate the efficacy of their association, not only in cancer chemotherapy but to treat severe nausea and vomiting of various origins.

THC shows to be useful in stimulating appetite and preventing weight loss in cancer and AIDS patients. Its use in these debilitating diseases raises reservations, because some authors report immunosuppressive properties of cannabinoids (Cabral and Dove Pettit, 1998; Zhu et al., 2000; Roth et al., 2002; Pacifici et al., 2003), while others do not (Killestein et al., 2003; Kraft and Kress, 2004). In this regard, work conducted with HIV-1 infected patients has not proved that smoked marijuana or oral THC affects the viral load, the number of $CD4^+$ and $CD8^+$ lymphocytes or the progression of the disease (Kaslow et al., 1989; Abrams et al., 2003; Furler et al., 2004). For a definitive elucidation of the question of the safety of long-term use of cannabinoids in immunodepressed subjects, in-depth studies are still necessary.

The results of the clinical trials on the antinociceptive efficacy of cannabinoids are equivocal. THC, benzopyranoperidine, CT-3 (ajulemic acid) and levonantradol exhibit analgesic effects against certain forms of pain. Other types of pain do not respond as well to cannabinoids. No controlled study has evaluated the analgesic power of smoked cannabis.

In animal and human studies, it has been proved that cannabinoids and opiates have synergistic actions on pain control (Iversen, 2003; Lynch and Clark, 2003; Maldonado and Valverde, 2003). Controlled clinical trials evaluating the combined analgesic effects of these two types of psychotropic drugs would thus be suitable.

Cannabinoids exhibit some antispasmodic and muscle relaxant properties which could be used beneficially to relieve certain symptoms of multiple sclerosis and spinal cord injuries. Considering all of the results obtained, it can be said that cannabinoids do objectively show a small noticeable beneficial effect on the spasticity of individuals suffering from these pathologies. They can also lead to a subjective improvement of this same spasticity and a moderate, albeit significant, improvement in the patients' motor capacity and general well-being (Derkinderen et al., 2004). Future clinical trials should improve quantitative assessments of spasticity and elude, if possible, the Ashworth scale due to its limitations in evaluating spasticity. Indeed, this method might not be sufficiently sensitive to detect clinically beneficial effects induced by cannabinoids (Pryce and Baker, 2005).

The results obtained with oral THC in the treatment of Tourette's syndrome are promising and suggest that it is effective and well tolerated for this pathology. Clinical trials provide evidence that THC reduces motor and vocal tics of Tourette's syndrome as well as its associated behavioral problems such as obsessive-compulsive disorders. It remains to be specified which cannabinoids are the most effective and what routes of administration should be privileged.

With only one controlled study available, the role of cannabinoids in the treatment of epilepsy remains speculative. Cannabidiol presents an interesting therapeutic potential but additional research on its anticonvulsant properties, whether alone or in association with the standard drugs, is necessary and justified. It is surprising to observe that such work has not yet been done, in view of this cannabinoid's absence of psychoactive effects.

Even though THC may offer some interest as an anti-glaucoma agent, there are currently several more effective and less toxic drugs to treat this pathology. There are no controlled clinical trials comparing the beneficial and undesirable effects of cannabinoids to the existing conventional drugs. Cannabinoids should be preferably applied topically and produce a sustained reduction in intraocular pressure without exhibiting unacceptable central and systemic effects. It should be possible to administer them in the long-term without developing a tolerance. It should also be possible to determine whether cannabinoids have additive effects with the anti-glaucoma agents available in order to also consider their eventual use as an adjuvant therapy.

Cannabinoids do not demonstrate an antiparkinsonian effect per se in controlled studies, nor do they provide convincing evidence of their effectiveness to treat dystonia.

Regarding other therapeutic applications, there is a growing interest in evaluating the potential of cannabinoids as anti-inflammatory (Burstein et al., 2004; Perrot, 2004) and anticancer agents (Bifulco and Di Marzo, 2002; Walsh et al., 2003; de Jong et al., 2005), as well as in the treatment of psychotropic drug dependence (Labigalini et al., 1999; De Vries et al., 2001; Piomelli, 2001; Robson, 2001; Yamamoto et al., 2004; Arnold, 2005). However, apart from the recent work of Blake et al. (2005) on rheumatoid arthritis, controlled clinical trials are lacking so far and, therefore, there is no solid evidence supporting their efficacy in such pathologies.

Until recently, two cannabinoids were marketed in Canada: nabilone (Cesamet®) and oral THC or dronabinol (Marinol®). On April 19, 2005, Health Canada approved Sativex® for the symptomatic relief of neuropathic pain in adults suffering from multiple sclerosis. This cannabis extract is administered via a spray into the mouth and contains 2.7 mg of THC and 2.5 mg of CBD per spray. It is available under prescription in the pharmacies of Canada since June 20, 2005. Nabilone (Cesamet®) and dronabinol (Marinol®) are not very popular in clinical practice, since the gap between the effective doses and the doses exhibit-

ing side effects on the central nervous system is rather narrow (Iversen, 2003). Although the adverse reactions reported are not generally considered serious, drowsiness, euphoria, dysphoria, dizziness and some other central effects limit the use of these two drugs in some patients. As for Sativex®, in view of its more recent use, its efficacy and toxicity profiles still have to be specified in the pathologies in which it will be used.

Compared to the intrapulmonary route, orally administered cannabinoids have a slower onset of action, a more erratic absorption and lower peak concentrations of drug. These three negative aspects explain why more and more patients turn to smoking marijuana for self-medication, which provides them with a more rapid and increased relief from the symptoms (Söderpalm et al., 2001). Furthermore, some patients who are experienced smokers find that this route of administration allows them to titrate more adequately the appropriate dose to control their symptoms and stop when the desired effect is obtained (Chang et al., 1979; Clark, 2000; Iversen, 2000; Abrams et al., 2003). Finally, inhaled THC is absorbed better than oral THC and cannabis contains other substances which increase the effects of THC and which could modulate its toxic effects (British Medical Association, 1997; Baker et al., 2003; Roncoroni, 2003; Wade et al., 2003; Carter et al., 2004). For all these reasons, smoked cannabis is preferred and considered more effective by many patients (Baker et al., 2003; Duran et al., 2004; Wingerchuk, 2004; Gorter et al., 2005).

Unfortunately, a marijuana cigarette is more harmful to health than oral THC. In theory, it can cause as many pulmonary problems as 4–10 regular cigarettes (Fehr et al., 1983; Kleber et al., 1997). Cannabis smokers are at greater long-term risk of suffering from pharyngitis, rhinitis, asthma, bronchitis, emphysema and lung cancer (van Hoozen and Cross, 1997; Hall and Solowij, 1998). This consideration is less important in the case of palliative care provided to terminally ill patients. Furthermore, the psychoactive effects of marijuana are likely to limit its clinical usefulness in the general population (Söderpalm et al., 2001).

In view of the current knowledge on cannabis and cannabinoids, the following methodological considerations should be pointed out:

1. Bioavailabilities and other pharmacokinetic parameters might conditionate the route of administration and the efficacy and toxicity of the treatment.
   - Cannabis is generally taken by smoking or ingestion. When inhalated, the bioavailability of THC varies from 18 to 50%, the onset of action is rapid (3–5 min), maximal effects are obtained within 30–60 min and euphoria is intense and might last 2–4 h. When cannabis is administered orally, the bioavailability ranges from 6 to 20%, the onset of action is slow (30–60 min), euphoria is less pronounced and effects are progressive and last longer (Ben Amar and Léonard, 2002).
   - Nabilone (synthetic analogue of THC) or Cesamet®, dronabinol (synthetic THC) or Marinol® and THC + CBD or Sativex®, the three current pharmaceutical preparations approved for medicinal use, have different pharmacokinetic profiles. Nabilone (Cesamet®) is administered orally and has a bioavailability of 60%. Dronabinol (Marinol®), also used orally, has a bioavailability of 10–20%. Sativex® is taken sublingualy as an oromucosal spray; its bioavailability is not well documented (CPA, 2005).
2. Placebo-controlled clinical trials involving cannabis or cannabinoids are problematic: although placebo is designed to match the appearance, smell and taste of the active formulation, the specific psychoactive properties of cannabinoids make many patients aware whether they are receiving the drug or placebo. This might influence the outcome, the statistical analysis and the value of the results. To mitigate this difficulty, the degree of blinding should be formally assessed in each study.
3. Side effects should be carefully taken into account depending on the population studied. Acute administration of cannabis should be pondered in elderly patients and sensitive individuals while psychotic or particularly vulnerable patients should avoid chronic use of cannabinoids. Although chronic psychosis induced by cannabis or cannabinoids remains controversial (Phillips et al., 2002; Degenhardt et al., 2003; Macleod et al., 2004), the possibility of such event should be seriously considered (Arseneault et al., 2002; van Os et al., 2002; Zammit et al., 2002; Fergusson et al., 2003) as well as other chronic toxic effects (i.e. respiratory and cardiovascular problems).
4. Rating of adverse reactions should be minutiaely categorized. Depending on the disease treated and the interpretation of the evaluator, the same side effect may be considered "minor" or "major". The lack of a standard scale that qualifies and quantifies the nature and severity of some toxic events related to cannabinoids raises the possibility of an underestimation of such events. Hence, a statement that there are no "major" side effects might be problematic, particularly if the research is funded by interested parties.
5. Drug interaction factors should also be analyzed. In some trials, more than one cannabinoid is evaluated and in other cases, the cannabinoid is administered in addition to the treatment drug. This might affect the efficacy and toxicity of the treatment applied. For example, the synergistic analgesic and sedative actions of cannabinoids and opiates are well documented (Lynch and Clark, 2003) while CBD has anticonvulsant and analgesic activities of its own and has the power to modulate the effects of THC (Rog et al., 2005).

To maximize the benefits (efficacy) and reduce the undesirable effects (toxicity), new formulations for administering and delivering cannabinoids are currently under investigation. These are smokeless oral inhalers (aerosols), sublingual preparations, nasal sprays, transdermal patches and rectal suppositories. The intravenous route is excluded because cannabinoids are insoluble in water. The sublingual spray is a compromise between the inhaled and oral routes: compared to the oral administration, it reduces the first-pass metabolism, thus increasing the bioavailability of the drug and allowing a greater dose-titration (Pryce and Baker, 2005).

Whatever the case may be, few controlled studies have been performed to date with smoked marijuana to evaluate rigorously the advantages and inconveniences of this pharmaceutical form. Comparative studies of smoked marijuana and various cannabinoids administered via different routes are necessary to specify the role that smoked cannabis may play in various therapeutic applications. Relaxation of the regulations on access to cannabis for medical purposes and a greater interest from the pharmaceutical industry in including this type of preparation in their research protocols would facilitate the realization of such clinical trials.

5. Conclusion

The progress achieved over the past 15 years in understanding the action mechanisms of THC and other cannabinoids has revived the therapeutic interest in these substances.

The relaxation of the regulatory norms for therapeutic cannabis and the accomplishment of a greater number of controlled clinical trials make it possible to affirm that cannabinoids exhibit an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, as well as in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

However, based on the available data, oral cannabinoids should not be used as first-line antiemetics. They may, however, prove effective to treat refractory emesis and have their place as adjuvants to other antiemetic medications. There is insufficient evidence on the efficacy of cannabis and its derivatives to control epilepsy. Further clinical trials, well-designed, carefully executed and powered for efficacy, are essential to clearly define the role of cannabinoids as appetite stimulants, as well as in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome and glaucoma.

For each pathology, it remains to be determined what type of cannabinoid and what route of administration are the most suitable to maximize the beneficial effects of each preparation and minimize the incidence of undesirable reactions.

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REVIEW ARTICLE

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Therapeutic Potential of Cannabinoids in CNS Disease

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Abstract

The major psychoactive constituent of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein–coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signalling is mostly inhibitory and suggests a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial.

Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic agent in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexanabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical

trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and cancer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of Δ^9-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity.

Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexanabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB_1 receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB_1 receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment.

This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders.

The anecdotal use of cannabis as a therapeutic agent dates back about 5000 years, with descriptions of its numerous effects including alterations in mood, cognitive functions, memory and perception of the user.[1] However, until recently there has been little scientific evidence to support these largely observational data.

The plant *Cannabis sativa*, commonly known as marijuana, contains many different compounds, although the major psychoactive constituent is Δ^9-tetrahydrocannabinol (Δ^9-THC).[2] Other compounds found in cannabis include Δ^8-THC (less potent than Δ^9-THC and found in smaller quantities), cannabidiol (CBD; a nonpsychoactive compound) and cannabinol (CBN).

Following the isolation of Δ^9-THC from cannabis, numerous synthetic cannabinoids, based on the structure of Δ^9-THC, were synthesised. These were shown to induce behavioural effects such as hypothermia, catalepsy and hypomobility, similar to the *in vivo* effects of Δ^9-THC, when injected into animals.[3] Upon the identification and cloning of a specific G-protein–coupled cannabinoid receptor in the brain that mediated the effects of Δ^9-THC (the CB_1 receptor),[4] an endogenous agonist of this receptor, anandamide, was identified.[5] Importantly, this suggested the presence of an endogenous cannabinoid system in the CNS. Other endocannabinoids such as 2-arachidonyl-glycerol (2-AG) and palmitoylethanolamide (PEA) have also been isolated and shown to be present in the CNS.

Interestingly, the CB_1 receptors localise to important structures within the brain that are associated with various neurological diseases. The inhibitory effects of stimulation of these receptors on neurotransmitter release at these sites has focused the study of cannabinoids as therapeutic agents on disorders such as Parkinson's disease, brain trauma and multiple sclerosis (MS).

A second cannabinoid receptor (the CB_2 receptor) is found preferentially in the periphery.[6] The CB_2 receptor is highly expressed on cells of the immune system. The presence of the CB_2 receptor in the lymphoid organs suggests that, in addition to

its psychoactive effects in the CNS, the endocannabinoid system may have a role in modulating the immune system. Indeed, cannabinoids have profound effects on cell-mediated immunity including the inhibition of T-cell proliferation, proinflammatory cytokine secretion and the humoral responses from B cells.[3] This has prompted the study of the therapeutic potential of cannabinoids as anti-inflammatory agents and has become the focus of study in a number of diverse animal models of disease.

This article reviews current knowledge of the endocannabinoid system and discusses the isolation of new cannabinoid agonists, as well as the evidence for the presence of various cannabinoid receptors. The use of cannabinoid agonists and antagonists as potential therapeutic agents for a number of CNS disorders is then reviewed. The numerous adverse effects associated with cannabinoid administration and potential methods of dissociating these from the therapeutic effects are also discussed.

1. The Endocannabinoid System

Currently, two subtypes of cannabinoid receptors have been isolated and cloned: CB_1 and CB_2.[4,6,7] The inhibitory effects of CB_1 receptor signalling on cyclic adenosine monophosphate (cAMP) accumulation and its blockade by pertussis toxin[8,9] are consistent with the CB_1 receptor belonging to the family of G-protein–coupled receptors.

The human CB_1 receptor exhibits 68% homology with the human CB_2 receptor at the transmembrane level and 44% overall.[6] Interestingly, cannabinoid receptors, especially CB_1 receptors, have been shown to be present and relatively conserved in many species including fish, hydra, mollusc, leech and sea urchin, suggesting the evolutionary conservation of the endocannabinoid system.[10-14] However, it is not thought to be present in insects.[15] A splice variant of the CB_1 receptor, CB_{1A}, has also been described.[16]

The discovery of endogenous cannabinoid compounds, such as anandamide, that act as agonists at these receptors has revealed the presence of an endocannabinoid system. This has subsequently intensified research into the production of synthetic agonists and antagonists, which has been the cornerstone from which the modern study of the neuropharmacology of cannabinoids has been derived.

1.1 Cannabinoid CB_1 Receptor Expression

CB_1 receptors are predominately found presynaptically on neurons in the CNS, although they are expressed to a lesser degree in the periphery, on cells of the immune system, testis, vascular endothelium, small intestine and peripheral nerve presynapses (table I).[17]

CB_1 receptors are most abundant in the regions and structures of the brain responsible for the behavioural and pharmacological effects seen following cannabinoid administration (table I). In addition, anecdotal evidence related to the adverse effects of cannabis usage supports the presence of cannabinoid receptors in these areas. Although CB_1 receptors are present in extremely high concentrations throughout the brain, they are most dense in the hippocampus, basal ganglia and cerebellum.[18,35] The hippocampus is involved in the storage and processing of newly acquired information, and the CB_1 receptor is highly expressed on cells of the molecular layer of Ammon's Horn.[20] The presence of CB_1 receptors in this region may correlate with the reported loss of short-term memory in users of cannabis.[36] A synthetic CB_1 receptor antagonist, rimonabant (SR-141716A), has been shown to antagonise a number of effects mediated by cannabinoid ligand binding and signalling through the CB_1 receptor.[37] However, when used alone, this drug has been reported to act as an 'inverse agonist': that is, it elicits the opposite effect to that of the agonist, as it has been shown to *improve* memory in a rodent model.[38]

Another common adverse effect associated with cannabis use is decreased locomotor activity, which may correlate with the presence of CB_1 receptors in regions that mediate coordination of motor function and motor learning such as the basal ganglia, substantia nigra and cerebellum. In the cerebellum, CB_1 receptors are highly expressed in the molecular lay-

Table I. Location of cannabinoid receptors

Location	Structure	Function	References
CB_1 receptors			
CNS	Hippocampus	Memory storage	18
	Cerebellum	Coordination of motor function, posture, balance	19, 20
	Basal ganglia	Movement control	18, 19
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite	18, 21
	Spinal cord	Nociception	22, 23
	Cerebral cortex	Emesis	24, 25
Periphery	Lymphoid organs	Cell-mediated and innate immunity	26
	Vascular smooth muscle cells	Control of blood pressure	27
	Duodenum, ileum, myenteric plexus	Control of emesis	28
	Lung smooth muscle cells	Bronchodilation	29
	Eye ciliary body	Intraocular pressure	30, 31
CB_2 receptors			
Periphery	Lymphoid tissue	Cell-mediated and innate immunity	6, 26
	Peripheral nerve terminals	Peripheral nervous system	32
	Retina	Intraocular pressure	33
CNS	Cerebellar granule cells mRNA	Coordination of motor function	34

er, which is important for the relay of distal limb coordination and balance information between the thalamus and spinal cord.[20]

The presence of cannabinoid receptors in these important brain structures and the inhibitory effects of cannabinoids on neuropeptide secretion[3] suggest that cannabinoids may have potential as therapeutic agents in a wide variety of CNS disorders.

1.2 CB_2 Receptor Localisation

The CB_2 receptor is often described as the 'peripheral' cannabinoid receptor, as many studies have shown high levels of CB_2 receptor expression in a number of peripheral tissues, including cells of the immune system in the spleen.[6,39] The high level of expression of CB_2 receptors on cells of the immune system has led investigators to study the potential role of cannabinoids in modulating the immune system in a variety of clinical applications. In addition, CB_2 receptors are expressed in the tonsils, bone marrow, thymus and pancreas,[26] adult rat retina,[33] and peripheral nerve terminals in the mouse vas deferens[32] (table I). Although the CB_2 receptor is not thought to be expressed in the CNS,[6] it is not clear at present whether CB_2 receptor expression can be induced in the CNS in some circumstances. In addition, mRNA coding for the CB_2 receptor has been detected in cerebellar granule cells.[34]

1.3 Cannabinoid Receptor Signalling

CB_1 and CB_2 receptors are $G_{i/o}$-protein–coupled receptors that, following cannabinoid agonist binding and signalling, exert an inhibitory effect on adenylate cyclase (AC) activity. This inhibits the catalytic reaction converting cyclic adenosine triphosphate to cAMP, an important cellular secondary messenger involved in cellular regulation.[40,41] In addition to the effects on cAMP, cannabinoid signalling through CB_1, but not CB_2, receptors can also interact with ion channels.[42] It has been well established that CB_1 receptor signalling negatively regulates calcium currents through both N- and P/Q-type voltage-sensitive Ca^{2+} channels[43,44] but activates G-protein–coupled inwardly rectifying K^+ channels.[44]

CB_1 receptor signalling also leads to the downstream activation of mitogen-activated protein kinase,[45] p38 and c-jun amino terminal kinase,[46] which are involved in cellular regulation of proliferation and differentiation.

One outcome of presynaptic CB_1 receptor stimulation on neurons is to reduce neuronal cell activity and attenuate, via retrograde signalling, the release of neurotransmitters such as dopamine, noradrenaline (norepinephrine), serotonin, GABA and glutamate.[47-51] This property of cannabinoid agonist signalling is an attractive characteristic for the utilisation of cannabinoids in the treatment of numerous medical disorders.

There is also evidence that other undiscovered G-protein–coupled receptors may exist in the cannabinoid system. The binding of the cannabinoid receptor agonist [^{3}H]R(+)WIN55,212-2 to CNS structures, including the hippocampus, cortex and brain stem, in CB_1 receptor knockout (CB1 -/-) mice suggests the presence of other cannabinoid-like receptors.[52] Interestingly, R(+)WIN55,212-2 and anandamide, but not Δ^9-THC or CP-55940 (another cannabinoid agonist), stimulated guanosine 5′-O-(γ[^{35}S]-thio)triphosphate ([^{35}S]GTPγS) binding in CB1 -/- mice, indicating that they are signalling through a G-protein–coupled receptor.[52] The stimulation of both basal and anandamide-induced [^{35}S]GTPγS binding could be inhibited by the addition of the CB_1 receptor antagonist rimonabant.[52]

Apart from cannabinoid agonist binding and G-protein involvement, these unknown receptors appear to mediate some of the effects associated with cannabinoid signalling through the known cannabinoid receptors. A number of behavioural effects induced by anandamide were still present in CB_1 -/- mice.[53] The addition of anandamide, but not Δ^9-THC, to CB_1 -/- mice was shown to decrease their spontaneous activity, induce antinociception and increase immobility.[53]

The presence of undiscovered cannabinoid receptors is not only limited to the CNS. Mesenteric arteries isolated from either CB_1 -/- or CB_1 and CB_2 -/- mice were responsive to both 'abnormal CBD' [(2)-4-(3-3,4-*trans*-*p*-menthadien-1,8)-yl-olivetol, a cannabidiol derivative produced by transposition of the phenolic hydroxyl group and the pentyl side chain of CBD] and anandamide-induced vasodilation through a mechanism independent of both CB_1 and CB_2 receptors.[54] These responses were sensitive to the antagonist effect of rimonabant[54] and suggest the presence of undefined receptors for which anandamide is an agonist and rimonabant is an antagonist.

1.4 Endocannabinoid Ligands

Following the discovery of cannabinoid receptors, which mediate the effects of naturally occurring plant cannabinoids, a number of endogenous cannabinoid ligands have been identified (table II).

Anandamide, the first endogenous ligand to be identified, was isolated and purified from porcine brain.[5] Anandamide is an unsaturated fatty acid ethanolamide, derived from arachidonic acid, and is synthesised and secreted by neurons and immune system cells. It mediates cannabinoid-type effects such as antinociception, hypoalgesia and catalepsy. It has a higher affinity for the CB_1 receptor (inhibition constant [Ki] 89 nmol/L) than the CB_2 receptor (Ki 371 nmol/L).[55]

Concentrations of anandamide have been measured by a variety of techniques in pig, rat, mouse and human brain.[5,56-59] The findings from these studies suggest that anandamide is present at pmol/g concentrations in the CNS. In addition, the highest concentrations measured in specific structures of rat and human brain were observed in the hippocampus, striatum and cerebellum, corresponding to areas of high CB_1 receptor expression and indicating a role for anandamide in CB_1 receptor signalling. However, high anandamide concentrations were also recorded in the thalamus, an area with low levels of CB_1 receptor expression.[58] Anandamide has also been identified in peripheral structures such as the spleen (which expresses high concentrations of CB_2 receptors),[60] kidney,[61] skin,[58] uterus[62] and blood.[63] Release of anandamide has been shown from neuronal cells stimulated with glutamate[64] and following dopamine D_2–like receptor stimulation in conjunction with a high K^+ stimulus.[65] Anandamide has also been shown to activate the vanilloid receptor (VR_1), a nonselective cation channel expressed by primary afferent nociceptive neurons and activated by capsaicin, although the

Table II. Cannabinoid receptor agonists and antagonists

Class	Ligand	Selectivity of receptor binding
Agonists		
Endogenous	Anandamide	CB_1>CB_2>VR_1
	2-Arachidonyl-glycerol	CB_1
	Palmitoylethanolamine	CB_2?
	Noladin ether	CB_1>CB_2
	Virodhamine	CB_2
Classical cannabinoids	Δ^9-THC	CB_1>CB_2
	Δ^8-THC	CB_1>CB_2
	Cannabinol	CB_1>CB_2
	Cannabidiol	Low binding affinity
	HU-308	CB_2
	JWH-133	CB_2
	Dexanabinol (HU-211)	No binding to CB_1/CB_2
	HU-210	CB_1>CB_2
	Nabilone	CB_1>CB_2
	Levonantradol	CB_1>CB_2
Nonclassical cannabinoids	CP-55940	CB_1>CB_2
Aminoalkylindoles	R(+)WIN55,212-2	CB_1>CB_2
	S(−)WIN-55213	Low binding affinity
	JWH-015	CB_2
Others	Arvanil	CB_1>VR_1
Antagonists		
	Rimonabant (SR-141716A)	CB_1
	SR-144528	CB_2
	AM-630	CB_1>CB_2
	Virodhamine	CB_1

THC = tetrahydrocannabinol; **VR** = vanilloid receptor; **?** indicates no CB_2 binding, but effects of the ligand signalling are inhibited by SR-144528 (CB_2 receptor antagonist); > indicates higher binding affinity.

VR_1 receptor does not have homology with either CB_1 or CB_2 receptors.[66-69]

Recently, a second endogenous cannabinoid, 2-AG, was isolated from canine intestinal tissue.[70] Although present in the brain in greater quantities than anandamide,[71] it has a lower affinity for the CB_1 receptor (Ki 472 nmol/L)[70] and is also inactivated by fatty acid amide hydrolase (FAAH) more rapidly than anandamide.[72]

PEA has also been proposed as an endocannabinoid agonist and is produced by both neurons and immune cells.[73,74] However, PEA has been shown to mediate both anti-inflammatory and analgesic effects similar to other endocannabinoids.[75,76] Although this effect can be inhibited by the addition of the CB_2 receptor antagonist SR-144528, there is evidence to suggest that PEA does not bind to CB_1 or CB_2 receptors.[77,78] This may indicate the presence of further, as yet undiscovered, CB_2-like cannabinoid receptors. However, the mechanism of action of PEA may be to increase concentrations of anandamide by inhibiting FAAH activity.[78] Furthermore, PEA can enhance the stimulation of VR_1 receptors by anandamide.[79] The antinociceptive effects of PEA are particularly interesting, as it seems that this is a peripherally mediated effect. This implies that it may be possible to dissociate therapeutic effects from CB_1 receptor–mediated effects, and that this may lead to better tolerated, clinically useful nonpsychoactive cannabinoids.

A further endogenous cannabinoid receptor agonist, noladin ether, has recently been identified from porcine brain.[80] It has been shown to bind to CB_1 receptors with a higher affinity than CB_2 receptors,

and to induce sedation, hypothermia and intestinal immobility in mice.[80]

Recently, a novel endocannabinoid, virodhamine, has been isolated and characterised.[81] Virodhamine is expressed in the rat CNS, with concentrations comparable to anandamide present in the hippocampus, cortex and cerebellum.[81] Interestingly, the concentrations of virodhamine are much higher in the high CB_2 receptor–expressing peripheral tissues such as skin, spleen, kidney and heart, in comparison with anandamide.[81] The higher concentrations of virodhamine in the periphery suggest that its affinity for CB_1 and CB_2 receptors may differ. Indeed, functional assays measuring guanosine triphosphate binding have determined that virodhamine is a full CB_2 receptor agonist.[81] In contrast, it has been shown to be a partial agonist at the CB_1 receptor *in vitro* and a CB_1 receptor antagonist *in vivo*.[81] In addition, virodhamine inhibits transport of anandamide and, similar to other cannabinoids, induces hypothermia in mice.[81] Further study is required to determine the areas of production, storage and degradation of virodhamine, as well as how it regulates other cannabinoids in the endocannabinoid system.

The low concentrations of anandamide in serum, plasma and CSF[58] and the short duration and magnitude of its effects suggest that this compound is inactivated rapidly at the site of action. Indeed, it has now been shown that anandamide is inactivated by a two-step mechanism. First, a high-affinity specific transporter transports it across the plasma membrane.[74] Reuptake of endocannabinoids has been shown in both rat neurons and astrocytes[82] and human neuroblastoma and astrocytoma cells.[83,84] In addition, peripheral mechanisms of anandamide reuptake also exist in macrophages and human endothelial cells.[73,85] Blockade of this transporter by AM-404 potentiates the anandamide-induced inhibition of AC in cortical neurons by a receptor-mediated mechanism, which can be inhibited by rimonabant.[82] Recent studies have supported the specificity of AM-404 as an inhibitor of endocannabinoid transport.[82] AM-404 has no affinity for G-protein–coupled receptors and ligand-gated ion channels,[86] although there is evidence to suggest that it can activate vanilloid receptor channels.[69,87]

Following the transportation of anandamide across the plasma membrane, it is rapidly metabolised to arachidonic acid and ethanolamine by a specific enzyme, FAAH.[88,89] FAAH has been identified in both neurons and astrocytes in the CNS,[82,90] human platelets[91] and lymphocytes,[92] rat macrophages[93] and renal endothelial and mesangial cells.[61] Furthermore, following administration of anandamide, mice lacking FAAH exhibit intense behavioural effects such as hypomotility, analgesia and hypothermia compared with normal mice.[94] The mice lacking FAAH also possessed 15-fold higher concentrations of anandamide in the brain than normal animals.[94] In addition, inhibition of FAAH by AM-374 results in the increased effect of anandamide on receptor-mediated acetylcholine release from neurons.[95] This provides further evidence of a specific intricate system for the release, signalling and inactivation of endocannabinoids.

1.5 Synthetic Cannabinoid Agonists and Antagonists

Cannabinoid receptor agonists can be classified as belonging to one of four groups: eicosanoid cannabinoids (which include the endocannabinoids), classical cannabinoids, nonclassical synthetic cannabinoids and aminoalkylindoles (AAIs) [table II].

The classical cannabinoids include compounds isolated from cannabis, mainly Δ^9-THC, Δ^8-THC (less potent than Δ^9-THC), CBN and CBD (the latter two are both present in greater quantities than Δ^9-THC but are less potent, both in terms of affinity for and activation of cannabinoid receptors). These compounds, with the exception of CBD (which has a very low affinity for CB_1 and CB_2 receptors and does not activate the receptor upon binding), signal through both CB_1 and CB_2 receptors. Other classical compounds that demonstrate CB_2-selective binding, such as HU-308 and JWH-133, have been developed.

Nonclassical cannabinoids include CP-55940, which has been used extensively in cannabinoid receptor–binding studies.

AAIs are structurally different from classical/nonclassical cannabinoids and the endocannabinoids themselves. However, they mediate cannabimimetic effects via a stereo-selective receptor-mediated mechanism, which is G-protein dependent. R(+)WIN55,212-2 is an AAI with activity at both CB_1 and CB_2 receptors.[96] A CB_2 receptor–selective compound, JWH-015, based on R(+)WIN55,212-2, has recently been described (Ki 14 ± 5 nmol/L).[97]

Importantly, selective antagonists for CB_1 and CB_2 receptors have been synthesised: rimonabant for the CB_1 receptor[98] and S-144528 for the CB_2 receptor.[99] These have allowed the dissection of cannabinoid effects related to either CB_1 or CB_2 receptors. It has been reported that both antagonists possess inverse agonist properties.[100-102] Chinese hamster ovary cells transfected to express the CB_1 receptor (CHO-CB_1) exhibit constitutive CB_1 receptor activity compared with nontransfected CHO cells.[100,101] Agonist signalling through CB_1 receptors *in vitro* has been shown to upregulate the receptor-mediated activation of G-proteins, as measured by [^{35}S]-GTPγS binding.[101] Upon the addition of either R(+)WIN55,212-2 or CP-55940, the incorporation of [^{35}S]-GTPγS is increased.[101] However, following the addition of rimonabant, constitutive [^{35}S]-GTPγS concentrations are reduced.[100,101] This could be explained by either inverse agonism or the antagonism of a cannabinoid agonist endogenously released from tissue culture cells. However, the addition of an anandamide synthase inhibitor to CHO-CB_1 cells had no effect on the basal concentrations of [^{35}S]-GTPγS. In addition, similar effects were seen using CB_2 receptor–transfected CHO cells and SR-144528.[102] Therefore, it appears that rimonabant and SR-144528 are potentially inverse agonists; however, it remains to be seen whether this is relevant to *in vivo* systems.

2. Clinical Applications of Cannabinoids

There exists much anecdotal evidence for the use of cannabis to relieve some of the symptoms associated with CNS disorders such as MS and pain. Some patients with numerous disorders find prescription medicines have little or no effect upon severe disease symptoms and in addition may experience serious adverse effects. Therefore, following the historical reports of the use of cannabis for medicinal purposes, recent research has highlighted the great potential of cannabinoids to treat a wide variety of clinical disorders. The number of clinical trials investigating the therapeutic potential of cannabinoids is increasing, and trials are currently underway in a number of CNS disorders including emesis, neurodegeneration and brain trauma, spasticity associated with MS, loss of appetite/nausea (in patients with AIDS and those receiving chemotherapy) and pain (table III).[103]

2.1 Multiple Sclerosis

MS is an autoimmune inflammatory disease of the CNS that affects roughly 2.5 million individuals worldwide.[119] Symptoms of MS usually include muscle stiffness and spasticity, tremor, fatigue, pain, incontinence and sexual dysfunction, which can lead to increased anxiety and depression. Control of these MS-associated symptoms can be difficult, and current drug therapies for MS-associated spasticity, including oral or intrathecal baclofen, dantrolene, diazepam, tizanidine[120] and gabapentin,[121] can have considerable adverse effects including hallucinations, hypotension, seizures, anxiety, weakness, nausea and flu-like symptoms.[122]

Many patients who have MS have reported the beneficial effects of cannabis on spasticity, tremor, pain and anxiety.[123] Although the mechanisms of spasticity and motor dysfunction in MS are not fully understood, they may involve the presence of demyelinating lesions in the cerebellum, hypersensitivity of neurons due to denervation, damage to descending motor pathways in the spinal cord and alterations in sodium channel conduction of damaged neurons.[124] The relatively high concentration of CB_1 receptors in the cerebellum and the inhibitory

Table III. Recent clinical trials of cannabinoids for the treatment of CNS disorders

Disorder	Target symptoms	Therapeutic cannabinoid	Clinical outcome	References
Multiple sclerosis	Spasticity	Oral THC, CBD	In progress	104
	Neurogenic pain	Sublingual THC, CBD	Phase II trial in progress	105
	Bladder dysfunction	Sublingual THC, CBD	Phase II trial in progress	105
Parkinson's disease	Dystonia	Nabilone	No effect	106
	Dyskinesia	Nabilone	↓ Dyskinesia	107
	Tremor	Δ9-THC	No effect	108
Cancer	Pain	Sublingual THC, CBD	Phase III trial in progress	105
Postoperative pain	Pain	Intramuscular levonantradol	↓ Pain but less effective than existing therapies	109
Spinal cord injury	Pain	Sublingual THC, CBD	Phase II trial in progress	105
Gastrointestinal tract pain	Pain	THC	Reduced morphine requirement	110
Traumatic brain injury/ stroke	Neurodegeneration	Intravenous dexanabinol (HU-211)	↓ Intracranial pressure, ↓ mortality; phase III trial in progress	111-113
	Neurodegeneration	CBD	In progress	105
HIV wasting syndrome	Appetite loss, nausea	Smoked cannabis	In progress	114, 115
	Appetite loss, nausea	Dronabinol	↑ Appetite, ↓ nausea	116, 117
Tourette's syndrome	Behavioural disorders	THC	Undetermined	118

CBD = cannabidiol; **THC** = tetrahydrocannabinol; ↓ indicates reduced; ↑ indicates increased.

effect of cannabinoids on neuronal conduction, neuromuscular transmission and neurotransmitter release suggest that cannabinoids may be effective in treating spasticity. Another CB_1 receptor–rich structure of the brain, the substantia nigra, is targeted by muscle-relaxing drugs such as baclofen, a GABA agonist, to reduce spasticity.[125] In normal circumstances, the substantia nigra regulates motor function via both excitatory neurotransmitters such as glutamate and inhibitory neurotransmitters such as GABA by signalling to the thalamus, and in turn to the motor cortex and spinal motor neurons. It is accepted that cannabinoid agonists such as R(+)WIN55,212-2 can inhibit glutamate release and enhance the effect of GABA signalling.[51,126,127]

Recent studies using a mouse model of MS (chronic relapsing-experimental allergic encephalomyelitis [EAE])[128] have demonstrated the potential therapeutic usefulness of both CB_1- and CB_2-selective agonists in treating spasticity.[59,129] Interestingly, it was found that antagonism of the cannabinoid receptors led to mice with mild spasticity becoming significantly more spastic, an effect that did not occur in pre-acute EAE mice lacking spasticity.[129] This suggests that the presence of an endogenous cannabinoid agonist or 'tone' in the CNS may have a role in the control of fine motor function. Whether the effect of the cannabinoid receptor antagonists is due to inverse agonism or simply the antagonism of an endogenous cannabinoid tone in the CNS remains to be elucidated. Furthermore, the concentrations of the endocannabinoids anandamide and PEA were found to be increased in the spinal cord of mice exhibiting spasticity compared with normal or postrelapse remission mice, possibly in an attempt to limit spasticity.[59] In addition, spasticity could also be ameliorated by the inhibition of anandamide reuptake and enzymatic hydrolysis, generating a subsequent increase in anandamide concentrations in the CNS.[59] This provides a therapeutic regimen that could take advantage of the endocannabinoid system of synthesis and reuptake and may bypass the adverse effects seen following exogenous synthetic drug administration.

A recent study has shown that administration of arvanil, a structural hybrid between capsaicin and anandamide, can effectively inhibit spasticity and persistent pain in animal models.[130] Although arvanil has agonist properties at both cannabinoid and vanilloid receptors, it was still effective in CB_1

receptor gene–deficient mice and in the presence of both cannabinoid and vanilloid receptor antagonists.[130] The effects of arvanil may be mediated via actions at either nonreceptor targets such as inhibition of the anandamide transporter[131] or through an unidentified cannabinoid and/or vanilloid receptor.

Cells of the immune system and the cytokines (soluble inflammatory factors) that they secrete are thought to play a major role in the pathogenesis of MS and EAE, which are thought to be T helper 1 (T_H1)-type cytokine-mediated diseases. The effects of cannabinoids on T cells, which are important in cell-mediated immunity, include a decrease in mitogenic stimulation and T_H1 cytokine expression.[132-134] Tumour necrosis factor (TNF)-α, a T_H1 cytokine, is an important mediator of inflammation and has been implicated in the pathology of MS.[135,136] Blockade of T_H1 cytokines or the administration of T_H1-inhibitory T_H2 cytokines and transforming growth factor-β has been shown to be effective at inhibiting clinical disease in animal models of MS and rheumatoid arthritis.[137-142]

Using this rationale, the administration of cannabinoids in the EAE model was studied. Preventative oral Δ^9-THC administration in Lewis rats or intraperitoneal injection to strain 13 guinea pigs with EAE was effective in reducing the severity of disease and delaying onset of disease.[143] A second study used Δ^8-THC, a more stable and less psychoactive cannabinoid analogue than Δ^9-THC, in the Lewis rat EAE model. Oral, but not intraperitoneal, administration reduced the severity and incidence of EAE and increased circulating corticosterone concentrations 2-fold.[144] However, Δ^8-THC treatment did not prevent the number and tissue penetrance of inflammatory infiltrates in the CNS. Dexanabinol is a nonpsychotropic cannabinoid that has been shown to inhibit TNFα secretion from lipopolysaccharide-stimulated macrophages.[145] A recent study found that intravenous administration of dexanabinol in the Lewis rat EAE model reduced disease severity when the drug was administered at the onset of disease but not prophylactically.[146]

Cannabinoids may also protect from EAE by inhibiting glutamate release. Glutamate toxicity has been suggested as a possible mediator of CNS damage to neurons and oligodendrocytes during MS and EAE,[147,148] and CB_1 receptor agonists and PEA have been demonstrated to protect cerebellar granule cells from glutamate toxicity.[34] Although these studies hint at possible mechanisms of disease amelioration, the mechanism of action has yet to be elucidated and requires further study.

In the UK, a number of short-term, large-scale clinical trials are currently underway to investigate the use of cannabinoids for the relief of spasticity in patients with MS following the publication of experimental evidence suggesting the efficacy of cannabinoids in the symptomatic relief of spasticity in a mouse model of MS[59,104,129] (table III).

2.2 Parkinson's Disease

Parkinson's disease is a chronic progressive neurodegenerative disease caused by the progressive loss of the pigmented dopaminergic neurons of the substantia nigra compacta, which innervate the striatum. The loss of dopaminergic neurotransmission subsequently interferes with the functions of the basal ganglia critical to coordinated motor function. Parkinson's disease is characterised by bradykinesia (slowness of movement), akinesia (postural immobility), muscular rigidity, resting tremor and postural instability. Current therapies include the oral administration of anticholinergics or dopamine agonists.[149] Although these can be effective in controlling tremor, some patients are unresponsive, and in some cases neurosurgical pallidotomy is performed.

The high level of CB_1 receptor expression present in the basal ganglia suggests that cannabinoids could have a therapeutic role in the treatment of the movement disorders associated with Parkinson's disease, although very few studies have been published. As cannabinoids have been shown to inhibit glutamate release,[3] this may provide a new therapeutic target by protecting against glutamate-mediated toxicity of dopaminergic neurons in the substantia nigra. In addition, the cannabinoid agonist nabilone has been shown to alleviate dyskinesia induced by levodopa, which is used to control trem-

or associated with Parkinson's disease.[107] However, a recent double-blind, randomised clinical trial demonstrated that nabilone had no significant effect on dystonia in patients with generalised and segmental primary dystonia (table III).[106] In addition, one small clinical trial (five patients) reported no clinical effect of Δ^9-THC on Parkinson's disease–induced tremor.[108]

In contrast, other studies have suggested that the endocannabinoid system may be involved in the symptomatology of Parkinson's disease. CB_1 receptors are present on GABAergic neural terminals from the striatum to the substantia nigra and globus pallidus,[150] and stimulation of these receptors decreases the reuptake of GABA, an inhibitory neurotransmitter, resulting in a reduction of voluntary movement[151] similar to the symptoms of Parkinson's disease.

In addition, cannabinoid agonists can induce catalepsy in rodents that resembles akinesia in humans with Parkinson's disease.[152,153] The blockade of dopamine receptors or lack of dopamine secretion, as in Parkinson's disease, results in akinesia in humans.[154] Furthermore, akinesia can be augmented by CB_1 receptor agonists,[152,153] which may reduce dopamine neurotransmission.[155] Moreover, a recent study has described enhanced concentrations of 2-AG in a rat model of Parkinson's disease.[156] Increased concentrations of 2-AG were present in the globus palladia (located within the basal ganglia) but not in other brain regions such as the hippocampus, cerebellum, cortex or striatum,[156] further suggesting that cannabinoids may play a role in Parkinson's disease symptoms such as akinesia. Following the administration of reserpine to rats, locomotion is dramatically reduced. However, reversal of the effects of reserpine with quinpyrole, a dopamine agonist, resulted in a reduction of 2-AG concentrations, while administration of rimonabant potentiated the effect of increased locomotion when given in conjunction with quinpyrole.[156] This suggests that cannabinoid antagonists could be therapeutically useful in combination with dopamine agonists in reversing the endocannabinoid effects upon inhibitory motor function seen in Parkinson's disease.

2.3 Neuroprotection

Cannabinoids may also play a role in neuroprotection in disorders such as stroke, Parkinson's disease, MS, Huntingdon's disease, cerebral trauma and epilepsy. Neuronal destruction may be caused by the generation of free radicals, reactive oxygen species and/or pro-inflammatory cytokines such as TNFα, or the over-stimulation of synaptic excitatory amino acid receptors, mediated by glutamate, and the subsequent increase in intracellular Ca^{2+}. Excess glutamate can induce neuronal death,[157] and this is mediated in part by the excessive stimulation of NMDA ligand-gated ion channels.

Studies have demonstrated the protective effect of cannabinoids on the glutamate-induced excitotoxicity of neurons.[155,156,158,159] In addition, animal models have shown the potential benefit of early treatment of ischaemia and brain trauma by both synthetic cannabinoids such as dexanabinol and R(+)WIN55,212-2 and the endocannabinoids anandamide and 2-AG.[160-165] Studies suggest that both anandamide and 2-AG may be endogenous neuroprotective agents released on demand, which may also have benefit when administered following damage. Treatment results in long-term functional improvement, survival of neurons and a reduction in infarct volume and brain oedema.[160-165] In addition, CBD was shown to have neuroprotective antioxidant properties in rat cortical neuron cultures exposed to toxic concentrations of glutamate.[155]

Both PEA and 2-AG have been shown to accumulate in ischaemic tissues, suggesting that these endocannabinoids may play a role in neuroprotection.[34,163] The severity of brain trauma may induce differences in endocannabinoid accumulation at the site of damage. Following severe trauma induced by intracarotid injection of NMDA, anandamide, but not 2-AG, was upregulated 13-fold.[166] However, upregulation was less evident following mild brain trauma, induced by mild concussion or by blockade of NMDA receptors with dizocilpine (MK-801).[166]

The potential for CB_1 receptor signalling may also be differentially regulated depending upon the severity of insult. Following severe trauma, a significant loss of CB_1 receptor binding in the cortex, hippocampus and thalamus was noted.[166] However, following mild concussive trauma, CB_1 receptor binding was significantly increased at the site of concussion as well as the hippocampus.[166] This suggests that endogenous neuroprotective responses involving endocannabinoid accumulation and signalling in the CNS may exist.

Interestingly, no difference in 2-AG accumulation was observed following mild or severe brain trauma,[166] in contrast to the studies in ischaemia,[34,163] although anandamide concentrations were increased, suggesting a difference in the mechanisms of biosynthesis of anandamide and 2-AG following brain trauma. However, a recent study reported no increase in either anandamide or 2-AG following ouabain-induced brain injury, although exogenous administration of anandamide could reduce neuronal damage.[162]

The mechanisms of cannabinoid neuroprotection are not yet clear, but evidence supports both cannabinoid receptor– and nonreceptor-mediated modes of action in blocking NMDA signalling[156] and in the inhibition of free radicals and TNFα secretion.[155,160,167,168] It is apparent that the strength of neurotoxic stimuli may induce different putative mechanisms of endocannabinoid-induced neuroprotection.

A recent phase II clinical trial investigating the use of dexanabinol to treat severe closed-head injury found that intravenous administration of the drug was safe and well tolerated (table III).[112] Dexanabinol-treated patients exhibited significantly lower cerebral perfusion pressure, systolic blood pressure and percentage of time with an intracranial pressure above 25mm Hg compared with placebo-treated groups.[112] There was no evidence of increased adverse effects of dexanabinol treatment compared with patients given placebo.[112] In addition, after 6 months the dexanabinol-treated patient group appeared to achieve a better neurological outcome than the control group.[112] A phase III clinical trial is underway to confirm the phase II trial results with a larger study sample. In addition, a clinical trial investigating the protective properties of CBD in neurodegeneration is also in progress (table III).[105]

2.4 Analgesia

Cannabinoids have been shown to be potent analgesics in animal models of hyperalgesia and therefore may be of benefit in the treatment of both postoperative and neuropathic pain, as well as pain associated with MS and cancer, in cases where patients are unresponsive to standard analgesic drugs.

The presence of a putative cannabinergic pain-suppression system has led to advances in the use of cannabinoids to treat painful conditions. Following the *in vivo* electrical stimulation of rat periaqueductal grey matter (PAG), there is a marked local release of anandamide, accompanied by a significant reduction in the tail-flick response to thermal pain.[169] The analgesic effect of anandamide release can be inhibited by rimonabant, suggesting a CB_1 receptor–mediated analgesic system.[169] Interestingly, release of anandamide in the PAG can also be induced following subcutaneous injection of formalin, a chemical irritant.[169] This further suggests a role for the endocannabinoids in a pain-suppression system.

Evidence suggests that the analgesic effects of cannabinoids may be mediated in part at the level of the spinal cord. CB_1 receptors are expressed in the dorsal horn and lamina X in the spinal cord,[170] which can regulate nociception.[18] The intravenous administration of cannabinoid agonists can inhibit noxious stimuli–induced firing of both wide dynamic range and nociceptive-specific neurons in the spinal cord, as reviewed by Walker et al.[171] Blockade of this effect by rimonabant suggests a CB_1 receptor–mediated response in the spinal cord. Similar effects were observed in nociceptive neurons in the thalamus.[171]

Importantly, suppression of the neurophysiological responses correlates with the suppression of behavioural responses to thermal stimuli (tail-flick test).[171] Transection of the spinal cord, however,

eradicates the analgesic effects of cannabinoids.[171] The induction of analgesia following injection of cannabinoid agonists into either the PAG, amygdala or rostral ventrolateral medulla supports evidence suggesting that the major site of cannabinoid-induced analgesia is at the supraspinal descending pathway.[171] Interestingly, this is also part of the pain-suppressing opiate pathway.[171]

There is also evidence to suggest that cannabinoids can induce antinociception via supraspinal mechanisms and peripheral CB_2 receptors.[75] Peripheral administration of anandamide, HU-210, CP-55940 or R(+)WIN55,212-2 can inhibit the induction of hyperalgesia, oedema and neuropathic pain due to thermal, noxious and mechanical stimuli and sciatic nerve injury by CB_1 receptor–mediated mechanisms.[172-175] Administration of anandamide, R(+)WIN55,212-2 or HU-210 can inhibit formalin-induced pain, and the effect is selectively blocked by the administration of rimonabant, suggesting a CB_1 receptor–mediated mechanism.[75] The analgesic effect was suggested to be peripheral, as administration of anandamide was more effective (100-fold) following intraplantar injection compared with intravenous or intraperitoneal injection.[75] In addition, no psychoactive effects were observed following intraplantar administration of anandamide.[75]

Peripheral CB_2-like receptors may also play a role in mediating the analgesic effects of cannabinoids. Local administration of PEA, which is not thought to bind to either CB_1 or CB_2 receptors, can also inhibit formalin-induced pain, whereas intracarotid injection of PEA has no effect on the behavioural responses to pain.[75] Interestingly, this effect can be inhibited by administration of the CB_2 selective antagonist, SR-144528.[75] A synergistic analgesic effect (100-fold over each compound alone) was noted when both anandamide and PEA were administered to formalin-treated rodents.[75] This is important clinically, as it may be possible to administer cannabinoid agonists locally to sites of pain without inducing CB_1-mediated adverse effects.

Cannabinoids may also modulate pain by inhibiting neuropeptide secretion from nociceptive primary afferent fibres.[176] Additionally, there is evidence for the tonic control of pain thresholds, as administration of rimonabant to the spinal cord induces NMDA-dependent hyperalgesia.[177]

Despite the use of cannabinoids in many animal model studies of pain, there have been few human studies. Human randomised controlled trials have been performed with patients who have postoperative pain and pain associated with cancer, spinal cord injury or gastrointestinal tract disorders (table III).[103] Δ^9-THC has been found to be superior to placebo in most cases and to provide dose-related analgesia, which peaks at 5 hours. It has generally been found to be as effective as codeine, but high dose regimens induce adverse effects including sedation.[103]

A systematic review of the use of cannabinoids for the management of pain in human clinical trials has been undertaken.[178] Nine human clinical trials were assessed in which Δ^9-THC (5–20mg), a synthetic nitrogen analogue of Δ^9-THC (1mg) or benzopyranoperidine (2–4mg) was administered orally or levonantradol (1.5–3mg) was given by intramuscular injection to "patients with acute, chronic malignant, or cancer pain".[178] The study concluded that the cannabinoids were more effective than placebo but only as effective as codeine. However, adverse effects were much more common with the cannabinoid treatment. These included mental clouding, ataxia, dizziness, numbness, disorientation, muscle twitching and blurred vision.[178] In addition, the high dose (20mg) of Δ^9-THC resulted in 100% of the patients experiencing sedation.[178] It was concluded that the low efficacy of cannabinoids compared with current analgesics or NSAIDs and the high rate of adverse effects experienced by cannabinoid users would preclude treatment with cannabinoids.[178]

Evidence suggests that the major site of cannabinoid-induced analgesia is either spinal or supraspinal. The lack of efficacy of cannabinoids in human clinical trials following promising preliminary studies may suggest that the current routes of administration are ineffective. In these trials, oral administration of cannabinoids may reduce the bioavailability of the compound compared with other

systemic routes such as intravenous injection and inhalation, thereby requiring larger doses to achieve the same effect. None of the trials compared the effects of smoked cannabis with oral ingestion. Therefore, other routes such as intrathecal administration may need to be explored to deliver the therapeutic agents to the correct sites of action. Intrathecal administration of a number of cannabinoids including levonantradol, CP-55940 and Δ^9-THC could inhibit thermal-induced pain independently of opiate mechanisms.[179] Further human studies are required to determine the efficacy of cannabinoids in analgesia, but promising animal studies suggest that if the psychotropic effects can be dissociated from the therapeutic effects, cannabinoids may be useful in pain management.

2.5 Emesis

The CB_1 receptor is expressed in the myenteric plexus of the stomach and duodenum and CB_1 receptors and FAAH in the dorsal vagus complex of the brainstem in ferrets, suggesting that cannabinoids may inhibit emesis and vomiting via a CB_1 receptor–mediated mechanism.[179] Recent studies have demonstrated that blockade of CB_1 receptor signalling induces or potentiates vomiting, suggesting that the endocannabinoid system could have tonic control of emesis.[180,181] In addition, administration of CP-55940, R(+)WIN55,212-2, methanandamide or Δ^9-THC inhibits emesis and vomiting in a number of animal models.[180,182,183] Importantly, a recent study has demonstrated the effective use of CBD, a nonpsychoactive component of cannabis, to inhibit lithium chloride–induced nausea in rats.[184]

This suggests that cannabinoids can be used effectively as antiemetic agents without CB_1 receptor–related adverse effects, which may have important implications clinically. For this reason, a number of clinical trials have investigated the use of cannabinoids as potential antiemetic agents. Both oral nabilone (a synthetic Δ^9-THC analogue) and dronabinol (a commercially available form of Δ^9-THC), as well as intramuscular injections of levonantradol, have been used.[185] The cannabinoids dronabinol and nabilone are currently prescribed in some countries as antiemetics in cancer patients undergoing chemotherapy.

Early clinical trials demonstrated that cannabinoids were more efficacious than conventional antiemetics, such as prochlorperazine, metoclopramide, chlorpromazine and thiethylperazine.[185] However, despite their efficacy, there is a higher risk of cannabis-related adverse effects including dizziness, dysphoria, hallucinations, paranoia and arterial hypotension, although some adverse effects could be classed as beneficial (e.g. euphoria and sedation).[185] Despite the higher chance of adverse effects, it was noted that patients chose cannabinoids over other available treatments.[185]

The standard treatment for emesis is ondansetron, a selective serotonin 5-HT_3 receptor antagonist. It is prescribed as an antiemetic in cases of nausea and vomiting caused by chemotherapy or general anaesthesia and has a low rate of associated adverse effects compared with other antiemetic compounds.[186] Currently, there are no studies comparing the effectiveness of ondansetron and cannabinoids as antiemetics. As a result of their high potential for adverse effects, cannabinoids may be an unlikely first-choice treatment for emesis.[186] However, in approximately 40–60% of patients receiving ondansetron, vomiting can persist. Therefore, cannabinoids may be useful in combination therapy to enhance the effect of ondansetron.

Interestingly, nabilone appears to be a useful alternative to conventional antiemetic agents, such as prochlorperazine and domperidone, in children undergoing cancer chemotherapy (70% efficacy compared with 30% for domperidone and prochlorperazine).[187,188] Although adverse effects were reported, including dizziness, drowsiness and mood alteration, generally nabilone was the treatment of first choice (66% of patients, compared with prochlorperazine [17%] and no preference [17%]).[188] Adverse effects were dose related and did not occur under a dosage of 60 mg/kg/day.[188]

2.6 Anorexia and Obesity

Anecdotal evidence suggests that smoking cannabis can stimulate the appetite and therefore may be useful in treating patients with anorexia following cancer chemotherapy or AIDS.[189,190] Clinical trials using dronabinol reported improved appetite and stabilised bodyweight in patients with AIDS (table III).[191-193]

Anandamide has been shown to stimulate the appetite via CB_1 receptor–mediated mechanisms;[194,195] therefore, blockade of the CB_1 receptor may be useful in treating obesity. In animal models, treatment with rimonabant blocked the stimulating effect of anandamide on appetite, and rimonabant alone inhibited appetite stimulation and therefore induced weight loss, suggesting a role for endocannabinoids in the tonic control of feeding behaviour.[194-197] Importantly, oral administration of rimonabant to rats was effective in appetite suppression, and no tolerance to its effect was seen over a 3-day period of administration.[196] Furthermore, the use of rimonabant to treat obesity has been successful in human clinical trials.[198]

A recent study has further demonstrated the role of cannabinoids in appetite stimulation. Endocannabinoids present in the hypothalamus appear to be under partial control of leptin, which modulates food intake via signalling in the hypothalamus. In mice that lack leptin, there is an increase in hypothalamic endocannabinoid concentrations, which can be reduced following leptin administration.[199] Again, this suggests that endocannabinoids may tonically activate CB_1 receptors in the hypothalamus to maintain food intake and that this system is under the control of leptin.

3. Adverse Effects of Cannabinoids

As previously discussed, many of the beneficial effects of cannabinoid therapy rely on CB_1 receptor–mediated mechanisms. The high expression of CB_1 receptors in the CNS in structures such as the cerebellum and hippocampus means that therapeutic doses of cannabinoids often are accompanied by unwanted effects.

Cannabinoids are highly lipophilic compounds and therefore are sequestered from the bloodstream into lipid-rich areas. They are then slowly released back into the bloodstream. Although the half-life of Δ^9-THC in plasma from smoked cannabis is around 56 and 28 hours in occasional and long-term users, respectively, the absorption by fat increases the tissue half-life to around 7 days.[200,201] Interestingly, Δ^9-THC is quickly metabolised to another psychoactive compound, 7-hydroxy-Δ^1-THC(11-hydroxy-Δ^9-THC), which can be detected in the blood, faeces and urine in humans.

Following intravenous administration of Δ^9-THC 5.0mg, plasma concentrations reach a peak of 200 μg/L after 3 minutes and rapidly decline to 15 μg/L at 60 minutes and 3 μg/L after 4 hours, as reviewed by Agurell et al.[202] By 3 hours, the psychological 'high' has disappeared. The plasma concentrations of Δ^9-THC from smoking (Δ^9-THC 13mg) and intravenous injection (Δ^9-THC 5.0mg) were similar,[202] although there is less variation in concentrations in subjects receiving intravenous injections. This is probably due to the different smoking techniques among smokers, including speed of puffs, volume of inhalation and loss resulting from side-stream smoke.[202]

Interestingly, the pharmacokinetics of Δ^9-THC are substantially different following administration by the oral route. Following oral ingestion of Δ^9-THC 20mg, there is a slow, slight increase of Δ^9-THC concentrations to a peak of 6 μg/L by 1 hour.[202] Following this, plasma Δ^9-THC concentrations decline steadily. In some subjects, the peak Δ^9-THC plasma concentrations were not obtained until 4–6 hours postingestion.[202]

In assessing bioavailability associated with the different routes of administration, after inhalation of Δ^9-THC there is a loss of initial dose as a result of side-stream smoke, inefficient absorption through the lung and pyrolysis prior to entering the bloodstream. Following oral ingestion, however, the low bioavailability of Δ^9-THC may be due to the 'first pass' effect through the gut and liver, as well as Δ^9-THC sensitivity to the stomach acidity.[202] In addition, following intravenous administration of

Table IV. Potential adverse effects of cannabinoid therapy

Adverse effects	Description	References
Acute effects		
Euphoria	Decreased anxiety, alertness, tension, depression	205
Sedation	CNS depression, drowsiness	206
Perception	Temporal and spatial distortion	206
Motor function	Ataxia, incoordination, reduced reaction time	206, 207
Psychomotor function	Impaired hand-eye coordination	208
Cognition	Deficit in short-term memory, mental confusion	206
Psychosis	Anxiety, confusion, disorientation, may aggravate schizophrenia	207, 209
Tolerance	Reduced acute effects of cannabis use	207, 204
Immunosuppression	No evidence for long-term immunosuppression	210
Chronic effects		
Respiratory system	Bronchitis, emphysema as with normal cigarette smoking	211
Cardiovascular system	Tachycardia, postural hypotension, decreased body temperature, may aggravate existing heart disease	212
Reproductive system	Decreased sperm counts	213, 207

Δ^9-THC, the compound may also be subject to the 'first pass' effect.

Some of the more common adverse effects of cannabinoid administration are listed in table IV and have been recently reviewed by Ashton.[203] The acute actions of cannabinoid administration include euphoria, sedation, reduced memory and cognitive functions, and ataxia. In addition, it has been suggested that cannabinoid usage may increase psychosis in patients with mental disease, especially schizophrenia.[204]

Volunteers intoxicated with Δ^9-THC exhibit 3-dimensional inversion illusion, which has similarities to a neuropsychological cognitive impairment in the regulation of perception seen in patients with schizophrenia.[214] Interestingly, the impaired perception due to nabilone administration could be partially inhibited by administering CBD concurrently.[215] A recent report describes an increase in the endocannabinoids anandamide and PEA, but not 2-AG, in the CSF of patients with schizophrenia, but not in control individuals.[211] In addition, an increase in CB_1 receptor binding in the dorsolateral prefrontal cortex was observed in the patients with schizophrenia.[211] This evidence suggests that a dysfunctional imbalance in the endocannabinoid system may play a role in the pathogenesis of schizophrenia. However, CBD, also used as an anti-anxiety agent, was successful in treating a schizophrenic patient experiencing the adverse effects of antipsychotics and was effective at reducing psychosis including 'thought disturbance' and 'hostility-suspiciousness'.[216] Following withdrawal of CBD, the patient's symptoms became worse.

In individuals who use cannabis regularly, the development of tolerance to the effects is thought to limit the associated adverse effects compared with casual users, although there is the possibility of long-term cognitive impairment. Although anecdotal evidence suggests that long-term cannabis users have an increased susceptibility to infection, probably as a result of an impaired immune system, studies of various immune cells from regular users of cannabis suggest that the effects on the immune system are transient and reversible.[132,134]

Where cannabinoids have been used in clinical trials for nausea and vomiting, the most common adverse effects include somnolence, dry mouth, ataxia, dizziness and dysphoria.[217] Despite the presence of adverse effects from cannabinoids, they are usually transient and 'acceptable' compared with those often associated with other drugs.[103]

3.1 Hypothetical Solutions to Dissociating Unwanted from Therapeutic Effects

Adverse events following cannabinoid administration can be correlated to the site of CB_1 receptor expression in the CNS, which may limit the therapeutic potential of CB_1 receptor–specific compounds. The identification of novel endocannabinoid agonists and receptors or use of inhibitors of cannabinoid degradation and reuptake may help overcome this issue. Furthermore, the production of nonpsychoactive compounds such as dexanabinol and CBD and the elucidation of their modes of action will be of benefit. It is also believed that other compounds in natural cannabis extracts may augment the response to Δ^9-THC. Compounds such as PEA do not appear to bind to either CB_1 or CB_2 receptors, yet they can have an effect in addition to enhancing that of Δ^9-THC. Therefore, further study of these augmenting compounds may allow a lower dose of Δ^9-THC to be administered concurrently, resulting in fewer adverse effects but maintaining the therapeutic benefit.

In diseases where CB_2 receptor agonists may be effective, the CB_1 receptor–mediated adverse effects may be eliminated completely by the use of CB_2 receptor–specific compounds. The finding of a novel endocannabinoid, virodhamine, may prove useful clinically, as not only is it a CB_2 receptor agonist, but it also has some CB_1 receptor antagonist properties.[81] Therefore, the role of the CB_2 receptor in many diseases requires further study.

The optimal dose and route of administration of the numerous cannabinoid compounds has not been fully studied and may lead to improved efficacy of cannabinoid treatment. By administering a low dose of cannabinoids directly to the target site or organ, it may be possible to reduce high systemic concentrations and therefore decrease adverse effects.

Current clinical trials are administering Δ^9-THC by the oral route. However, this may reduce the bioavailability, thereby resulting in a reduced therapeutic effect. It is likely that the low pH of the stomach and the acid contained therein may degrade Δ^9-THC and cause isomerisation to Δ^6-THC and protonation to CBD, as reviewed by Agurell et al.[202] Although smoking is an effective method of delivering Δ^9-THC to the bloodstream, it is unacceptable as a delivery route for therapy. The transient nature of cannabinoid effects makes it likely that frequent administration will be required to maintain efficacy, and therefore intravenous injection may prove too invasive. Aerosolised administration of THC to mice using a small-particle aerosol generator nebuliser can elicit antinociceptive effects without associated adverse effects such as decreased spontaneous locomotor activity and hypothermia.[218] Nevertheless, the antinociceptive effect seen following inhalation of Δ^9-THC was submaximal and may have been due to a lower blood concentration of Δ^9-THC compared with the usual dose administered intravenously.[218]

A possible explanation for the difference in Δ^9-THC action, depending upon the route of administration, may be that Δ^9-THC is a more potent antinociceptive agent than for the other two indices, spontaneous locomotor activity and hypothermia. Consequently a submaximal dose may still have antinociceptive effects without producing unwanted adverse effects. Additionally, oral administration of Δ^9-THC (which is the route used in many clinical trials) is subject to first-pass metabolism and has a delayed onset of action, between 30 minutes and 2 hours, whereas aerosolised Δ^9-THC can inhibit nociception in between 5 and 40 minutes.[218,219] Therefore, inhalation of Δ^9-THC allows for an immediate elevation of the arterial blood drug concentration.[219] The difference between the duration and bioavailability of circulating active Δ^9-THC, following either oral or aerosolised delivery, may account for the difference in the mode of action of Δ^9-THC. The use of inhalers to deliver Δ^9-THC directly to the lungs therefore is a feasible route of administration and is currently being studied in a clinical trial in patients with MS. In addition, the use of Δ^9-THC analogues with shorter half-lives or different vehicle compounds may also limit unwanted effects.

4. Conclusions

Currently, there is good evidence to suggest that cannabinoids and their antagonists could be useful alternative drugs in a variety of diseases, but further study in animal models is required to fully elucidate their mechanisms of action. As we investigate further the role of endocannabinoids, both ligands and receptors, in normal and disease states, new therapeutic targets may be identified. Furthermore, defects in the endocannabinoid system may be involved in the pathogenesis of disease, and the modulation of the endocannabinoid system may provide us with novel therapeutic agents. As further scientific study reveals additional mechanisms involved in the endocannabinoid system, we will be able to produce more effective and specific tools with which to manipulate this system and treat disease.

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REVIEW ARTICLE

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Role of Cannabinoids in Multiple Sclerosis

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Abstract

Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS).

The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged.

Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established.

1. Cannabis and Cannabinoids

Cannabis sativa is a flowering plant thought to have originated in the mountainous regions of the northwest Himalayas. It has long been used for fibre in rope and cloth (hemp), for medicinal purposes and as a recreational drug. Cannabinoids, terpenoids, flavonoids, carotenoids and other compounds are secreted by glandular trichomes, which are most numerous in the flowers of female plants.[1] Over 60 separate cannabinoids have been identified from the original plant. These are low-molecular-weight lipophillic compounds, with a varying degree of affinity at specific cannabinoid receptors (CBRs). Wood, Spivey and Easterfield[2] isolated the first cannabinoid, cannabinol, in 1896, in the Agricultural Chemistry Laboratory in Cambridge, UK and Cahn[2] worked out its chemical structure in the 1930s. Cannabinol was later synthesized in 1940 by both Adams et al. and Ghosh et al.[3-5] The major psychoactive cannabinoid, delta-9-tetrahydrocannabinol (Δ^9-THC) or dronabinol, was isolated and characterized in 1964 by the team of Raphael Mechoulam[6] in Israel. In addition to Δ^9-THC, most cannabis extracts contain cannabidiol,[7] which is not psychoactive.

1.1 Cannabinoid Receptors and Endocannabinoids

The pharmacology of cannabinoids is becoming increasingly complex. Although most cannabinoid effects appear to be mediated through G protein-coupled CBRs, a number of effects that are not related to binding to CBRs are being described. Two types of CBR have been identified, CB_1 and CB_2. CB_1 was cloned in 1990[8] and CB_2 was cloned in 1993.[9] Cannabinoids may also show activity at other receptors including G protein-coupled receptor 55[10] (GPR-55), transient receptor potential vanniloid-1[11] (TRPV-1) and adenosine receptors.[12] CBRs are negatively coupled to adenylate cyclase and positively coupled to mitogen-activated protein (MAP) kinases. CB_1 receptors are coupled through $G_{i/o}$ proteins to potassium and calcium channels and thereby affect other neurotransmitter systems including dopamine and glutamate.[13]

The CB_1 receptor is the most common G protein-coupled receptor within the CNS, and autoradiographic studies demonstrated high CB_1 receptor densities in the cerebellum, basal ganglia, hippocampus and cerebral cortex.[14] The CB_2 receptor is most abundant on cells of the immune system.[15]

The discovery of endogenous CBRs led to the identification of endogenous cannabinoid ligands or endocannabinoids, the most common of which are anandamide[16] and 2-arachidonoylglycerol.[17,18] Rather than being stored in presynaptic vesicles as are conventional neurotransmitters, endocannabinoids are rapidly synthesized *de novo* from postsynaptic membrane-lipid precursors, act on presynaptic CBRs and are then degraded or transported. There is therefore increasing interest in compounds that alter endogenous endocannabinoid tone, by reducing degradation – particularly using inhibitors of fatty-acid amide hydrolase.[19] This may provide a more specific method of adjusting CBR activity in those receptors most active, rather than introducing exogenous cannabinoids that may have a much wider range of activities.

1.2 Neuroprotection and Inflammation

Genetic knockout animal studies have demonstrated roles for the cannabinoid system in a variety of normal responses, including memory, learning,[20,21] emotion,[22] locomotion,[22,23]

appetite,[24] cardiovascular responses[23] and nociception.[22] Neuroprotective effects have been demonstrated in animal models of cranial injury[25,26] and experimental allergic encephalomyelitis (EAE).[26,27] CB_1 receptor knockout mice demonstrate considerably more neuronal damage in EAE inflammation,[28] and CB_2 receptor knockout mice are associated with increased excitotoxicity in models of Huntington's disease.[29] Cannabinoids may be helpful by reducing glutamate release[30] and calcium flux (reducing excitotoxicity),[31,32] as well as being antioxidants,[30] thereby reducing free radical damage. In addition, of significance for the disease process in multiple sclerosis (MS), cannabinoids may reduce oligodendrocyte apoptosis,[33] ameliorate the inflammatory response and increase remyelination.[34] It is interesting to note that the market withdrawal of a CB_1 receptor antagonist (rimonabant) was largely due to its association with CNS side effects, but a case of MS has been reported following its use.[35]

1.3 Medical Cannabis Use and Approved Treatments

The prevalence of people using cannabis, mainly for recreational purposes, is around 162 million.[36] Word-of-mouth reporting of beneficial effects of smoked cannabis on MS symptoms – including pain, urinary disturbance, tremor and spasticity – led to newspaper reports and anecdotal accounts being published in the medical literature. This caused widespread unlicensed and often illegal use of cannabinoids in MS. A number of varying formulations and routes of administration, ranging from use of the smoked cannabis leaf to oral preparations including cannabis oil, extracted cannabinoids and synthetic cannabinoids (such as nabilone), have been used.

The UK MS society estimates that 1–4% of the MS population in the UK are illegally using cannabis for symptom relief (around 2750 patients).[37] This figure is thought to be higher in Canada (14–16%).[38,39]

There is no cannabinoid preparation that is licensed for treating MS across Europe or North America. Nabilone (in the US and Canada) and dronabinol (in the US) are licensed for treating nausea related to cancer chemotherapy, and availability on a named-patient basis or for off-license indications varies across Europe. Nabiximols (Sativex®) is licensed for treating MS symptoms in Canada, and is available in parts of Europe on a named-patient basis. Nabiximols was approved in UK in 2010 for treating spasticity due to MS on a prescription basis.[38,40-43]

1.4 Route of Administration and Pharmacokinetics

Cannabinoids are notoriously difficult to work with in the laboratory. They are highly lipophillic, and extracts are therefore generally dissolved either in alcohol or some form of lipid. When ingested orally, they undergo first-pass metabolism in the liver, and there is considerable interindividual dose variation. Serum levels bear little correlation with activity. Cannabinoids are then stored in fat, and since they may build up over time, cannabinoids can be detected in the urine some weeks after discontinuation. This probably explains why withdrawal responses are not a major issue.[44,45]

These factors mean that it is impossible to predict what dose may benefit any single person when administered orally. Some people will experience adverse events with as little as 2.5 mg of dronabinol at night, whereas others may not notice any effects at 15 mg twice daily. These issues have led to a search for alternative routes of administration, ranging from sublingual spray (nabiximols) to suppositories. Despite these attempts, the issue of interindividual dose variation has not been adequately investigated, and to date all preparations require a dose-titration phase. Although, in theory, sublingual preparations may be suitable for acute pain, in MS most pain tends to be more chronic, and therefore single oral doses at night may both avoid side effects and improve sleep, and work best to provide amelioration of chronic problems.

2. Multiple Sclerosis (MS) Clinical Course and Symptoms

MS is the most common cause of neurological disability in young people, with an average age of

onset around 30 years, and a prevalence of about 120/100 000 in most of Northern Europe and North America.[37] It most commonly starts as a neurological event explicable by inflammation in the CNS. At the stage of a single episode, the disease is termed a 'clinically isolated syndrome'. Evidence for further inflammation, demonstrated either by MRI or another clinical event, constitutes a diagnosis of relapsing-remitting MS (RRMS).[46] Around 85% of MS starts with these clinical episodes, occurring in more females than males with a ratio about 3 : 1. The remaining 15% of MS often starts a little later in life, occurs equally in females and males, has a progressive course from the outset and is termed primary progressive disease. In patients who are initially diagnosed with RRMS, the majority will change to a more progressive clinical course after a variable time period, and this type of MS is termed secondary progressive disease. There is an increasing array of treatments for RRMS, almost all based on the assumption that MS is a primary autoimmune disease, and these treatments are therefore immunomodulatory in some way.

Despite increasing optimism over the availability of apparent disease-modifying treatments for RRMS, the majority of people with MS tend to accumulate symptoms over time, the most common being fatigue. Other prevalent symptoms include muscle stiffness and spasticity, poor mobility, pain, memory problems, tremor and balance trouble, urinary disturbance and sexual dysfunction. A major problem in determining whether any drug has efficacy in patients in MS has been the lack of adequate means of measuring its associated symptoms beyond overly simplistic visual analogue scales. In addition, the potential for unblinding in randomized controlled trials (RCTs) in which patients are treated with cannabinoids has also been a major problem in determining the efficacy of these agents.

3. Evidence for a Therapeutic Role of Cannabinoids in Treating MS

We performed a search of the PubMed database and also of the NHS Evidence healthcare databases EMBASE and MEDLINE, with no date or language limits, for articles in order to locate studies of cannabis and cannabinoid use in MS. Keywords used in the search were: 'multiple sclerosis', 'cannabis', 'marijuana', 'cannabinoids', 'cannabinol', 'dronabinol', 'Δ9-THC', 'cannabidiol', 'Cannador®', 'Sativex®', 'trial', 'cannabinoid receptors', 'endocannabinoids', 'pharmacokinetics of cannabinoids', 'neuroprotection', 'inflammation', 'spasticity', 'spasms', 'treatment', 'pharmacotherapy', 'baclofen', 'tizanidine', 'benzodiazepines', 'dantrolene', 'bladder', 'nocturia', 'continence', 'incontinence', 'antimuscarinics', 'oxybutinin', ' tolterodine', 'desmopressin', 'tremor', 'nystagmus', 'pain', 'neuropathic pain', 'antiepileptics', 'antidepressants', 'sleep', 'cognition' and 'adverse effects'. In NHS Athens (a secure login that gives NHS professionals in England access to professional academic resources), we used the advanced search facility and Thesaurus mapping mainly on the EMBASE and MEDLINE databases. The searches have been enriched further by checking the references of the various articles uncovered during the initial work-up. We included only relevant articles published in peer-reviewed journals.

3.1 Anecdote and Postal Surveys

The relative paucity of treatments in MS, particularly for symptoms and progressive disease, has led to a wide variety of treatments being used by people with MS, often without evidence for benefit beyond anecdote. Unfortunately, when such treatments are tested they often prove far from efficacious. Whilst such desperation is understandable from the perspective of the person with MS, it often raises unfulfilled hopes and can lead to unscrupulous exploitation. Nonetheless, it is incumbent on researchers to acquire as much information as possible where RCT evidence is lacking.

There has been some evidence provided from postal surveys on the use of cannabinoids in MS. One surveyed 53 UK and 59 US MS patients who had used cannabis.[47] More than 70% of patients found cannabis to reduce spasticity, pain, sensory symptoms, tremor, anxiety and depression, and 60–70% reported cannabis to reduce weight loss, fatigue, double vision and sexual dysfunction.

Fewer than 60% reported reduction of bladder and bowel dysfunction, vision dimness, walking disability, impaired balance and memory loss. Another survey of cannabis use in Canada among 205 people with MS reported 34 using cannabis for medical reasons.[38] Cannabis use was strongly correlated with male sex ($p = 0.03$), use of tobacco ($p < 0.001$) and recreational use of cannabis ($p = 0.009$). The self-reported effects were relief of stress (moderate/complete relief vs no/mild relief: 20 patients : 1 patient), sleep disturbance (17 : 1), stiffness (16 : 1), mood disturbance (16 : 0), spasm (14 : 1), pain (10 : 2) and weight loss (4 : 1).

3.2 Clinical Trials

3.2.1 Spasticity and Spasms

The treatment of spasticity in MS is unsatisfactory. Current treatments include baclofen (a GABA agonist, given orally or intrathecally), tizanidine, benzodiazepines and gabapentin. The most common side effect of these drugs is sedation, which is dose dependent and dose limiting. Botulinum toxin injection in combination with physiotherapy can also be useful. The evidence base behind any of these drugs is not large. Baclofen was studied in very few limited-scale, blinded studies >30 years ago.[48,49] It seemed to be better tolerated than diazepam but side effects were common. Tizanidine was studied in a number of trials, with varying results. The UK Tizanidine Trial[50] showed a 21% reduction on the Ashworth score in comparison with placebo, whereas another study failed to find this.[51] The evidence for an effect from gabapentin is just as limited, coming from a single double-blind, placebo-controlled, crossover trial.[52]

Initial studies of cannabinoid use in patients with MS were small, and some seemed to show an improvement in spasticity with dronabinol compared with placebo.[53,54] Another study in 16 patients with MS found no effect on spasticity with dronabinol or a cannabis extract (Cannador®); however, the maximum dosage used was 5 mg twice daily, which is probably too low to see an effect.[55] Adverse effects were more common with the cannabis extract.

Table I summarizes the key efficacy data for cannabinoids in the treatment of MS-related spasticity. The CAMS (Cannabinoids in MS) study is the largest parallel-group RCT to date to examine whether cannabinoids are beneficial in the treatment of MS symptoms.[56] In this study, 667 patients from 33 centres in the UK were randomized to either synthetic dronabinol in sesame oil (Marinol®), a whole-plant extract of cannabis (Cannador®, containing Δ^9-THC 2.5 mg and cannabidiol 1.25 mg per capsule) or placebo capsules for a period of 15 weeks. No treatment effect on spasticity was found during the main study using the Ashworth score of spasticity, although patients felt active medication was much more helpful than placebo in alleviating some of their distressing symptoms (spasticity, spasms, pain levels, quality of sleep) [table II].

In the 12 months of follow-up there was a significant decrease in the Ashworth score in the dronabinol arm only, although both active treatment arms demonstrated a wider spectrum of symptomatic benefit than seen in the main short-term study.[57] There were also suggestions of improvements in some disability scores in the follow-up study. One of the problems with interpreting these data is knowing how much objectivity to place on patient-reported outcomes when a degree of unblinding is seen in such studies. Whether this unblinding is due to improved symptoms or unwanted side effects, or whether the unblinding matters at all, remains a matter for debate.

Another placebo-controlled trial in 57 MS patients with poorly controlled spasticity provided some further support for therapeutic benefit when Cannador® capsules were given.[58] Although they were unable to confirm benefit for spasticity, there was a positive effect with Cannador® versus placebo on spasm frequency, mobility and sleep.

A further recent study of Cannador® in people with MS and significant spasticity has been reported.[59] This placebo-controlled, parallel-group study of 279 patients across 22 UK centres demonstrated very similar efficacy to the CAMS study. The primary outcome measure of a spasticity rating scale at 12 weeks showed highly significant

Table I. Key efficacy data for cannabinoids in the treatment of multiple sclerosis-related spasticity in randomized studies

Study (year)	Study design	N	Product	Results	Level of evidence[a]
Killestein et al.[55] (2002)	db, pc, 2-fold co	16	Oral Δ^9-THC, oral cannabis extract (Cannador®)	No effect on spasticity	Class I
Zajicek et al.[56] CAMS (2003)	mc, db, pc	667	Oral Δ^9-THC, oral cannabis extract (Cannador®)	No effect on spasticity using Ashworth scale Symptomatic benefit on spasticity, spasms, pain levels and quality of sleep Tremor improvement not statistically significant	Class I
Zajicek et al.[57] (2005)	12-month follow-up	502	Oral Δ^9-THC, oral cannabis extract (Cannador®)	Significant decrease in Ashworth score for the synthetic Δ^9-THC group only Statistical improvement in 7 of 9 self-rated symptoms	Class I
Vaney et al.[58] (2004)	db, pc, co	57	Oral cannabis extract (Cannador®)	No statistical difference with placebo on spasticity Symptomatic benefit on spasm frequency, mobility and sleep	Class I
Zajicek et al.[59] (2009)	mc, pc	279	Oral cannabis extract (Cannador®)	Relief of muscle stiffness twice as large with cannabis extract on category rating scale, reduced pain	Class I
Wade et al.[60] (2004)	mc, db, pc	160	Nabiximols	No improvement in primary outcome measure of worst symptom Improvement of spasticity and quality of sleep	Class I
Collin et al.[61] (2007)	db, pc	189	Nabiximols	No statistical significance on Ashworth scale Improvement of spasticity on numerical rating scale	Class I
Ambler et al.[62] (2009)	'Enriched' study; pc study on responders from first part	241	Nabiximols	Spasticity numerical rating score clearly improved in responders	Class II (unmasked in part 1)
Wissel et al.[63] (2006)	pc, db, co	13	Nabilone	Significant decrease in pain, no change in spasticity	Class I
Freeman et al.[64] (2006)	Based on CAMS	667	Oral Δ^9-THC, oral cannabis extract (Cannador®)	Significant reduction in incontinence episodes	Class II (dropouts)
Fox et al.[65] (2004)	db, pc	14	Oral cannabis extract (Cannador®)	Not functionally significant, only subjective improvement in tremor	Class I
Svendsen et al.[66] (2004)	db, pc, co	24	Oral synthetic Δ^9-THC (Marinol®)	Pain intensity lower NNT 3.5	Class 1
Notcutt et al.[67] (2004)	db, pc, co	24	Δ^9-THC, cannabidiol, nabiximols	Pain lower	Class III or IV ('N of 1' study)
Rog et al.[68] (2005)	db, pc, pg	66	Nabiximols as adjunctive analgesic	Reduced intensity of pain and sleep disturbance NNT 3.7	Class I

a See table II.[2,69-71]

CAMS = Cannabinoids in Multiple Sclerosis study; **co** = crossover; **db** = double-blind; **mc** = multicentre; **NNT** = number needed to treat; **pc** = placebo-controlled; **pg** = parallel group; **THC** = tetrahydrocannabinol.

benefit with Cannador® compared with placebo ($p = 0.004$), with similar results at 4 and 8 weeks.

Nabiximols (Sativex®) is an oromucosal spray of cannabis extract containing similar cannabinoid proportions to Cannador®. One of the initial studies used nabiximols in a 10-week, placebo-controlled RCT in three centres involving 160 MS patients with significant problems from spasticity, spasms, bladder, tremor or pain.[60] The primary outcome measure was a visual analogue

score for each patient's most troublesome symptom. Although there was no overall improvement in the primary outcome measure of a visual analogue score of the worst symptom, in those patients whose main symptoms was spasticity, there was a significant reduction with nabiximols ($p = 0.001$). There were no significant adverse effects in recipients of nabiximols on cognition and mood, and intoxication was generally mild. A further RCT using nabiximols in 189 patients with MS[61] reported marginal benefits of this agent on the subject-recorded numerical rating scale of spasticity ($p = 0.048$), but the Ashworth scale and other secondary outcomes did not achieve statistical significance. Another recent phase III study investigated the use of nabiximols.[62] This study was not a conventional parallel-group RCT, but an 'enriched study', where all participants were initially provided active drug for 4 weeks, and responders (>20% reduction in spasticity visual analogue score) were then enrolled in a longer (12-week) placebo-controlled study. Significant benefit was reported in spasticity rating scores as well as spasms, sleep and Barthel activities of daily living (ADL) in recipients of nabiximols.

The synthetic cannabinoid nabilone (1 mg/day) has been investigated in a small placebo-controlled RCT in 13 patients with MS with disabling spasticity-related pain, and showed a significant decrease in pain using the 11-point box test but no change in spasticity, motor function and ADL.[63]

There seems to be a discrepancy between the favourable symptomatic effect of cannabinoids on spasticity and the lack of change in the Ashworth scale from most class I level of evidence studies. A potential explanation might be that the follow-up is too short.[57] Another explanation would be that the beneficial effect is more subtle than the detection range of the Ashworth scale, probably mediated through the relief of pain caused by spasms. The symptomatic benefit, with modest side effects, in recipients of cannabinoids is nonetheless clear from studies yielding class I level of evidence. On the basis of this evidence, there is a strong case for cannabinoids to be used as add-on treatment for MS-related spasticity.

Table II. American Academy of Neurology classification scheme requirements for therapeutic questions (reproduced from French and Gronseth,[72] with permission)

Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences The following are also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:[a] 1. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective) 2. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment 3. The interpretation of the results of the study is based on an observed-cases analysis
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e class I, above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class III	All other controlled trials (including well defined, natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements
Class IV	Studies not meeting class I, II or III criteria including consensus or expert opinion

a Note that numbers 1–3 in class Ie are required for class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to a class III.

3.2.2 Bladder Symptoms

As is the case with many symptom treatments in patients with MS, evidence for the use of commonly prescribed drugs for treating bladder symptoms is sparse. The most common bladder problems in MS are detrusor hyper-reflexia, with symptoms of urinary urgency and frequency, and detrusor/sphincter dys-synergia, where relaxation of the external sphincter and bladder contraction are not coordinated. Presently, detrusor hyper-reflexia is treated non-invasively with anti-muscarinics, including oxybutinin or tolterodine. Nocturia is treated with desmopressin.[73] A class III study showed symptomatic response to oxybutinin in 67% of patients, but 21% of patients had to stop the trial because of side effects.[74] Tolterodine proved superior to placebo and comparable to oxybutinin in enhancing bladder volume and improving continence in a very small class I trial.[75]

In patients with MS, fewer studies have investigated the effect of cannabinoids on urinary symptoms than on spasticity or pain. A small open-label pilot study of 15 MS patients used nabiximols or a Δ^9-THC spray for 8 weeks followed by a long-term extension. Urinary incontinence, number and volume of incontinence episodes, frequency of urination and nocturia all decreased in recipients of both agents versus baseline ($p < 0.05$).[76] Patient self-assessment of pain, spasticity and sleep also improved significantly. Pain improvement continued up to a median of 35 weeks and side effects were mild.

A sub-study of the main CAMS study looked specifically at lower urinary tract symptoms.[64] Although CAMS randomized 667 MS patients to receive Cannador®, Marinol® or placebo, it was primarily aimed at evaluating spasticity, and there were considerable missing data from the incontinence charts used to assess episodes of urge incontinence. Nevertheless, all three groups showed a significant reduction ($p < 0.01$) in adjusted episode rate (38% cannabis extract, 33% THC, 18% placebo), with both active treatments showing significant reduction over placebo.

There is therefore limited evidence for cannabinoid action in reducing incontinence episodes in comparison with placebo in a sub-study of the largest cannabinoid study to date, the level of evidence being class II (unintentional dropouts, not due to side effects).[64]

3.2.3 Tremor

One of the most disabling symptoms in MS is a coarse tremor, which is usually very resistant to pharmacological treatment. Traditional drugs include β-adrenoceptor antagonists and primidone. Other drugs used include carbamazepine, clonazepam, isoniazid and buspirone.[77-79] Levetiracetam seemed to work in a class III level of evidence study but not according to a class I level of evidence study.[80,81]

The evidence for beneficial effects of cannabinoids on MS-related tremor is weak. There was a single case report of an MS patient with acute improvement of chronic motor handicap while smoking marijuana.[82] Another uncontrolled study used oral Δ^9-THC in eight patients with severe ataxia and tremor, two of whom demonstrated improved motor coordination.[83]

Data from the CAMS study revealed Cannador® improved tremor in 48% of patients, Marinol® in 40% and placebo in 33%, according to patient reports; the difference between active treatments and placebo was not significant.[56]

A double-blind, placebo-controlled, crossover RCT investigated the effect of 4 weeks of treatment with oral Cannador® in 14 patients with MS and upper limb tremor.[65] The primary outcome was a validated tremor rating scale. Secondary outcomes were accelerometry, ataxia scale, spiral drawing, finger tapping and the nine-hole pegboard test. Although there was no improvement in any of the objective measures of upper limb tremor, finger tapping was faster in placebo recipients ($p < 0.02$) and five patients felt a subjective improvement of tremor whilst on active treatment ($p = 0.08$).

Data from a 10-week, placebo-controlled RCT in 160 MS patients treated with nabiximols cited in section 3.2.1 failed to show any improvement in a visual analogue scale for tremor between the baseline 2 weeks and the final 2 weeks of the trial.[60]

Overall, there is no evidence for objective improvement of tremor in the class I evidence studies using cannabinoids.

3.2.4 Nystagmus

Nystagmus treatment in patients with MS is disappointing. There are isolated reports of a potential effect of gabapentin on nystagmus (class IV, class II and again class II level of evidence in three trials, respectively).[84-86]

There is a case report on an MS patient with severe pendular nystagmus who took cannabis in several preparations, some of them in a blinded fashion.[87] A dramatic suppression of the nystagmus was documented by video and infrared oculography after smoking cannabis, whilst both nabilone tablets and cannabis oil-containing capsules (up to 40 mg of THC per day) had no effect.

We cannot recommend cannabinoids for nystagmus treatment based on the present class IV level of evidence.

3.2.5 Pain

Pain is very common in MS, affecting up to 70% of patients, and treatment is often unsatisfactory.[88] Many patients with MS experience more than one pain syndrome; combinations of dysaesthesia, headaches and/or back or muscle and joint pain are frequent. The most common pains are either central chronic neuropathic pain (often described as a burning, dragging or aching in association with spasticity) or paroxysmal neuralgias (usually lancinating and sometimes difficult to distinguish from nerve root irritation when outside the cranial nerves). However, the definition of, and conditions encompassing 'neuropathic pain' remain controversial. No universally accepted and validated clinical diagnostic criteria for neuropathic pain exist and assessment of patients based on clinical examination and bedside test to decide what is, and what is not, neuropathic is difficult, even for experts.

Current options for treating central pain conditions remain limited and are based mostly on the use of CNS drugs with known problems of tolerability, particularly antiepileptic drugs (e.g. carbamazepine, oxcarbazepine, gabapentin, pregabalin, lamotrigine and levetiracetam), and tricyclic antidepressants (TCAs) such as amitriptyline, short-term non-steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics.[89-91]

In two double-blind RCTs, lamotrigine failed to show any difference versus placebo as standalone or add-on treatment for pain in MS patients.[92,93] No other double-blind RCTs have been conducted to support the use of antiepileptic drugs for pain in MS. One follow-up study (class III evidence) reported a significant incidence of side effects in patients with MS prescribed antiepileptic drugs for pain, especially after the use of carbamazepine.[94] Gabapentin seemed to be effective in treating painful spasms in MS in an open-label unblinded trial (class III evidence).[95] Pregabalin was investigated in an open-label, pilot study in a small number of patients with MS and was found to reduce paroxysmal painful phenomena with mild side effects.[96] Levetiracetam was effective and well tolerated according to a small single-blinded, preliminary study.[97]

Nortriptyline seemed to be effective in sensory complaints and pain in a randomized trial in 59 MS patients that compared transcutaneous electrical nerve stimulation with nortriptyline (class II evidence).

Misoprostol seemed to be effective in pain due to trigeminal neuralgia in patients with MS in an open-label prospective trial (class III evidence).[98]

Pain is another area of MS-related symptoms where there is stronger evidence for an effect of cannabinoids. A crossover, double-blind RCT evaluated oral synthetic dronabinol on central neuropathic pain in 24 MS patients treated for 3 weeks with a maximum 10 mg of dronabinol or placebo, separated by a 3-week period of washout.[66] Median spontaneous pain intensity was measured with a numerical scale in the last week of treatment. The pain intensity was significantly lower ($p=0.02$) and the pain relief score higher ($p=0.035$) with dronabinol versus placebo.

A similar crossover RCT in 24 patients of whom 18 had MS found that pain levels were significantly lowered versus baseline when either dronabinol or nabiximols was used.[66]

A larger single-centre, double-blind RCT over 5 weeks in 66 MS patients with central pain states (59 dysaesthetic, 7 painful spasms) treated with nabiximols as adjunctive treatment was subsequently conducted.[68] Patients could self-titrate up to 48 sprays in 24 hours. Nabiximols was superior to placebo in reducing the mean intensity of pain ($p=0.005$) and sleep disturbance ($p=0.003$).

Most adverse effects in nabiximols recipients were minor, but were intense enough in two patients to warrant withdrawal from the study. The 2-year open-label follow-up study found that nabiximols was effective, with no evidence of tolerance in the 28 patients who completed the study.[99]

Results from the CAMS study again demonstrated significant patient-reported effects on pain with both dronabinol and Cannador® using category rating scales. These results were confirmed in the recent MUSEC (MUltiple Sclerosis and Extract of Cannabis) study using Cannador® conducted from 2006 to 2008 on 279 patients across 22 UK centres.[56,59]

A meta-analysis of nabiximols, cannabidiol and dronabinol in neuropathic and MS-related pain found a statistically significant effect of these agents on pain relief across studies. Side effects were generally mild, and the most common was dizziness.[100]

Evidence from these studies strongly suggests that cannabinoids (in the form of an oral cannabis extract,[56,59] synthetic Δ^9-THC[66] or nabiximols) are effective in pain relief.[68] The numbers needed to treat are very low at 3.5 or 3.7.[66,68] The side effects of these agents were rare, mild and well documented in the class I studies.

3.2.6 Sleep

Sleep disturbance in MS patients is improved with cannabinoid treatment. In the CAMS study, MS patients reported improved sleep with both Cannador® and dronabinol compared with placebo ($p=0.025$).[56] Other already cited studies (see section 3.2.1 and 3.2.5) demonstrated a beneficial effect of nabiximols on pain-related sleep disturbance ($p=0.003$)[68] and on the quality of sleep ($p=0.047$).[60]

4. Adverse Effects of Cannabinoid Treatment

Cannabinoids appear to be well tolerated when used medicinally. Side effects appear to be generally mild, and most serious adverse events from clinical trials appear to be either unrelated, or expected from the complications of MS. Greenberg et al.[101] evaluated the effect of smoking marijuana on balance in ten patients with MS and described postural reflexes being affected more than in normal subjects. Interestingly, patients perceived an improvement despite evidence to the contrary.

A follow-up, open-label study with nabiximols reported on safety and tolerability in 137 patients with MS.[102] Patients reported 292 side effects, of which 86% were mild to moderate including oral pain, dizziness, diarrhoea, nausea and oromucosal disorder. Three patients had five serious side effects: two seizures, one fall, one aspiration and one gastroenteritis. Four patients had first-ever seizures. Planned, sudden interruption of nabiximols in 25 patients for 2 weeks failed to demonstrate any evidence for a consistent withdrawal syndrome, although 11 reported tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams.

A systematic review of the published data over the last 40 years on cannabinoids, which excluded those studies referring to recreational use, retained 31 studies, from which 23 were RCTs and eight were observational studies.[103] In the RCTs the median exposure was 2 weeks and 96.6% of the adverse effects were not serious, the most common one being dizziness if receiving active treatment (15.5%). Serious side effects listed were relapse of MS (12.8%), vomiting (9.8%) and urinary tract infection (9.1%), and non-serious side effects were more frequent if receiving active treatment (95% CI 1.57, 2.21). The rate of serious adverse effects did not differ significantly between the treated patients and the controls.

Chronic use of cannabinoids for symptom relief by people affected by MS has raised the concern of potential cognitive side effects. Several studies have quantified the neuropsychological effects of cannabinoids, with conflicting results. CAMS-PEC, a substudy on 89 patients who completed psychological tests from the original CAMS study, found a significant reduction in performance on the California Adult Verbal Learning Test (verbal learning and memory) in those patients receiving cannabis extracts compared with placebo.[104,105] Another trial reported

on a worse performance in the Selective Reminding Test (long-term memory storage capacity).[68] Other studies have not demonstrated adverse effects on cognition.[58,60,106]

Most concern with cannabinoids has been directed towards potential psychiatric side effects, particularly in light of the association between excess recreational cannabis abuse during adolescence and subsequent schizophrenia. Although there have been occasional cases of toxic psychosis associated with clinical trials of cannabinoids, to date all of these have been reversible and dose related.[54,68] Indeed, some cases of psychosis have occurred in placebo-treated patients. Nevertheless, caution must always be exercised, and slow titration is usually the best method of obtaining symptom relief and compliance.

5. Conclusion and Future Directions

Considerable effort has been expended in the last decade to conduct clinical trials using cannabinoids and to start to test which cannabinoids may be therapeutically beneficial. At present there are a number of trials providing class I evidence demonstrating a beneficial effect of cannabinoids on pain and sleep disturbance, and a class II large follow-up study that has shown a significant reduction in incontinence episodes. The side effects were carefully reported and deemed to be mild. Evidence for a beneficial effect of cannabinoids on symptomatic spasms and spasticity is persuasive from a number of trials providing class I evidence – often considerably better than the evidence on which current treatment options are based.

This evidence for the therapeutic benefit of cannabinoids has been slow to gather, although most clinicians with experience of these drugs will generally vouch for their effectiveness. The number of positive studies is now accumulating, in parallel with developments in trial methodology, including improved symptom measurement (e.g. the new patient report spasticity scale, MSSS-88)[107] and newer trial designs. Licensing authorities tend to believe 'objective' measurements more than patient report, even when older 'objective' measures such as the Ashworth scale of spasticity are inadequate for detecting meaningful symptom change from the patient perspective. There is still a considerable way to go to fully understand how symptoms interact with disability, and how we can take account of placebo effects (evidence from the CAMS study suggests that these may last at least 12 months), together with ways of accommodating potential unblinding.

Advances need to be made in reducing cannabinoid side effects, including unwanted psychoactivity. This may result from developing peripherally active compounds that may affect peripheral receptors or blood flow for symptoms such as pain and spasticity. Newer compounds altering endocannabinoid tone may also not have the same degree of psychoactivity. Drug availability may be altered by developing water-soluble compounds and newer methods of administration.

Perhaps most exciting is the possibility that cannabinoids may be neuroprotective and have a much wider role than symptom alleviation. There is considerable experimental evidence for cannabinoids being associated with reduced excitotoxicity secondary to reduced neurotransmitter release, synaptic modulation, reduced free radical damage, improved mitochondrial function and reduced inflammation together with increased repair and remyelination. One of the long-term follow-up studies has also suggested a role for cannabinoids in possibly reducing disease progression that was not seen in the short-term, 15-week, main study.[57] A further pivotal study is now under way, expected to report in 2012, where 500 people with progressive MS have been recruited to a UK 3-year, randomized, placebo-controlled, follow-up study to see whether disability progression can be slowed with cannabinoids (CUPID [Cannabinoids Use in Progressive Inflammatory brain Disease] study). We await these results with interest.

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Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis

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Abstract

Background: Bladder dysfunction is a common feature of multiple sclerosis (MS).

Objective: In this study we aimed to assess the efficacy, tolerability and safety of Sativex® (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS.

Methods: We undertook a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial in 135 randomized subjects with MS and overactive bladder (OAB).

Results: The primary endpoint was the reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks). Other endpoints included incidence of nocturia and urgency, overall bladder condition (OBC), daytime frequency, Incontinence Quality of Life (I-QOL), Patient's Global Impression of Change (PGIC) and volume voided. The primary endpoint showed little difference between Sativex and placebo. Four out of seven secondary endpoints were significantly in favour of Sativex: number of episodes of nocturia (adjusted mean difference −0.28, $p = 0.010$), OBC (−1.16, $p = 0.001$), number of voids/day (−0.85, $p = 0.001$) and PGIC ($p = 0.005$). Of the other endpoints, number of daytime voids was statistically significantly in favour of Sativex (−0.57, $p = 0.044$). The improvement in I-QOL was in favour of Sativex but did not reach statistical significance.

Conclusions: Although the primary endpoint did not reach statistical significance, we conclude that Sativex did have some impact on the symptoms of overactive bladder in patients with MS, providing evidence of some improvement in symptoms associated with bladder dysfunction in these subjects.

Keywords

cannabinoid, detrusor overactivity, multiple sclerosis, overactive bladder, Sativex

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Introduction

Overactive bladder (OAB) was defined in 2002 by the International Continence Society as a condition characterized by urgency, with or without urge incontinence, usually with high void frequency and nocturia, in the absence of local pathological or hormonal factors.[1] The majority of multiple sclerosis (MS) sufferers (90%) develop lower urinary tract signs within 10 years of contracting the disease,[2] most commonly OAB. Symptoms of OAB such as episodes of leakage, increased frequency and urgency disrupt patients' daily routine, and reduce quality of life.[3]

Cannabis-containing medicines were almost certainly used in ancient times for female genito-urinary disorders.[4] Their use then lapsed, to enjoy a renaissance in the nineteenth century as a 'regulator of the catamenial function', for the treatment of a variety of pain syndromes, in particular of neuralgic origin, as an antispasmodic, and in the treatment of dysuria.[4,5] As recently as 1971 tincture of cannabis was prescribed by British doctors,[6] but since then it has not been available legally for medicinal use. However, thousands of patients continue to use cannabis for conditions such as AIDS, MS and chronic pain.[7]

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The scientific basis for the effect of cannabis on the uterus and bladder lies with the fact that these organs express CB_1 receptors. The effect of cannabis agonists, such as delta-9-tetrahydrocannabinol (THC), in the rodent experimental model is complex; in the inflamed rodent bladder, cannabinoid receptor agonists significantly increase the micturition threshold,[8–10] predominantly through a CB_1 receptor effect. Isolated tissue studies have shown both relaxation and contraction effects on bladder strips which may be mediated by THC at transient receptor potential vanilloid 1 ($TRPV_1$) receptors, resulting in the release of calcitonin-gene related peptide.[11] Cannabidiol (CBD) appears to have an antihyperalgesic action that is also mediated by $TRPV_1$ receptors.[12] The interaction between $TRPV_1$ and cannabinoid receptors is as yet undetermined, although the endogenous cannabinoid arachidonoylethanolamide (anandamide; AEA) is known to act at both. The bladder is rich in $TRPV_1$ receptors and these are increased in conditions of inflammation and OAB, particularly in neurogenic cases.[13] There may also be an effect at central nervous system (CNS) receptors, since CB_1 receptors have also been demonstrated in the vicinity of the periaqueductal grey, pons, hypothalamus and basal ganglia, as well as the lumbar spinal cord of the rat,[14] all regions known to be involved in bladder control. The use of CBD, which does not bind to CB_1 when given alongside THC, has been shown to reduce the possible adverse effects seen when subjects are dosed with THC alone.[15] CBD is also reported to have beneficial neuroprotective and anti-oxidant activity.[16,17]

A survey of 112 patients with MS who used 'street' cannabis reported improvements in urgency (64%), urgency incontinence (55%), and hesitancy (59%),[18] providing the rationale for a small open-label pilot study of the effect of Sativex in subjects with advanced MS.[2] Sativex was found to improve several MS-related urinary symptoms, with decreases in frequency, nocturia, incontinence, and urgency episodes and increases in the proportion of voids that were 'planned', or occurred with a normal desire to void. Side effects were few and good tolerability was observed. These results were considered sufficiently encouraging to warrant this multi-centre, randomized, double-blind, placebo-controlled clinical study designed to evaluate the efficacy, safety and tolerability of Sativex in subjects with OAB due to MS.

Methods

Study subjects

Adults with a diagnosis of MS with symptoms of OAB who had failed to respond adequately to first-line therapies, principally anticholinergics, were invited to participate in this 10-week, placebo-controlled study. Subjects at 15 centres (nine in the UK, three in Belgium and three in Romania) were screened to determine eligibility. Subjects were required to be on a stable dose of anticholinergic medication for at least 14 days prior to study entry which remained unchanged throughout the study, and to have had at least three incontinence episodes over five consecutive days during the baseline period, as assessed by a self-report voiding diary, completed daily.

Exclusion criteria included (i) the presence of symptomatic urinary tract infection or any other known cause for detrusor overactivity; (ii) performing intermittent self-catheterization; (iii) history of use of cannabis or cannabis-derived medicines (street cannabis, dronabinol or nabilone) within 7 days of study entry; (iv) hypersensitivity to cannabinoids or any of the excipients of the medication; (v) a history of major psychiatric disorder (other than depression associated with underlying condition); (vi) severe personality disorder or history of alcohol or substance abuse; (vii) severe cardiovascular disorder, history of epilepsy or significant renal or hepatic impairment; and (viii) concomitant use of fentanyl, levodopa, or sildenafil citrate. The study was conducted in accordance with the principles of the Declaration of Helsinki and ICH Good Clinical Practice. Eligible subjects gave written consent and the study protocol (dated 5 June 2002) was approved by the Research Ethics Committees appropriate to each investigator (12 in total).

Study medication

Sativex (nabiximols), an endocannabinoid system modulator, is produced by GW Pharma Ltd. It is derived from strains of *Cannabis sativa* L. plants developed to produce high and reproducible yields of a principal cannabinoid, in this case THC or CBD. Extraction of these Botanical Raw Materials produces Botanical Drug Substances (BDS) (extracts) which contain a principal cannabinoid, minor amounts of other cannabinoids and terpenes, are blended and then formulated in a solution containing ethanol, propylene glycol and peppermint oil flavouring to produce Sativex. It was administered as a pump-action oromucosal spray, each 100 µl actuation of the formulated THC BDS:CBD BDS delivering a dose of 2.7 mg THC and 2.5 mg CBD, and each actuation of placebo delivering excipients plus colorants and flavouring. The maximum permitted dose of study medication was eight actuations in any 3-h period, and 48 actuations in any 24-h period. Subjects self-titrated to their optimal dose, based on efficacy, tolerability and the maximum permitted dose, and were instructed not to increase their total daily number of sprays by more than 50% of the

previous day's dose. If intoxication was experienced at any time then either the next scheduled dose was omitted and/or the number of sprays per dose was reduced. Subjects recorded the time and number of actuations in their daily diaries each time they self-medicated, and the investigator was responsible for reconciling this diary data with the number of used and unused vials of study medication returned at each scheduled visit.

Study design

Eligible subjects entered a 2-week baseline period during which they kept a daily diary of their urinary function. At Visit 2, if still eligible, they were randomized to either an active or to a placebo group, using a pre-determined randomization code in which treatment allocation was made using permuted blocks of four (see Figure 1). The study medication was provided in glass vials labelled with the GW name, study code, subject number, visit number and expiry date. As Sativex is a plant-based extract with a distinctive smell, taste and colour, both it and the placebo contained peppermint oil to blind the smell and taste, and the placebo also contained colorants to match the colour of the plant extract. The identity of the study medication was contained in individually sealed envelopes sent to each centre, which could be opened only in the case of a medical emergency where knowledge of which study medication the subject had received would affect the course of treatment.

Study medication titration was introduced gradually at Visit 2 and the subject was observed for 4 h for any signs of intoxication, which were recorded on a 0–10 Numerical Rating Scale (NRS) (0 = No intoxication, 10 = Extreme intoxication). Subjects who satisfactorily completed initial dosing were instructed to continue titration over the next 2 weeks. No specific target dose was set. If intoxication was experienced subjects were advised to reduce or omit a dose. Visits 3 and 4 were telephone contacts after 2 and 5 weeks of treatment, respectively, to review titration, compliance and Adverse Events (AEs). Visit 5 was conducted at the end of treatment (week 8) or on withdrawal.

Physical examination, haematological and biochemical tests, and an electrocardiogram were performed at baseline and at the withdrawal/completion visit. Subjects completed a daily diary for the duration of the study, recording the time and number of doses of study medication taken, the time and frequency of incontinence episodes, micturition, feelings of urgency, nocturia and number of incontinence pads used. In addition, incontinence pad weight and daily voided volume data were collected for 3 days per week during baseline and weeks 7 and 8. The efficacy questionnaires consisted of the Incontinence Quality of Life (I-QOL),[19] a 0–10 NRS of their Overall Bladder

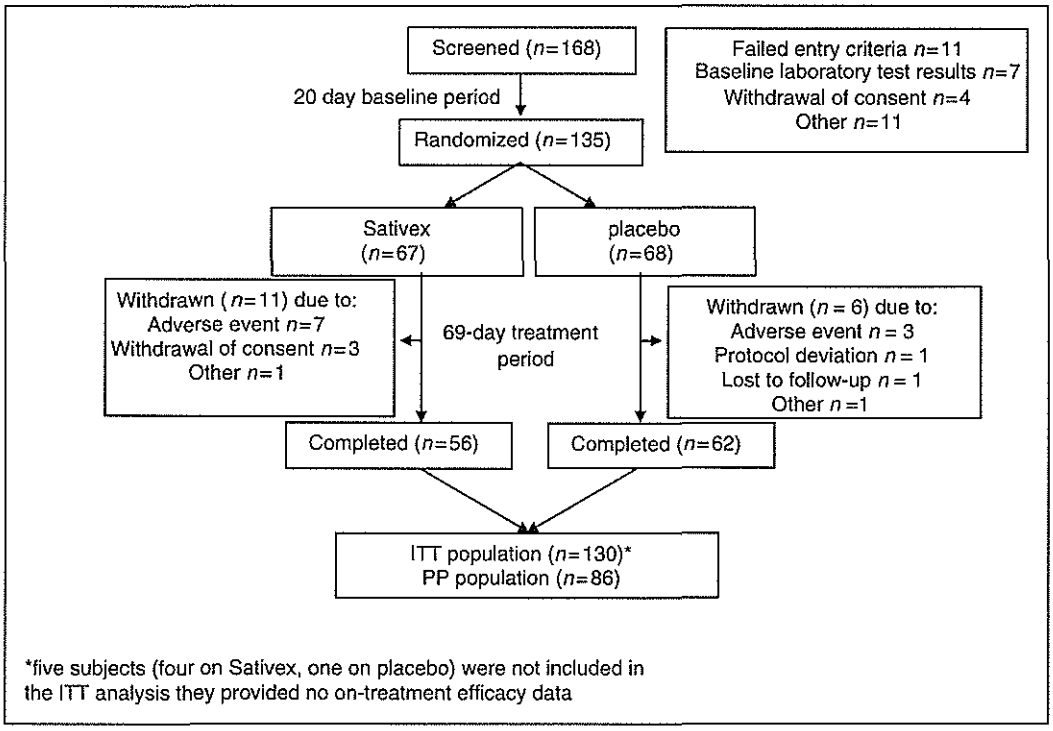


Figure 1. Disposition of subjects. ITT, indent to treat; PP, per protocol.

Condition (OBC) (0 = no problems to 10 = intolerable problems), and the Patient Global Impression of Change (PGIC). Details of AEs were recorded throughout the study. Subjects who completed the trial were offered the opportunity to participate in an open-label extension study.

At one study centre standard voiding cystometry was performed pre- and post-treatment using a 6 French urethral catheter and a 6 French rectal catheter with the fluid perfusion system on the Dantec Suite (Medtronic). All subjects were assessed in the sitting position. Three centres measured post-micturition residual volumes during the baseline period.

Statistical analysis

Primary endpoint. The primary measure of efficacy was the change in the number of incontinence episodes from baseline to end of treatment. End of treatment was defined as the last available data from weeks 7–8. If the subjects withdrew prior to this period, then end of treatment was considered at either week 3 or week 5.

The sample size was based on the primary variable of number of incontinence episodes. The sample size calculation from a previous open-label trial using the same medication suggested an estimated standard deviation for change from baseline in number of incontinence episodes/24 hours of 0–90. Using a two-sided hypothesis test at the 5% level, it was estimated that, allowing for dropouts, 130 subjects commencing treatment would be sufficient to provide 104 evaluable subjects (52 each arm) to detect a difference between treatments of 0.5 episodes of incontinence per 24 h at 80% power.

The intention to treat (ITT) and per protocol (PP) populations were used for all efficacy analyses (see Figure 1). The ITT population was defined as all subjects who entered the study and were randomized and received at least one dose of medication.

The primary endpoint of incontinence episode frequency was summarized by treatment group for baseline, weeks 3 and 5 on medication, or end of treatment. Change in frequency was compared between treatment groups using analysis of covariance (ANCOVA). The model included treatment and centre as factors, and baseline incontinence episode frequency score as a covariate. The primary analysis was based on the ITT population.

A post-hoc exploratory analysis of 49 subjects who were recruited at specialist urology centres and with data of post-micturition residual volumes enabled an ANCOVA of the primary endpoint to be undertaken, with post micturition volume and gender as covariates.

Secondary endpoints. Void urgency and nocturia episodes, the number of incontinence pads used per day, the change in symptoms measured on a 0–10 NRS of OBC, voided urine volume, the frequency of daytime voids and incontinence pad weight were summarized and analysed in the same manner as the primary efficacy endpoint. No allowance for multiplicity (multiple statistical analyses) was made.

A responder analysis of the frequency of urgency episodes was provided for those subjects reporting urgency at baseline. Responders were identified as those who at the end of treatment were not experiencing void urgency, and non-responders as those who continued to experience void urgency episodes. The results were presented by treatment group, and the percentage of responders was compared between groups using Fisher's exact test.

The I-QOL scale comprises 22 items assessing the impact of lower urinary tract symptoms on quality of life, each with a five-point response scale: 1 = Extremely, 2 = Quite a bit, 3 = Moderately, 4 = A little, 5 = Not at all. A higher score represented a better quality-of-life rating. The responses to each of the 22 items were summed and averaged for a total score and then transformed to a 0–100 scale for ease of interpretation. Descriptive statistics were provided for the total I-QOL and the three subscale scores (avoidance and limiting behaviour, psychosocial impacts, and social embarrassment). The total transformed I-QOL scores were analysed and summarized in the same manner as for the primary endpoint.

For the PGIC scale, subjects were asked at Visit 5 (on completion or withdrawal) to give their impression of the overall change in their condition since entry into the study using a seven-point scale; comparison between treatment groups was performed using Fisher's exact test.

Results

Study population

Recruitment took place between January 2003 and December 2004 with 168 subjects entering the baseline phase. Of these, 33 were excluded at screening, resulting in 135 subjects randomized, 67 to Sativex and 68 to placebo (Figure 1). Table 1 provides details of demographics of subjects enrolled into this study.

Of the 135 subjects who started the study, 17 (12.6%) withdrew (11 on the active treatment and six on placebo); 56 (83.6%) subjects completed the study in the Sativex arm and 62 (91.2%) in the placebo arm. Further details are summarized in Figure 1.

Five subjects were excluded from the ITT population (four from the active treatment group and one from the placebo group) because they did not provide any 'on-treatment' efficacy data. The PP population

Table 1. Baseline demographic details

		Number of subjects (%)		
		Sativex ($n=67$)	Placebo ($n=68$)	Total ($n=135$)
Gender	Male	15 (22.4)	22 (32.4)	37 (27.4)
	Female	52 (77.6)	46 (67.6)	98 (72.6)
Ethnic Origin	Caucasian	64 (95.5)	64 (94.1)	128 (94.8)
	Asian	2 (3.0)	3 (4.4)	5 (3.7)
	Black	0	1 (1.5)	1 (0.7)
	Other*	1 (1.5)	0	1 (0.7)
Previous Cannabis Use		21 (31.3)	27 (39.7)	48 (35.6)
			Mean (SD)	
Age (years)		48.6 (9.3)	46.8 (11.2)	47.7 (10.3)
Weight – Female (kg)		69.2 (17.3)	70.8 (12.3)	70.0 (15.2)
Weight – Male (kg)		75.4 (15.1)	77.2 (7.4)	76.5 (11.0)
Episodes of Incontinence/day		1.8 ($n=63$)	2.1 ($n=66$)	
Episodes of Nocturia/day		1.6 ($n=63$)	1.5 ($n=66$)	

*Subject was a Turkish Cypriot female.

comprised 42 subjects in the active medication group and 44 in the placebo group; reasons for exclusions of these 46 subjects are listed in Table 2. This high proportion of exclusions illustrates the difficulty in maintaining subject compliance with the study protocol.

Dosing

Subjects on placebo tended to take higher daily doses of study medication than those on Sativex: Sativex subjects took a mean of 8.91 actuations (median 7.19) compared with placebo subjects who took a mean of 17.05 actuations (median 14.22).

Efficacy measures

The primary endpoint of reduction in numbers of daily incontinence episodes at the end of treatment was only marginally improved in the Sativex group compared with placebo in the ITT population analysis, and did not reach statistical significance (Table 3).

There was a reduction in urinary urgency in favour of Sativex that approached statistical significance (Table 3). Similarly, the responder analysis (i.e. subjects with urgency at baseline but no episodes at the end of treatment) was in favour of Sativex but did not reach statistical significance.

When incontinence was ranked in order of severity in terms of the number of incontinence episodes per day, again there was a trend in favour of Sativex but no statistically significant difference.

The exploratory ANCOVA analysis of incontinence episode frequency in a subgroup of 49 subjects for whom post-void residual volumes were available showed a significant beneficial effect of Sativex in those with a residual volume <250 ml (−0.571 episodes per day, $p=0.0456$).

The number of daytime voids and the total number of voids per 24 h were significantly reduced in the Sativex group, as was the number of episodes of nocturia ($p=0.044$, $p=0.007$, $p=0.01$, respectively) (Table 3).

Table 2. Reasons for exclusion from efficacy analysis of per protocol data (some subjects had more than one reason for exclusion)

Reasons for non-inclusion for efficacy analysis	Sativex	Placebo
Total number of subjects	67	68
Violation of inclusion/exclusion criteria likely to affect efficacy	1	1
No record of study treatment record >50% days	5	3
Non-compliant with Visit 5 schedule	12	4
Use of prohibited drugs* (or change of dose) likely to effect primary endpoint during study period	4	7
Significant urinary tract infection	8	12
Change in diuretic during baseline	0	1
Baseline assessment >14 days prior to first dose of treatment	2	1
Total subjects excluded	21	23

*Prohibited drugs included tolterodine, oxybutinin, bendrofluazide, tamsulosin, methylprednisolone and prednisolone.

Sativex was significantly superior to placebo at all levels of severity of nocturia, but the size of effect was greater for more severely affected subjects (Figure 2); 16% of subjects on active treatment became nocturia free.

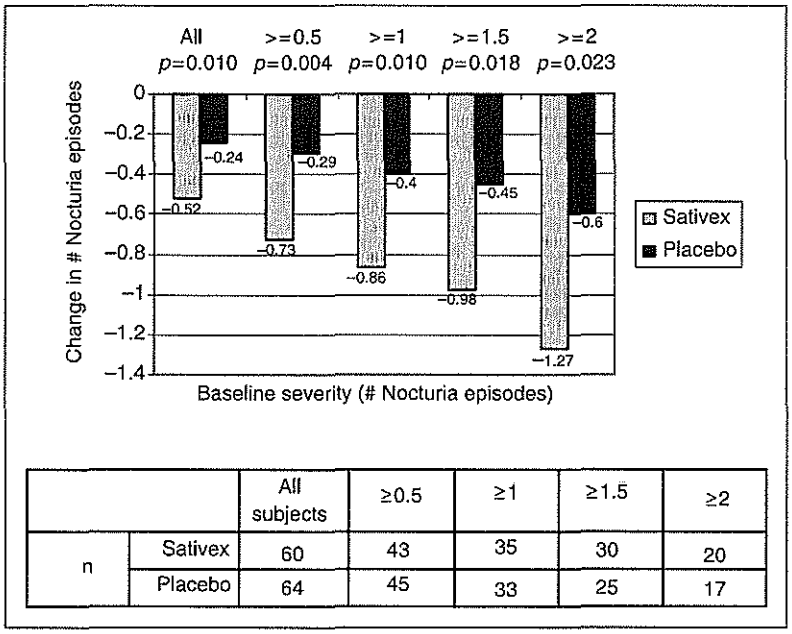
Daily use of incontinence pads and pad weight showed minimal treatment differences between Sativex and placebo (−0.08 pads per day and 11.4 g, respectively, in favour of Sativex) which were not statistically significant ($p=0.74$ and $p=0.76$, respectively).

The subject's opinion of OBC symptom severity (NRS) showed a significant difference in favour of Sativex at the end of treatment ($p=0.001$) (Figure 3). Further analysis showed the difference between the two groups was increasingly marked as the symptom severity at baseline worsened. Subjects on the active treatment were three times more likely to report an improvement of more than 30% compared with those on placebo (odds ratio 3.07, CI 1.41, 6.97, $p=0.006$). Figure 4 shows the PGIC scale data, which were highly significantly in favour of Sativex ($p=0.005$). There was a trend in favour of improvement in I-QOL in the Sativex-treated group but this did not reach statistical significance (Table 3).

Table 3. Efficacy data – change from baseline to end of study

	Mean change from baseline				
	Sativex		Placebo		
Endpoint	*n*	Adjusted Mean	*n*	Adjusted Mean	*p*-value
Daily incontinence episodes	60	−1.08	64	−0.98	0.569
Total number of voids (per 24 h)	60	−1.75	64	−0.9	0.007
Number Daytime voids (per day)	60	−1.23	64	−0.66	0.044
Nocturia episodes (per day)	60	−0.52	64	−0.24	0.01
Void urgency episodes (per day)	60	−1.88	64	−1.12	0.07
Bladder symptom severity (Overall Bladder Condition) NRS	61	−2.21	66	−1.05	0.001
Incontinence QOL	59	14.3	61	10.4	0.166
Patient Global Impression of Change (recorded at end of study)	61	84% improve	67	58% improve	0.005

NRS, numerical rating scale; QOL, quality of life.



		All subjects	≥0.5	≥1	≥1.5	≥2
n	Sativex	60	43	35	30	20
	Placebo	64	45	33	25	17

Figure 2. Change in number of nocturia episodes related to severity of baseline episodes.

The mean voided volume per 24 h between the two groups was similar at baseline (active treatment group 1508 ml, placebo 1410 ml) and changed little by the end of the study (active treatment group 1425 ml and placebo 1385 ml). Urodynamic traces were evaluable for 10 subjects in each group; findings revealed a change in maximum cystometric capacity of +85 ml for the active treatment group and −10 ml for the placebo group. The difference was not significant between treatment groups.

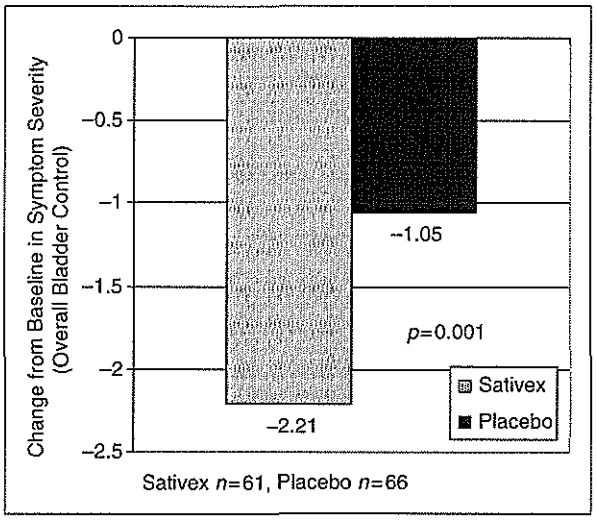


Figure 3. Subjects' opinion of bladder symptom severity (overall bladder condition). Subjects rated their condition on an 11-point scale (0 = no problems, 10 = intolerable problems).

Safety and tolerability results

Sativex was well tolerated in this study. There were no reported deaths during the study. Four subjects reported at least one serious adverse event (SAE) during the course of the study (two Sativex, two placebo). Three of the subjects reported SAEs that were considered treatment related; two were in the Sativex treatment group and one was in the placebo treatment group. One other placebo subject reported an MS relapse prior to treatment (placebo). A possible transient ischaemic attack (TIA) was reported for one Sativex subject 4 days after commencing study treatment, with symptoms of shaking, coordination problems and severe absence following a dose of 18 sprays in 1 day. Study treatment was withheld and the symptoms resolved. Sativex treatment was restarted the following day and the symptoms recurred a day later when the dose was again increased to 18 sprays. Based on the description of the event, there is a possibility that the episodes could have been caused due to intoxication rather than a TIA.

Haemorrhagic cystitis was reported in one Sativex subject approximately 1 month after commencing study treatment. The subject was treated with antibiotics, and developed a further SAE of dehydration, following a period of antibiotic-induced vomiting and diarrhoea. The haemorrhagic cystitis may have been related to the subject's underlying bladder instability.

One other placebo subject was hospitalized with dehydration and vomiting 8 days after completing

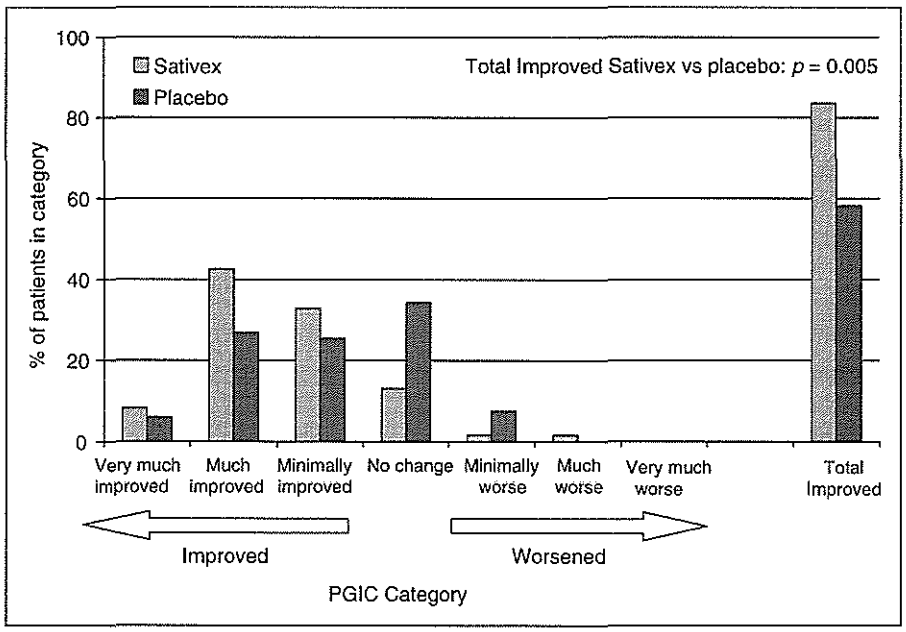


Figure 4. Histogram showing patients' global impression of change on Sativex or placebo.

60 days of study treatment. She was treated with trimethoprim, for an assumed urinary tract infection, and recovered.

Most AEs were considered mild or moderate in severity; many were possible CNS-type events (Table 4). Ten subjects stopped medication due to treatment-related AEs and withdrew from the study (seven on Sativex and three on placebo).

There were no significant changes in laboratory values or subjects' vital signs during the study. None of the subjects who were withdrawn from the study had clinically significant abnormal laboratory values.

At 50 min after the first dose of study medication, the mean intoxication score was 0.5 in the active treatment group and 0.4 in the placebo treatment group. At 2 h and 4 h after first dose, subjective mean intoxication scores were increased to 1.3 in the active treatment group and remained at 0.4 in the placebo treatment group. Mean scores at the final study visit were 1.4 for the active group and 0.2 in the placebo group. There was significant inter-individual variation in intoxication scores in both groups. The median scores were zero at all timepoints for both treatment groups.

Table 4. Adverse events on study medication. Events occurring in >5% of subjects.

	Number (%) of subjects			
	All causality		Treatment related	
All causality AEs Preferred Term	Sativex ($n=67$)	Placebo ($n=68$)	Sativex ($n=67$)	Placebo ($n=68$)
Dizziness#	12 (18%)	5 (7%)	12 (18%)	4 (6%)
Urinary tract infection	4 (6%)	7 (10%)	0	4 (6%)
Headache#	5 (8%)	5 (7%)	4 (6%)	2 (3%)
Vomiting	4 (6%)	2 (3%)	4 (6%)	2 (3%)
Nausea	3 (5%)	3 (4%)	3 (5%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	2 (3%)	2 (3%)
Disorientation#	4 (6%)	1 (2%)	4 (6%)	1 (2%)
Weakness	3 (5%)	2 (3%)	3 (5%)	1 (2%)
Pharyngitis	3 (5%)	2 (3%)	2 (3%)	0
Nasopharyngitis	3 (5%)	1 (2%)	0	0
Dissociation#	4 (6%)	0	4 (6%)	0
Feeling drunk	3 (5%)	0	3 (5%)	0
Constipation	3 (5%)	0	2 (3%)	0
Balance impaired#	3 (5%)	0	3 (5%)	0
Paraesthesia#	3 (5%)	0	2 (3%)	0
Cystitis	3 (5%)	0	2 (3%)	0

# Denotes possible central nervous system-related AEs.

Discussion

The primary endpoint (i.e. reduction in number of episodes of incontinence per day) did not reach statistical significance in this randomized, double-blind, placebo-controlled trial in subjects with MS and severe bladder dysfunction. Despite this, Sativex did have some significant positive effects on other bladder symptoms.

There are a number of possible reasons why the primary endpoint failed to reach statistical significance in this study. One possible explanation may be the large placebo effect which was observed in this study. Such a large effect is characteristic of studies looking at bladder control,[20] and is thought to be due to observation and an effect of keeping a micturition diary. In addition, it should be noted that the subjects who were recruited in this study were subjects who had previously failed to respond adequately to existing medication and had residual bothersome bladder symptoms despite the best available treatment, and were receiving study medication as an add-on treatment (i.e. subjects were refractory to other treatments). As a result, not all subjects will respond to treatment (something which is frequently observed when assessing the efficacy of cannabinoids on other symptoms of MS, such as spasticity); this is unsurprising and it is unreasonable to expect all such subjects to respond to a new treatment.

Given that all subjects remained on existing treatment, this may have contributed to a relatively low baseline number of incontinence episodes per day (median baseline number of incontinence episodes per day was 1.23 for the active treatment and 1.32 for the placebo groups, respectively – this is lower than would normally be the case for clinical studies of subjects with OAB who have been through a washout period). The inclusion criterion of a minimum of three incontinence episodes in 5 days meant that subjects with an average of 0.6 episodes a day were eligible for study entry, leaving little room for sufficient improvement to detect a significant difference between treatments. In addition, it is also possible that this treatment may have a limited effect on incontinence and more favourable effects on other bladder endpoints, such as frequency, urgency or nocturia.

The other issue worthy of note in this study is the difference in the size of the ITT population ($n=135$ subjects) and the PP population ($n=86$ subjects). This high proportion of exclusions ($n=46$) illustrates the difficulty in maintaining subject compliance with the study protocol; however, these exclusions were equally distributed between active and placebo groups ($n=23$ per group). Many of the protocol deviations were due to non-compliance in terms of the final visit assessment date and actual date of last dose of treatment (i.e. the

end of treatment assessments were not done whilst subjects were still on treatment or within 24 h of their last dose of 8 weeks of study treatment; 16 subjects). The fact that 20 subjects had a urinary tract infection (either at baseline or during treatment) further confounded the assessment of the study endpoints. Some subjects had more than one deviation, which excluded them from the PP population.

Freeman et al. reported on the effect of cannabis on urge incontinence in subjects with MS, comparing the oral administration of cannabis extract, THC and a matching placebo (the CAMS-LUTS study).[21] It was found that there was a significant difference in the number of episodes of incontinence between the cannabinoid treatment groups and the placebo group. This study used a different protocol, different active treatment and a larger number of subjects. An earlier open-label pilot study by Brady et al. demonstrated a reduced incidence of incontinence episodes following treatment with Sativex or THC extract.[2]

Sativex had a significant beneficial effect on other key parameters associated with OAB: urgency, nocturia and urinary frequency, and on the subject's assessment of the severity of their symptoms. As the urine volumes in the two groups (active and placebo) pre- and post-treatment were almost equal, these effects cannot be attributed to a change in urine volume, which was used as a surrogate marker for fluid intake.

There was also a significant improvement in subject perception of bladder symptom severity score which was mirrored in the PGIC results. Overall, despite the failure to hit the primary endpoint of the study, and the fact that there was no allowance made for multiplicity, taking into account the proportion of secondary outcomes that were positive and the levels of significance observed, this study does provide clinical evidence across a range of bladder-related endpoints that Sativex has some beneficial effect when used for treatment of the bladder symptoms in patients with MS. Similar symptomatic improvement has been reported in subjects with spasticity and pain.[22–24]

Another notable finding from the review of the concomitant medications taken by study subjects was that subjects in the placebo group appeared to use more prohibited drugs during the study than those in the Sativex group. This suggests improved efficacy within the Sativex group resulted in subjects requiring less in the way of additional medications to control their symptoms. Similarly, subjects in the placebo group took approximately twice as many sprays per day of study medication compared with those in the Sativex group, which could be considered as evidence that Sativex subjects achieved benefit (symptom control) from treatment at a lower dose of self-administered medication than those on placebo.

Blinding of treatment to subjects did not appear to be an issue in this study. The rates of self-reported mean 'intoxication' scores using an 'Intoxication' 0–10 NRS (using the anchors 0 = No intoxication and 10 = Extreme intoxication) were very similar between active and placebo groups, the greatest difference being observed at 2 h post-dose on Day 1 (change from baseline in mean NRS score = 1.2 (out of 10) on active compared with 0.4 on placebo). As with previous studies of Sativex in patients with MS, the data provide no evidence that the change from baseline in bladder symptoms was affected by prior use of cannabis overall or in combination with treatment group, or by CNS AE profile. The dosing of study drug (mean number of sprays per day) did not differ between the prior cannabis users and the cannabis-naïve subjects, neither overall, nor within each treatment group. This suggests that even if prior users of cannabis were able to distinguish between the treatments, this did not lead to bias in the assessment of efficacy. The most common CNS disorder reported as an AE in this study was dizziness (17.9% Sativex, 7.4% placebo) – all other CNS-type AEs in this system organ class were below 5% in incidence in the Sativex group. This was a relatively low incidence of dizziness compared with other studies of Sativex in patients with MS. The only other AEs over 5% incidence on Sativex were disorientation (6% Sativex vs. 1.5% placebo) and dissociation (6% Sativex vs. 0% placebo).

There are a number of limitations to this study. As discussed above, a number of factors may have contributed to a relatively low severity of incontinence at baseline, thereby contributing to the lack of significance with regard to the primary endpoint. In addition, in the analyses undertaken on these study data no allowance for multiplicity was made. However, it should be noted that there is a valid reason for this, in that a number of the variables measured in this study are not independent variables and indeed some are the direct sums of others – hence the use of a classical Bonferroni correction is inappropriate on this occasion. Thus, despite the lack of correction for multiplicity, it can be observed that the study endpoints (although multiple) are measuring similar variables in different ways and, within this framework, some consistency between endpoints has been obtained in this study. Thus, from this perspective, there is some consistent evidence that Sativex provided benefit with regard to certain bladder symptoms to the subjects in this study. One should bear both of these factors in mind when considering the data.

Also, the study had a number of subjects which were not available for the PP analysis. While the reasons for the exclusion were justified, this is not helpful when drawing conclusions from the study. Further, only small numbers of subjects had evaluable

cystometric traces. Similar findings for urodynamic investigations were reported in the CAMS subset study.[21]

Sativex appears to be well tolerated in patients suffering from MS – there were no deaths in the study, and only two SAEs were reported on treatment. The majority of AEs reported in this study (>80%) were mild to moderate in nature. Only 10 subjects withdrew from treatment due to AEs ($n=7$ Sativex, $n=3$ placebo), reflecting the tolerability. The mean doses of 9 sprays per day Sativex administered are comparable to those in previous studies in MS subjects.[22–24,27–29] There was no assessment of the double-blind study design effectiveness or potential unblinding within the study population group. An independent reviewer has previously assessed the possibility of unblinding against AE profiles in studies using comparable doses of Sativex.[30] There is no evidence to suggest that participants who have or have not previously used cannabis would be able to identify Sativex treatment from experiencing an AE from the Sativex profile. No safety concerns were identified and most of the reported AEs have been observed in other clinical trials of Sativex.[22–24,25–27] However, further long-term[28,29] data need to be evaluated.

Further studies investigating the mechanism of action of cannabinoids on bladder function may reveal more information about cannabinoid receptor expression and provide evidence as to the role of cannabinoid modulators in bladder control. Work by one of the co-authors (DD) suggests that CB_1 and CB_2 receptors are present on the human bladder, and that the beneficial effect of cannabinoid agonists in bladder function may not only be due to a cannabinoid action in the brain but also due to a peripheral contribution, either to activation of cannabinoid receptors at the spinal level or of those located in the bladder, or both.[31–33] In addition, it is known that the endocannabinoid anandamide has activity at the $TRPV_1$ receptor, which is also thought to regulate the frequency of bladder reflex contractions[34] Further, it has been reported that CB2 receptor expression is increased in acutely and chronically inflamed bladder of rats.[35] Given that it has been reported that endocannabinoids and cannabinoid agonists decrease motility in normal and inflamed bladder,[35] it is possible that the endocannabinoid system or related systems (such as the vanilloid system) may mediate functional effects of such compounds on the bladder.

As the neurological condition of patients with MS deteriorates, management of bladder symptoms can be difficult. Many anticholinergic drugs are less than ideal due to lack of efficacy, or because they are not well tolerated due to side effects. Recently intradetrusor injections of botulinum toxin have come to the fore in managing these patients' bladder symptoms, but intermittent self-catheterization is almost always necessary following injections.[36] There is therefore a need for a less invasive treatment, and the additional beneficial effects of Sativex on spasticity, spasms, pain and sleep mean that this therapy should be included in the armamentarium used to treat the troublesome bladder symptoms of MS.

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Conflict of interests

RK and CC have received sponsorship from GW Pharma Ltd to attend relevant conferences/scientific meetings and are paid consultants for GW Pharma Ltd. CS is an employee of GW Pharma Ltd.

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Cannabinoids in health and disease

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Cannabis sativa L. preparations, such as marijuana, hashish, and dagga, have been used in medicine for millenia.[1] Investigations into the chemistry of *Cannabis* began in the mid-19th century, following a major trend in chemical research at the time, which centered on the quest for active natural products. Numerous alkaloids were isolated in pure form from various plants, and many of them were fully or partially characterized. Morphine, cocaine, strychnine, and many others were purified and used in medicine. However, most of the terpenoids—a major class of secondary plant metabolites, to which the plant cannabinoids also belong—were not isolated until the end of the century or even much later, and in many cases their purity was doubtful.

Cannabis sativa L. *preparations have been used in medicine for millenia. However, concern over the dangers of abuse led to the banning of the medicinal use of marijuana in most countries in the 1930s. Only recently, marijuana and individual natural and synthetic cannabinoid receptor agonists and antagonists, as well as chemically related compounds, whose mechanism of action is still obscure, have come back to being considered of therapeutic value. However, their use is highly restricted. Despite the mild addiction to cannabis and the possible enhancement of addiction to other substances of abuse, when combined with cannabis, the therapeutic value of cannabinoids is too high to be put aside. Numerous diseases, such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name just a few, are being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds. In view of the very low toxicity and the generally benign side effects of this group of compounds, neglecting or denying their clinical potential is unacceptable—instead, we need to work on the development of more selective cannabinoid receptor agonists/antagonists and related compounds, as well as on novel drugs of this family with better selectivity, distribution patterns, and pharmacokinetics, and—in cases where it is impossible to separate the desired clinical action and the psychoactivity—just to monitor these side effects carefully.*

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Selected abbreviations and acronyms

ALS	*amyotrophic lateral sclerosis*
CBD	*cannabidiol*
DA	*dopamine*
HD	*Huntington's disease*
IOP	*intraocular pressure*
MS	*multiple sclerosis*
PD	*Parkinson's disease*
PTSD	*post-traumatic stress disorder*
THC	*tetrahydrocannabinol*

In 1840, Schlesinger was apparently the first investigator to obtain an active extract from the leaves and flowers of hemp.[2] A few years later, Decourtive described the preparation of an ethanol extract that on evaporation of the solvent gave a dark resin, which he named "cannabin."[3] For a detailed history of early *Cannabis* research see ref 4. The chemical research on the plant cannabinoids and their derivatives over nearly two centuries is described in ref 5. It was, however, not until 1964 that Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of *Cannabis*, was isolated in pure form and its structure was elucidated.[6] Shortly thereafter it was synthesized and became widely available. These chemical advances led to an avalanche of publications on Δ^9-THC, as well as on cannabidiol (CBD), a nonpsychoactive plant cannabinoid.[7] However, concern about the dangers of abuse led to the banning of marijuana and its constituents for medicinal use in United States and many other countries in the 1930s and 1940s. It took decades until cannabinoids came to be considered again as compounds of therapeutic value, and even now their uses are highly restricted. Here we present an overview of the addictive and side effects of cannabinoids vs their therapeutic potential.

Addiction to cannabis, and the influence of cannabis on addiction to other substances

Marijuana may produce mild dependence in humans.[8-12] This was shown to depend on the personality type of the addicts,[13] and can be successfully reversed by abstinence or treated by cognitive-behavioral therapy,[14] without the occurrence of major withdrawal symptoms. Cannabinoids act on brain reward processes and reward-related behaviors by a mechanism similar to that found with other addictive drugs. In animal models they enhance electrical brain-stimulation reward in the core meso-accumbens reward circuitry of the brain and neural firing of a core dopamine (DA) component and thus elevate DA tone in the reward-relevant meso-accumbens DA circuit. In some animal models they produce conditioned place preference (CPP) and self-administration.[15,16] Other studies, however, find THC to be a poor reinforcer, with no or little self-administration.[17]

The abuse of other substances is influenced by the cannabinoids. The cannabinoid system is involved in alcohol-consumption behavior. Cannabinoid CB1 receptor agonists have been found to specifically stimulate alcohol intake and its motivational properties in rats.[18] The high ethanol preference of young mice is reduced by the cannabinoid receptor 1 (CB1) antagonist SR141716A (rimonabant) to levels observed in their CB1 knockout littermates.[19] Dopamine release induced by ethanol in brain was reduced by SR141716A,[20] which can explain in part the antiaddictive effect of the drug. Cocaine is another substance of abuse in whose acquisition and consolidation cannabinoids may be involved. High prevalence of alcohol dependence and cannabis dependence can be found in patients with cocaine dependence.[21] Marijuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers.[22,23] Furthermore, a recent genetic study found an association between an n triplet repeat polymorphism in the CB1 encoding *CNR1* gene with cocaine addiction in the African-Caribbean population.[24] In another study it was found that withdrawal from repeated access or exposure to cocaine and then a reinstatement of cocaine-seeking behavior or a sensitized locomotor response to a single cocaine challenge, respectively, was potently reduced by pretreatment with rimonabant.[25] Similarly, acute administration of rimonabant blocked expression of nicotine-induced conditioned place preference.[26] Rimonabant also reduces nicotine self-administration, and may be effective not only as an aid for smoking cessation, but also in the maintenance of abstinence.[27] As the endocannabinoid system plays a role in nicotine addiction,[28] the potential of cannabinoid antagonists to treat it is self-evident.[29-31] Opiate and CB1 receptors are coexpressed in the nucleus accumbens and dorsal striatum, and the interaction between the two systems is well known.[32] The reinforcing properties of morphine and the severity of the withdrawal syndrome are strongly reduced in CB1-knockout mice[33]; this observation opens an opportunity to treat opiate addiction with rimonabant, as noted with alcohol, cocaine, and nicotine addiction.[34,35]

Negative effects of cannabis other than addiction

There are some negative effects of cannabis use other than addiction, most of them related to alterations of attentional and cognitive functions or other neuropsychological and behavioral effects. Most of them are noted as a result of early-onset cannabis use (during adolescence).[36] Electrophysiological measures have revealed long-term deficits in attention among cannabis users.[37] In another study, impairment both in cognitive function and mood following cannabis use was noted.[38] However, in another study, cannabis users and controls performed equally well in a working memory task and a selective attention task. Furthermore, cannabis users did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions.[39] Prenatal exposure to cannabis is associated with only minor impaired cognitive and attentional effects.[40-42] Cannabis use in adolescence increases the risk of schizophrenia-like psychoses.[43] Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.[44] Also, evidence exists that cannabis use may trigger acute schizophrenic psychosis.[45,46] Cannabis was found to produce a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses.[46] Amotivational syndrome is a chronic psychiatric disorder characterized by a variety of changes in personality, emotions, and cognitive functions such as lack of activity, inward-turning, apathy, incoherence, blunted affect, inability to concentrate, and memory disturbance. The syndrome was first described in the 1960s among patients with a history of longtime cannabis use.[47] A useful animal model for this disorder was found in rat, where the cannabis-caused catalepsy-like immobilization is related to a decrease in catecholaminergic and serotonergic neurons in the nucleus accumbens and amygdaloid nucleus, and thus can serve as a model for amotivational syndrome.[48] In another study, heavy cannabis use was found to cause an amotivational syndrome in adolescents.[49] The treatment of cannabis use disorders has recently been reviewed.[12] However, the occurrence of amotivational syndrome as a result of cannabis exposure remains controversial.[50] The data from other studies do not support the hypothesis that marijuana impairs motivation.[51,52] Although most of the cannabis-related negative effects relate to its neuropsychologic and behavioral effects, other negative reactions to cannabis are sometimes found. For example, cannabis can cause acute pancreatitis, although the exact mechanism remains unknown.[53]

Therapeutic uses of cannabinoids

Obesity, anorexia, emesis

Cannabis has been known for centuries to increase appetite and food consumption.[54] More recently this propensity of the drug was substantiated when the CB1 receptor was shown to have a role in central appetite control, peripheral metabolism, and body weight regulation.[55] Genetic variants at CB1 coding gene *CNR1* are associated with obesity-related phenotypes in men.[56] In animals, CB1 receptor antagonism decreases motivation for palatable foods. Rimonabant administration caused suppression of the intake of a chocolate-flavored beverage over a 21-day treatment period, without any apparent development of tolerance.[57] CB1 receptors were found to be preferentially involved in the reinforcing effects of sweet, as compared to a pure fat, reinforcer.[58] Rimonabant selectively reduces sweet rather than regular food intake in primates,[59] which suggests that rimonabant is more active on the hedonic rather than nutritive properties of diets.

Rimonabant leads to significant weight loss in obese human subjects. Treatment with rimonabant was also associated with beneficial effects on different metabolic parameters and cardiovascular risk factors linked with overweight.[60,61] In clinical trials rimonabant was found to cause a significant mean weight loss, reduction in waist circumference, increase in HDL cholesterol, reduction in triglycerides, and increase in plasma adiponectin levels.[62] Patients who were switched from the rimonabant treatment to placebo after a 1-year treatment regained weight, while those who continued to receive rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors.[63,64] Rimonabant was shown to be safe and effective in treating the combined cardiovascular risk factors of smoking and obesity.[65] It also diminishes insulin resistance, and reduces the prevalence of metabolic syndrome. Many of the metabolic effects, including adiponectin increase, occur beyond weight loss, suggesting a direct peripheral effect of rimonabant.[66] Therapy with rimonabant is also associated with favorable changes in serum lipids and an improvement in

glycemic control in type 2 diabetes.[67] The activity of rimonabant in the management of obesity has been described in recent reviews.[31,68] It has been approved for the treatment of obesity in the European Union, and is sold under the trade name Acomplia. Surprisingly, the US Food and Drug Administration has declined to approve rimonabant, primarily due to its slight potential to enhance anxiety and suicidal thoughts. The atmosphere of consternation of possible legal action due to side effects may have led to this decision.

The other side of the same coin is anorexia. While in obese populations weight loss is the main goal, in other populations, such as patients with cancer or AIDS, it is an immense problem. Dronabinol (synthetic THC, known as Marinol and approved for the treatment of nausea and vomiting in cancer and AIDS patients) is associated with consistent improvement in appetite.[69] It was found to be safe and effective for anorexia associated with weight loss in patients with AIDS, and is associated with increased appetite, improvement in mood, and decreased nausea. In clinical trials, weight was stable in dronabinol patients, while placebo recipients lost weight.[70,71] Dronabinol was found to be safe and effective for treatment of HIV wasting syndrome,[72] as well as in patients with Alzheimer's disease[73] and with advanced cancer,[73,74] The possible mechanisms of these actions have been reviewed.[75] Cannabinoids have a positive effect in controlling chemotherapy-related sickness.[76] They are more effective antiemetics than the dopamine receptor antagonists such as chlorpromazine-type drugs.[77] Direct comparisons with serotonin (5-HT)3 antagonists, which are widely used as antiemetics, have not been reported. However, while these antagonists are not effective in delayed vomiting, THC is known to reduce this side effect of chemotherapy.

Pain

Cannabis has been used for millennia as a pain-relieving substance. Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they were proposed to be a promising therapeutic approach for the clinical management of trigeminal neuralgia.[78] THC, CBD, and CBD-dimethyl heptyl (DMH) were found to block the release of serotonin from platelets induced by plasma obtained from the patients during migraine attack.[79] However, in other reports cannabinoids are much less successful in pain-relieving. In a clinical trial THC did not have any significant effect on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain.[80] Similarly, in an additional clinical trial, no evidence was found[81]of analgesic effect of orally administered THC in postoperative pain in humans. Other studies show much better results of pain relief. When THC was given to a patient with familial Mediterranean fever, with chronic relapsing pain and gastrointestinal inflammation, a highly significant reduction in pain was noted.[82] Mild improvement was noted with cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion.[83] In neuropathic pain patients, median spontaneous pain intensity was significantly lower on THC treatment than on placebo treatment, and median pain relief score (numerical rating scale) was higher.[84] It was also effective in treating central pain.[85] The administration of single oral doses of THC to patients with cancer pain demonstrated a mild analgesic effect.[86,87] Patients who suffer from pain also tend to self-medicate with marijuana. In an anonymous cross-sectional survey, 72 (35%) of chronic non-cancer pain patients reported having used cannabis for relieving pain.[88] Cannabis-treated AIDS patients reported improved appetite, muscle pain, nausea, anxiety, nerve pain, depression, and paresthesia.[89] Not only THC, but also other cannabinoids can potentially affect different types of pain. Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy.[90] In Canada, the United States, and the United Kingdom, nabilone is marketed as Cesamet. A significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found with nabilone.[91] Another cannabinoid, ajulemic acid (AJA), was effective in reducing chronic neuropathic pain,[92] although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted. Cannabimimetic effects with ajulemic acid in rodents have also been recorded.[93]

The combination of THC with the nonpsychotropic cannabis constituent CBD has a higher activity than THC alone.[94] The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS).[95] Chronic neuropatic pain can also

be treated with cannabis extracts containing THC, or CBD, or with Sativex.[96,97] The latter also was effective in reducing sleep disturbances in these patients and was mostly well tolerated.[97] Sativex is the first cannabis-based medicine to undergo conventional clinical development and be approved as a prescription drug. It is efficacious and well tolerated in the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain.[98] Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada [for reviews on Sativex and on pain see refs 94, 99, and 100].

Multiple sclerosis, neuroprotection, inflammation

Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease. In clinical trials, it has been shown that cannabis derivatives are active on the pain related to MS,[84,85,95,97,98] However, this is not the only positive effect of cannabinoids in this disease. In rat experimental autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexanabinol (HU-211 a nonpsychoactive synthetic cannabinoid).[101] In another trial in rats, all animals treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%.[102] WIN-55,212-2, another synthetic cannabinoid, also was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2.[103] Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210.[104] To more fully inderstand the involvement of the endocannabinoid system in MS, the status of cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase (FAAH) enzyme in brain tissue samples obtained from MS patients was investigated. Selective glial expression of cannabinoid CB1 and CB2 receptors and FAAH enzyme was found to be induced in MS.[105] In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.[106] Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s.[107] In an experiment in mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid receptors.[108] In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo.[109] In one case report nabilone improved muscle spasms, nocturia, and general well-being.[110] In another case report, the chronic motor handicaps of an MS patient acutely improved while he smoked a marijuana cigarette.[111] THC significantly reduced spasticity by clinical measurement. Responses varied, but benefit was seen in patients with tonic spasms.[112] At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility.[113] However, in other clinical trials, cannabinoids appeared to reduce tremor but were ineffective in spasticity.[114,115] Moreover, in one trial marijuana smoking further impaired posture and balance in patients with spastic MS.[116] The inconsistent effects noted might be due to dose-dependency. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia, were given oral THC.[117] In another study, cannabis extract did not produce a functionally significant improvement in MS-associated tremor.[118] Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil.[119] There are also findings suggestive of a clinical effect of cannabis on urge incontinence episodes in patients with MS.[120] In the treatment of MS, as well as in pain reduction described earlier, there is a preferential effect of a THC+CBD combination (Sativex).[121] A mixture of 2.5 mg THC and 0.9 mg cannabidiol (CBD) lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs.[122] Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo.[123] Long-term use of Sativex maintains its effect in those patients who perceive initial benefit.[124] Zajicek et al origi-

nally reported that cannabinoids did not have a beneficial effect on spasticity; however, there was an objective improvement in mobility and some patients reported an improvement in pain.[125] Later the same group also found positive effects on muscle spasticity with prolonged treatment.[126] The subject has been thoroughly reviewed.[99,127-130]
MS is not the only disease state where the neuroprotective potential of cannabinoids can be seen. In animal experiments, 2 weeks after the application of 6-hydroxydopamine, a significant depletion of dopamine contents and a reduction in tyrosine hydroxylase activity in the lesioned striatum were noted, and were accompanied by a reduction in tyrosine hydroxylase-messenger ribonucleic acid (mRNA) levels in the substantia nigra. Daily administration of THC over 2 weeks produced a significant irreversible waning in the magnitude of these changes, which may be relevant in the treatment of Parkinson's disease (see below).[131] The cannabinoids have a neuroprotective activity not only in vitro but also in vivo: HU-210, a potent synthetic analog of THC, increases survival of mouse cerebellar granule cells exposed to 6-hydroxydopamine.[131] In a model of experimental stroke, rimonabant reduced infarct volume by approximately 40%. Rimonabant exerted neuroprotection independently of its cannabinoid receptor-blocking effect.[132] In clinical trials, dexanabinol-treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure. A trend toward faster and better neurologic outcome was also observed.[133] However, in further experiments, dexanabinol was not found to be efficacious in the treatment of traumatic brain injury.[134] A wide range of cannabinoids has been shown to help in pathologies affecting the central nervous system (CNS) and other diseases that are accompanied by chronic inflammation.[130,135,136] In a rodent model of chronic brain inflammation produced by the infusion of lipopolysaccharide into the fourth ventricle of young rats, the cannabinoid agonist WIN-55212-2 reduced the number of LPS-activated microglia.[137] Direct suppression of CNS autoimmune inflammation was seen by activation of CB1 receptors on neurons and CB2 receptors on autoreactive T cells.[138]
Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and stroke in Western countries. Oral treatment with a low dose of THC inhibits atherosclerosis progression in an apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC may be a valuable target for treating atherosclerosis.[139] N-palmitoyl-ethanolamine is an endogenous endocannabinoid-like compound. Its concentrations are significantly increased in three different inflammatory and neuropathic conditions. The enhanced levels may possibly be related to a protective local anti-inflammatory and analgesic action.[140]
CBD has been shown to exert potent anti-inflammatory and antioxidant effects. High-glucose-induced mitochondrial superoxide generation, NF-kappaB activation, nitrotyrosine formation, iNOS and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs) were attenuated by CBD pretreatment.[141]
In experiments with obese vs lean rats, rimonabant was found to be a potent inhibitor of sensory hypersensitivity associated with CFA-induced arthritis in obese rats, in which the inflammatory reaction is more severe than in lean rats. It may thus have therapeutic potential in obesity-associated inflammatory diseases.[142]

Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder. The main pathological feature of PD is the degeneration of dopamine (DA)-containing neurons of the substantia nigra, which leads to severe DAergic denervation of the striatum. The irreversible loss of the DA-mediated control of striatal function leads to the typical motor symptoms observed in PD, ie, bradykinesia, tremor, and rigidity. It has been proposed that cannabinoids may have some beneficial effects in the treatment of PD.[129] In animal experiments cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro.[131]
The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic suggest that CB1 receptor antagonists could prove useful in the treatment of both parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have value in reducing levodopa-induced dyskinesia.[143] In the reserpine-treated rat model of PD, the dopamine D2 receptor agonist quinpirole caused a significant alleviation of the akinesia. This effect was significantly reduced by coinjec-

tion with the cannabinoid receptor agonist WIN 55,212-2. The simultaneous administration of the CB1 antagonist rimonabant with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia.[144] In animal experiments, chronic levodopa produced increasingly severe orolingual involuntary movements which were attenuated by WIN 55,212-2. This effect was also reversed by rimonabant.[145] In other studies, rimonabant was found to possess some beneficial effects on motor inhibition typical of PD, at least in some doses. The injection of 0.1 mg/kg of rimonabant partially attenuated the hypokinesia shown by PD animals with no effects in control rats, whereas higher doses (0.5-1.0 mg/kg) were not effective.[146] A nigrostriatal lesion by MPTP is associated with an increase in CB1 receptors in the basal ganglia in humans and nonhuman primates; this increase could be reversed by chronic levodopa therapy, which suggests that CB1 receptor blockade might be useful as an adjuvant for the treatment of parkinsonian motor symptoms.[147] High endogenous cannabinoid levels are found in the cerebrospinal fluid of untreated PD patients.[148] Administration of inhibitors of endocannabinoid degradation reduced parkinsonian motor deficits in vivo.[149] Thus, both agonists and antagonists of CB receptors seem to help in some parkinsonian symptoms. In clinical trials, the cannabinoid receptor agonist nabilone significantly reduced levodopa-induced dyskinesia in PD.[150] THC improved motor control in a patient with musician's dystonia.[151] In contrast to these findings, some studies find no effect of cannabinoids on PD: orally administered cannabis extract resulted in no objective or subjective improvement in either dyskinesias or parkinsonism,[152] no significant reduction in dystonia following treatment with nabilone,[153] and rimonabant could not improve parkinsonian motor disability.[154] However, an anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of the respondents had taken cannabis and 45.9% of these described some form of benefit.[155] Thus cannabinoids seem to be able to treat at least some symptoms of neurological diseases.[156-158]

Huntington's disease (HD) or Huntington's chorea ("chorea" meaning "dance" in Greek) is a disorder characterized by a distinctive choretic movement, progressive motor disturbances, dementia, and other cognitive deficits. Neuropathologically, HD is characterized by a degeneration of medium spiny striato-efferent γ-aminobutyric acid (GABA)ergic neurons and by an atrophy of the caudate nucleus. Advanced grades of HD showed an almost total loss of CB1 receptors and a further depletion of D1 receptors in the caudate nucleus, putamen, and globus pallidus internus, and an increase in $GABA_A$ receptor binding in the globus pallidus internus.[159,160] Loss of cannabinoid receptors is also seen in the substantia nigra in HD.[161] These findings suggest a possible therapeutic role of cannabinoid agonists in HD. Indeed, arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of HD generated by bilateral intrastriatal application of 3-nitropropionic acid (3-NP).[162] The reduction in the increased ambulation exhibited by 3NP-lesioned rats in the open-field test caused by AM404 (anandamide's transport inhibitor, which also binds to vanilloid receptor 1) was reversed when the animals had been pretreated with capsazepine (VR1 antagonist), but not with SR141716A, thus suggesting a major role of VR1 receptors in the antihyperkinetic effects of AM404. However, both capsaicin (VR1 agonist) and CP55,940 (an CB1 agonist) had antihyperkinetic activity.[163] Quinolinic acid (QA) is an excitotoxin which, when injected into the rat striatum, reproduces many features of HD by stimulating glutamate outflow. Perfusion with WIN 55,212-2 significantly and dose-dependently prevented the increase in extracellular glutamate induced by QA. Thus, the stimulation of CB1 receptors might lead to neuroprotective effects against excitotoxic striatal toxicity.[164] In a clinical trial CBD was neither symptomatically effective nor toxic in neuroleptic-free HD patients.[165]

Tourette syndrome (TS) is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Anecdotal reports have suggested that the use of cannabis might improve tics and behavioral problems in patients with TS. Indeed, THC reduced tics in TS patients,[166] without causing acute and/or long-term cognitive deficits.[167] In another clinical trial, where tic severity was assessed using a self-rating scale and examiner ratings, patients also rated the severity of associated behavioral disorders. There was a significant improvement of motor tics, vocal tics and obsessive-compulsive behavior after treatment with THC. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration, suggesting a possible role of this THC metabolite on the positive effect of THC.[168] In another, longer clinical trial, THC was also found to be effective and safe in the treatment of tics.[169] In view of the positive effect of CB1 agonists in the treatment of TS, CB1 gene mutations were investigated. However, TS was not found to be caused by mutations in the *CNR1* gene.[170]

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. Many effects of marijuana may be applicable to the management of ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, its strong antioxidative and neuroprotective effects may prolong neuronal cell survival.[171] Indeed, treatment of postsymptomatic, 90-day-old SOD1G93A mice (a model of ALS) with WIN 55,212-2, significantly delayed disease progression. Furthermore, genetic ablation of the FAAH enzyme, which results in raised levels of the endocannabinoid anandamide, prevented the appearance of disease signs in these mice. Surprisingly, elevation of cannabinoid levels with either WIN 55,212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in these mice, but significantly extended life span. Together these results show that cannabinoids have significant neuroprotective effects in this model of ALS, and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms.[172] THC was also found to delay the progression of disease.[173,174] Treatment with AM1241, a CB2-selective agonist, was effective at slowing signs of disease progression, when administered after onset of signs in an ALS mouse model. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls[175]; moreover, AM-1241 prolonged survival in these mice.[176]
In a survey among ALS patients, cannabis was reported to be moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, and drooling.[177]
Cannabinoids were also proposed to have a role in the treatment of *Alzheimer's disease (AD)*. THC competitively inhibits acetylcholinesterase (AChE) and prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of AD.[178] THC treatment also decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC.[179] Compared with baseline, THC led to a reduction in nocturnal motor activity. These findings were corroborated by improvements in the Neuropsychiatric Inventory total score, as well as in subscores for agitation, aberrant motor, and nighttime behaviors; no side effects were observed.[180]
Studies on *cannabinoid anticonvulsant activity* began in 1975, when CBD, and four CBD derivatives, (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-tri-acetate and 9-hydroxy-CBD-triacetate) were shown to protect against maximal electroshock convulsions in mice, to potentiate pentobarbital sleeping-time and to reduce spontaneous motor activity.[181] Later additional CBD analogs were shown to be active.[182-184] CBD was found to be an effective anticonvulsant with specificity more comparable to drugs clinically effective in major, but not in minor seizures. Furthermore, it appears that CBD enhances the anticonvulsant effects of drugs in major seizures and reduces their effects in minor seizures.[185,186] Hence, CBD was suggested as a drug for the treatment of children with pharmacoresistant epilepsy.[187]
The application of the CB1 receptor antagonists SR141716A or AM251 to "epileptic" neurons caused the development of continuous epileptiform activity, resembling electrographic status epilepticus. The induction of status epilepticus-like activity by CB1 receptor antagonists was reversible and could be overcome by maximal concentrations of CB1 agonists.[188] Arachidonyl-2'-chloroethylamide (ACEA), a highly selective cannabinoid CB1 receptor agonist, enhances the anticonvulsant action of valproate in a mouse maximal electroshock-induced seizure model.[189] There are currently insufficient data to determine whether occasional or chronic marijuana use influences seizure frequency.[190] In one case report, marijuana smoking was proposed to induce seizures.[191] In another study, patients suffering from secondary generalized epilepsy with temporal focus treated with CBD remained almost free of convulsive crises throughout the experiment; other patients demonstrated partial improvement in their clinical condition.[192]

Bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), depression, anxiety, insomnia

Cannabis use is common in patients with *bipolar disorder*, and anecdotal reports suggest that some patients use marijuana to alleviate symptoms of both mania and depression.[193] In a case report, one female patient found that cannabis curbed her manic rages; others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects.[194]
The effect of cannabinoids on *schizophrenia* is controversial. Neuropsychological results in THC-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schiz-

ophrenic psychoses, as regards disturbances in internal regulation of perceptual processes.[195] In a recent study, it was found that anandamide levels are enhanced in first-episode schizophrenic patients, and that THC downregulates anandamide signaling.[196] This observation possibly means that THC lowers endogenous production of anandamide, which may actually be a defense mechanism—presumably comparable to the known observation that administration of corticosteroids blocks corticosteroid synthesis. Data from experimental-psychological tests show that personality changes generated by schizophrenia progression are comparable to psychopathological phenomenon due to cannabis intoxication.[197] In another study, psychosis, which develops or recurs in the context of cannabis use, did not have a characteristic psychopathology or mode of onset.[198] First-episode schizophrenic patients with long-term cannabis consumption were significantly younger at disease onset, mostly male, and suffered more often from paranoid schizophrenia (with a better prognosis) than those without cannabis consumption.[199] However, a trend towards more insight and of fewer abusive or accusatory hallucinations was seen amongst cannabis users. This argues against a distinct schizophrenia-like psychosis caused by cannabis.[200] Less avolition and fewer apathy symptoms were detected in patients with schizophrenia and cannabis abuse than in those with no abuse.[201] In another clinical trial, the role of CB1 receptors in schizophrenia was studied by administration of CB1 antagonist to patients. The group receiving the CB1 antagonist did not differ from the group receiving placebo on any outcome measure.[202]

CBD causes antipsychotic effects.[203] It was found to be a safe and well-tolerated alternative treatment for schizophrenia.[204] (See, however, also ref 205).

Post-traumatic stress disorder (PTSD) is a term for severe psychological consequences of exposure to, or confrontation with, stressful, highly traumatic events. Cannabinoids are believed to help in such cases. AM404-treated animals showed decreased shock-induced reinstatement of fear.[206] In conditioned fear and Morris water maze experiments, FAAH (-/-) mice and mice treated with the FAAH inhibitor OL-135 did not display any memory impairment or motor disruption, but did exhibit a significant increase in the rate of extinction. SR141716 blocked the effects of OL-135, suggesting that endogenous anandamide plays a facilitator role in extinction through a CB1 receptor mechanism of action. In contrast, THC failed to affect extinction rates, suggesting that FAAH is a more effective target facilitating extinction than a direct-acting CB1 receptor agonist.[207] Acutely, the absence of CB1 receptors reduces the neuroendocrine response and does not affect the behavioral response to moderate stress. However, upon repeated stress or acute severe stress, CB1 receptor deficiency causes persistent behavioral inhibition. Repeated bell stress seemed to cause a cumulative fear in CB1 receptor knockout mice.[208] In self-reports of substance use among help-seeking veterans, PTSD diagnosis was significantly associated with marijuana use.[209] These observations suggest that the endocannabinoid system can be modulated to enhance emotional learning, and that endocannabinoid modulators may be therapeutically useful as adjuncts for exposure-based psychotherapies, such as those used to treat PTSD and other anxiety disorders. CB1 receptor gene polymorphism is known to modify transcription of the gene. In patients with Parkinson's disease, the presence of two long alleles, with more than 16 repeated AAT trinucleotides in the CNR1 gene, was associated with a reduced prevalence of depression.[210]

CBD, and some derivatives, were found to cause a selective anxiolytic effect in the elevated plus-maze, within a limited range of doses.[211,212] A single dose of nabilone produced only mild improvement in anxiety[213]; in a repeated-dose treatment a dramatic improvement in anxiety was noted in the nabilone group.[214]

The effects of marijuana on human sleep patterns were noticed long ago.[215-217] Reduced eye movement density was seen, with some tolerance developing to this effect.[218,219] THC is sedative, while CBD has alerting properties as it increased awake activity and counteracted the residual sedative activity of THC.[220]

Asthma, cardiovascular disorders, glaucoma

Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus. In animal experiments, after methacholine-induced or exercise-induced bronchospasm, marijuana caused a prompt improvement of the bronchospasm and associated hyperinflation.[221] In humans, habitual smoking of marijuana may cause mild, but significant, functional lung impairment[222]; However, a mild and inconstant bronchodilatory action was found for THC.[223] In other clinical trials, smoking marijuana or ingesting THC were found to increase airway conduction.[224,225] Other plant cannabinoids did not provide

effective bronchodilation. The daily use of THC was not associated with clinical tolerance.[226] THC administered in metered volumes by inhalation from an aerosol device to patients judged to be in a steady state, increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) and produced bronchodilatation.[227] In another study, salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were not detected by radioimmunoassay. The mode of action of THC differed from that of sympathomimetic drugs.[228]

In another study, THC induced sympathetic stimulation and parasympathetic inhibition of *cardiovascular control pathways*. The peak heart rate rise after THC was attenuated by atropine and by propranolol, and nearly abolished by atropine-propranolol pretreatment.[229] Acute THC significantly increased heart rate, shortened pre-ejection period (PEP) and prolonged left ventricular ejection time (LVETc) without any change in afterload; it enhanced cardiac performance. Partial inhibition of this effect was achieved with prior β-adrenergic blockade.[230] In contrast, following the smoking of one to three marijuana cigarettes, the heart rate rose, cardiac output rose, stroke volume, ejection fraction, PEP and LVET did not change; thus, in long-term heavy users of cannabis, marijuana has no significant effect on myocardial contractility independent of its effect on heart rate.[231] Cardiovascular effects of acute THC administration included increased sympathetic and reduced parasympathetic tone; supine tachycardia and increased blood pressure with upright hypotension were observed. With repetitive dosing supine bradycardia and decreased blood pressure with tolerance to orthostatic hypotension were observed.[232,233] Rimonabant attenuated the hypotensive effect of smoked marijuana in male smokers, suggesting a role for the CB1 receptor in cannabinoid hypotensive action.[234]

A number of studies suggest that there is a correlative, but not necessarily causal, relationship between *glaucoma* and systemic hypertension. Ocular hypertension (OHT) refers to any situation in which intraocular pressure is higher than normal, and is the most important risk factor for glaucoma. THC, CBN, and nabilone were active in lowering intraocular pressure (IOP) in rabbits, while CBD was inactive.[235] Certain derivatives of THC were more active in lowering IOP than the parent cannabinoid[236]; some topically used soft analogs that have no systemic effects were also active in IOP reduction.[237] The effect on IOP of 2-AG was biphasic (ie, an initial increase in IOP followed by a reduction). In contrast, noladin ether decreased IOP immediately after topical administration, and no initial IOP increase was observed. AM251 blocked the effect on IOP of noladin ether, but did not affect the action of 2-AG.[238] Topical administration of anandamide and arachidonyl propionitrileamide decreased IOP; rimonabant antagonized the IOP reduction, suggesting that cannabinoids lower IOP through CB1 receptors.[239,240] Significantly, higher levels of CB1 mRNA levels were found in the ciliary body than in the iris, retina, and choroid. CB2 mRNA was undetectable. This expression pattern supports a specific role for the CB1 receptor in controlling IOP.[241] When delivered topically to cat eyes with osmotic minipumps, whole marijuana extract, THC and other plant cannabinoids reduced IOP, while cannabichromene was inactive. Ocular toxicity was seen after THC treatment, consisting of conjunctival erythema and chemosis as well as corneal opacification. Although these changes also occurred with marijuana extract, their intensity was much reduced. In contrast, no ocular toxicity was apparent during administration of plant cannabinoids other than THC.[242-244] Marijuana smoking was shown to reduce IOP as early as 1971; the effect was later confirmed.[245-248] The peak effect of THC on the central nervous system coincided well with the reduction in intraocular pressure induced by the drug; However, hypotonia outlasted euphoria. The results indicate that THC may have value as a hypotonizing ocular drug.[249] The functional responses after THC inhalation in sitting normotensive and hypertensive patients included invariable increases in heart rate followed by substantial decreases in systolic pressure, diastolic pressure, and intraocular pressure. The intensity and duration of the arterial and ocular pressure responses to THC were greater in hypertensives than in normotensive patients; the changes in ocular pressure paralleled the changes in blood pressure in glaucoma patients.[250] A single sublingual dose of THC, but not cannabidiol, reduced the IOP temporarily and was well tolerated by most patients.[251]

Cancer

The antiproliferative action of cannabinoids on cancer cells was first noticed in the 1970s. Since then cannabinoids were found to act on various cancer cell lines, through various mechanisms.[252,253] Cannabinoids were

also found to be suppressors of angiogenesis and tumor invasion.[254] Our knowledge on the anticancer activity of cannabinoids is rapidly expanding; hence only results of recent research on this topic are presented here. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner. Moreover, cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo.[255] The nonpsychoactive cannabidiol triggered caspase activation and oxidative stress in human glioma cells.[256] Human melanomas express CB1 and CB2 [illegible]

had clear evidence of tumour progression, were administered THC intratumorally. THC inhibited tumor-cell proliferation in vitro, decreased tumor-cell Ki67 immunostaining and prolonged the survival time of two of the patients.[261]

Conclusion

Many drugs used today can cause addiction and are misused and abused, for example opiates,[265] cocaine,[266] benzodiazepines,[267] barbiturates,[268] cholinergic agonists,[269] ket[illegible]

Selected abbreviations and acronyms

ALS	*amyotrophic lateral sclerosis*
CBD	*cannabidiol*
DA	*dopamine*
HD	*Huntington's disease*
IOP	*intraocular pressure*
MS	*multiple sclerosis*
PD	*Parkinson's disease*
PTSD	*post-traumatic stress disorder*
THC	*tetrahydrocannabinol*

In 1840, Schlesinger was apparently the first investigator to obtain an active extract from the leaves and flowers of hemp.[2] A few years later, Decourtive described the preparation of an ethanol extract that on evaporation of the solvent gave a dark resin, which he named "cannabin."[3] For a detailed history of early *Cannabis* research see ref 4. The chemical research on the plant cannabinoids and their derivatives over nearly two centuries is described in ref 5. It was, however, not until 1964 that Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of *Cannabis*, was isolated in pure form and its structure was elucidated.[6] Shortly thereafter it was synthesized and became widely available. These chemical advances led to an avalanche of publications on Δ^9-THC, as well as on cannabidiol (CBD), a nonpsychoactive plant cannabinoid.[7] However, concern about the dangers of abuse led to the banning of marijuana and its constituents for medicinal use in United States and many other countries in the 1930s and 1940s. It took decades until cannabinoids came to be considered again as compounds of therapeutic value, and even now their uses are highly restricted. Here we present an overview of the addictive and side effects of cannabinoids vs their therapeutic potential.

Addiction to cannabis, and the influence of cannabis on addiction to other substances

Marijuana may produce mild dependence in humans.[8-12] This was shown to depend on the personality type of the addicts,[13] and can be successfully reversed by abstinence or treated by cognitive-behavioral therapy,[14] without the occurrence of major withdrawal symptoms. Cannabinoids act on brain reward processes and reward-related behaviors by a mechanism similar to that found with other addictive drugs. In animal models they enhance electrical brain-stimulation reward in the core meso-accumbens reward circuitry of the brain and neural firing of a core dopamine (DA) component and thus elevate DA tone in the reward-relevant meso-accumbens DA circuit. In some animal models they produce conditioned place preference (CPP) and self-administration.[15,16] Other studies, however, find THC to be a poor reinforcer, with no or little self-administration.[17]

The abuse of other substances is influenced by the cannabinoids. The cannabinoid system is involved in alcohol-consumption behavior. Cannabinoid CB1 receptor agonists have been found to specifically stimulate alcohol intake and its motivational properties in rats.[18] The high ethanol preference of young mice is reduced by the cannabinoid receptor 1 (CB1) antagonist SR141716A (rimonabant) to levels observed in their CB1 knockout littermates.[19] Dopamine release induced by ethanol in brain was reduced by SR141716A,[20] which can explain in part the antiaddictive effect of the drug. Cocaine is another substance of abuse in whose acquisition and consolidation cannabinoids may be involved. High prevalence of alcohol dependence and cannabis dependence can be found in patients with cocaine dependence.[21] Marijuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers.[22,23] Furthermore, a recent genetic study found an association between an n triplet repeat polymorphism in the CB1 encoding *CNR1* gene with cocaine addiction in the African-Caribbean population.[24] In another study it was found that withdrawal from repeated access or exposure to cocaine and then a reinstatement of cocaine-seeking behavior or a sensitized locomotor response to a single cocaine challenge, respectively, was potently reduced by pretreatment with rimonabant.[25] Similarly, acute administration of rimonabant blocked expression of nicotine-induced conditioned place preference.[26] Rimonabant also reduces nicotine self-administration, and may be effective not only as an aid for smoking cessation, but also in the maintenance of abstinence.[27] As the endocannabinoid system plays a role in nicotine addiction,[28] the potential of cannabinoid antagonists to treat it is self-evident.[29-31] Opiate and CB1 receptors are coexpressed in the nucleus accumbens and dorsal striatum, and the interaction between the two systems is well known.[32] The reinforcing properties of morphine and the severity of the withdrawal syndrome are strongly reduced in CB1-knockout mice[33]; this observation opens an opportunity to treat opiate addiction with rimonabant, as noted with alcohol, cocaine, and nicotine addiction.[34,35]

Negative effects of cannabis other than addiction

There are some negative effects of cannabis use other than addiction, most of them related to alterations of attentional and cognitive functions or other neuropsychological and behavioral effects. Most of them are noted as a result of early-onset cannabis use (during adolescence).[36] Electrophysiological measures have revealed long-term deficits in attention among cannabis users.[37] In another study, impairment both in cognitive function and mood following cannabis use was noted.[38] However, in another study, cannabis users and controls performed equally well in a working memory task and a selective attention task. Furthermore, cannabis users did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions.[39] Prenatal exposure to cannabis is associated with only minor impaired cognitive and attentional effects.[40-42] Cannabis use in adolescence increases the risk of schizophrenia-like psychoses.[43] Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.[44] Also, evidence exists that cannabis use may trigger acute schizophrenic psychosis.[45,46] Cannabis was found to produce a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses.[46] Amotivational syndrome is a chronic psychiatric disorder characterized by a variety of changes in personality, emotions, and cognitive functions such as lack of activity, inward-turning, apathy, incoherence, blunted affect, inability to concentrate, and memory disturbance. The syndrome was first described in the 1960s among patients with a history of longtime cannabis use.[47] A useful animal model for this disorder was found in rat, where the cannabis-caused catalepsy-like immobilization is related to a decrease in catecholaminergic and serotonergic neurons in the nucleus accumbens and amygdaloid nucleus, and thus can serve as a model for amotivational syndrome.[48] In another study, heavy cannabis use was found to cause an amotivational syndrome in adolescents.[49] The treatment of cannabis use disorders has recently been reviewed.[12] However, the occurrence of amotivational syndrome as a result of cannabis exposure remains controversial.[50] The data from other studies do not support the hypothesis that marijuana impairs motivation.[51,52] Although most of the cannabis-related negative effects relate to its neuropsychologic and behavioral effects, other negative reactions to cannabis are sometimes found. For example, cannabis can cause acute pancreatitis, although the exact mechanism remains unknown.[53]

Therapeutic uses of cannabinoids

Obesity, anorexia, emesis

Cannabis has been known for centuries to increase appetite and food consumption.[54] More recently this propensity of the drug was substantiated when the CB1 receptor was shown to have a role in central appetite control, peripheral metabolism, and body weight regulation.[55] Genetic variants at CB1 coding gene *CNR1* are associated with obesity-related phenotypes in men.[56] In animals, CB1 receptor antagonism decreases motivation for palatable foods. Rimonabant administration caused suppression of the intake of a chocolate-flavored beverage over a 21-day treatment period, without any apparent development of tolerance.[57] CB1 receptors were found to be preferentially involved in the reinforcing effects of sweet, as compared to a pure fat, reinforcer.[58] Rimonabant selectively reduces sweet rather than regular food intake in primates,[59] which suggests that rimonabant is more active on the hedonic rather than nutritive properties of diets.

Rimonabant leads to significant weight loss in obese human subjects. Treatment with rimonabant was also associated with beneficial effects on different metabolic parameters and cardiovascular risk factors linked with overweight.[60,61] In clinical trials rimonabant was found to cause a significant mean weight loss, reduction in waist circumference, increase in HDL cholesterol, reduction in triglycerides, and increase in plasma adiponectin levels.[62] Patients who were switched from the rimonabant treatment to placebo after a 1-year treatment regained weight, while those who continued to receive rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors.[63,64] Rimonabant was shown to be safe and effective in treating the combined cardiovascular risk factors of smoking and obesity.[65] It also diminishes insulin resistance, and reduces the prevalence of metabolic syndrome. Many of the metabolic effects, including adiponectin increase, occur beyond weight loss, suggesting a direct peripheral effect of rimonabant.[66] Therapy with rimonabant is also associated with favorable changes in serum lipids and an improvement in

glycemic control in type 2 diabetes.[67] The activity of rimonabant in the management of obesity has been described in recent reviews.[31,68] It has been approved for the treatment of obesity in the European Union, and is sold under the trade name Acomplia. Surprisingly, the US Food and Drug Administration has declined to approve rimonabant, primarily due to its slight potential to enhance anxiety and suicidal thoughts. The atmosphere of consternation of possible legal action due to side effects may have led to this decision.

The other side of the same coin is anorexia. While in obese populations weight loss is the main goal, in other populations, such as patients with cancer or AIDS, it is an immense problem. Dronabinol (synthetic THC, known as Marinol and approved for the treatment of nausea and vomiting in cancer and AIDS patients) is associated with consistent improvement in appetite.[69] It was found to be safe and effective for anorexia associated with weight loss in patients with AIDS, and is associated with increased appetite, improvement in mood, and decreased nausea. In clinical trials, weight was stable in dronabinol patients, while placebo recipients lost weight.[70,71] Dronabinol was found to be safe and effective for treatment of HIV wasting syndrome,[72] as well as in patients with Alzheimer's disease[73] and with advanced cancer,[73,74] The possible mechanisms of these actions have been reviewed.[75] Cannabinoids have a positive effect in controlling chemotherapy-related sickness.[76] They are more effective antiemetics than the dopamine receptor antagonists such as chlorpromazine-type drugs.[77] Direct comparisons with serotonin (5-HT)3 antagonists, which are widely used as antiemetics, have not been reported. However, while these antagonists are not effective in delayed vomiting, THC is known to reduce this side effect of chemotherapy.

Pain

Cannabis has been used for millennia as a pain-relieving substance. Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they were proposed to be a promising therapeutic approach for the clinical management of trigeminal neuralgia.[78] THC, CBD, and CBD-dimethyl heptyl (DMH) were found to block the release of serotonin from platelets induced by plasma obtained from the patients during migraine attack.[79] However, in other reports cannabinoids are much less successful in pain-relieving. In a clinical trial THC did not have any significant effect on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain.[80] Similarly, in an additional clinical trial, no evidence was found[81]of analgesic effect of orally administered THC in postoperative pain in humans. Other studies show much better results of pain relief. When THC was given to a patient with familial Mediterranean fever, with chronic relapsing pain and gastrointestinal inflammation, a highly significant reduction in pain was noted.[82] Mild improvement was noted with cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion.[83] In neuropathic pain patients, median spontaneous pain intensity was significantly lower on THC treatment than on placebo treatment, and median pain relief score (numerical rating scale) was higher.[84] It was also effective in treating central pain.[85] The administration of single oral doses of THC to patients with cancer pain demonstrated a mild analgesic effect.[86,87] Patients who suffer from pain also tend to self-medicate with marijuana. In an anonymous cross-sectional survey, 72 (35%) of chronic non-cancer pain patients reported having used cannabis for relieving pain.[88] Cannabis-treated AIDS patients reported improved appetite, muscle pain, nausea, anxiety, nerve pain, depression, and paresthesia.[89] Not only THC, but also other cannabinoids can potentially affect different types of pain. Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy.[90] In Canada, the United States, and the United Kingdom, nabilone is marketed as Cesamet. A significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found with nabilone.[91] Another cannabinoid, ajulemic acid (AJA), was effective in reducing chronic neuropathic pain,[92] although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted. Cannabimimetic effects with ajulemic acid in rodents have also been recorded.[93]

The combination of THC with the nonpsychotropic cannabis constituent CBD has a higher activity than THC alone.[94] The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS).[95] Chronic neuropatic pain can also

be treated with cannabis extracts containing THC, or CBD, or with Sativex.[96,97] The latter also was effective in reducing sleep disturbances in these patients and was mostly well tolerated.[97] Sativex is the first cannabis-based medicine to undergo conventional clinical development and be approved as a prescription drug. It is efficacious and well tolerated in the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain.[98] Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada [for reviews on Sativex and on pain see refs 94, 99, and 100].

Multiple sclerosis, neuroprotection, inflammation

Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease. In clinical trials, it has been shown that cannabis derivatives are active on the pain related to MS,[84,85,95,97,98] However, this is not the only positive effect of cannabinoids in this disease. In rat experimental autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexanabinol (HU-211 a non-psychoactive synthetic cannabinoid).[101] In another trial in rats, all animals treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%.[102] WIN-55,212-2, another synthetic cannabinoid, also was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2.[103] Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210.[104] To more fully inderstand the involvement of the endocannabinoid system in MS, the status of cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase (FAAH) enzyme in brain tissue samples obtained from MS patients was investigated. Selective glial expression of cannabinoid CB1 and CB2 receptors and FAAH enzyme was found to be induced in MS.[105] In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.[106] Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s.[107] In an experiment in mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid receptors.[108] In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo.[109] In one case report nabilone improved muscle spasms, nocturia, and general well-being.[110] In another case report, the chronic motor handicaps of an MS patient acutely improved while he smoked a marijuana cigarette.[111] THC significantly reduced spasticity by clinical measurement. Responses varied, but benefit was seen in patients with tonic spasms.[112] At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility.[113] However, in other clinical trials, cannabinoids appeared to reduce tremor but were ineffective in spasticity.[114,115] Moreover, in one trial marijuana smoking further impaired posture and balance in patients with spastic MS.[116] The inconsistent effects noted might be due to dose-dependency. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia, were given oral THC.[117] In another study, cannabis extract did not produce a functionally significant improvement in MS-associated tremor.[118] Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil.[119] There are also findings suggestive of a clinical effect of cannabis on urge incontinence episodes in patients with MS.[120] In the treatment of MS, as well as in pain reduction described earlier, there is a preferential effect of a THC+CBD combination (Sativex).[121] A mixture of 2.5 mg THC and 0.9 mg cannabidiol (CBD) lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs.[122] Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo.[123] Long-term use of Sativex maintains its effect in those patients who perceive initial benefit.[124] Zajicek et al origi-

nally reported that cannabinoids did not have a beneficial effect on spasticity; however, there was an objective improvement in mobility and some patients reported an improvement in pain.[125] Later the same group also found positive effects on muscle spasticity with prolonged treatment.[126] The subject has been thoroughly reviewed.[99,127-130]
MS is not the only disease state where the neuroprotective potential of cannabinoids can be seen. In animal experiments, 2 weeks after the application of 6-hydroxydopamine, a significant depletion of dopamine contents and a reduction in tyrosine hydroxylase activity in the lesioned striatum were noted, and were accompanied by a reduction in tyrosine hydroxylase-messenger ribonucleic acid (mRNA) levels in the substantia nigra. Daily administration of THC over 2 weeks produced a significant irreversible waning in the magnitude of these changes, which may be relevant in the treatment of Parkinson's disease (see below).[131] The cannabinoids have a neuroprotective activity not only in vitro but also in vivo: HU-210, a potent synthetic analog of THC, increases survival of mouse cerebellar granule cells exposed to 6-hydroxydopamine.[131] In a model of experimental stroke, rimonabant reduced infarct volume by approximately 40%. Rimonabant exerted neuroprotection independently of its cannabinoid receptor-blocking effect.[132] In clinical trials, dexanabinol-treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure. A trend toward faster and better neurologic outcome was also observed.[133] However, in further experiments, dexanabinol was not found to be efficacious in the treatment of traumatic brain injury.[134] A wide range of cannabinoids has been shown to help in pathologies affecting the central nervous system (CNS) and other diseases that are accompanied by chronic inflammation.[130,135,136] In a rodent model of chronic brain inflammation produced by the infusion of lipopolysaccharide into the fourth ventricle of young rats, the cannabinoid agonist WIN-55212-2 reduced the number of LPS-activated microglia.[137] Direct suppression of CNS autoimmune inflammation was seen by activation of CB1 receptors on neurons and CB2 receptors on autoreactive T cells.[138]
Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and stroke in Western countries. Oral treatment with a low dose of THC inhibits atherosclerosis progression in an apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC may be a valuable target for treating atherosclerosis.[139] N-palmitoyl-ethanolamine is an endogenous endocannabinoid-like compound. Its concentrations are significantly increased in three different inflammatory and neuropathic conditions. The enhanced levels may possibly be related to a protective local anti-inflammatory and analgesic action.[140]
CBD has been shown to exert potent anti-inflammatory and antioxidant effects. High-glucose-induced mitochondrial superoxide generation, NF-kappaB activation, nitrotyrosine formation, iNOS and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs) were attenuated by CBD pretreatment.[141]
In experiments with obese vs lean rats, rimonabant was found to be a potent inhibitor of sensory hypersensitivity associated with CFA-induced arthritis in obese rats, in which the inflammatory reaction is more severe than in lean rats. It may thus have therapeutic potential in obesity-associated inflammatory diseases.[142]

Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder. The main pathological feature of PD is the degeneration of dopamine (DA)-containing neurons of the substantia nigra, which leads to severe DAergic denervation of the striatum. The irreversible loss of the DA-mediated control of striatal function leads to the typical motor symptoms observed in PD, ie, bradykinesia, tremor, and rigidity. It has been proposed that cannabinoids may have some beneficial effects in the treatment of PD.[129] In animal experiments cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro.[131]
The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic suggest that CB1 receptor antagonists could prove useful in the treatment of both parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have value in reducing levodopa-induced dyskinesia.[143] In the reserpine-treated rat model of PD, the dopamine D2 receptor agonist quinpirole caused a significant alleviation of the akinesia. This effect was significantly reduced by coinjec-

tion with the cannabinoid receptor agonist WIN 55,212-2. The simultaneous administration of the CB1 antagonist rimonabant with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia.[144] In animal experiments, chronic levodopa produced increasingly severe orolingual involuntary movements which were attenuated by WIN 55,212-2. This effect was also reversed by rimonabant.[145] In other studies, rimonabant was found to possess some beneficial effects on motor inhibition typical of PD, at least in some doses. The injection of 0.1 mg/kg of rimonabant partially attenuated the hypokinesia shown by PD animals with no effects in control rats, whereas higher doses (0.5-1.0 mg/kg) were not effective.[146] A nigrostriatal lesion by MPTP is associated with an increase in CB1 receptors in the basal ganglia in humans and nonhuman primates; this increase could be reversed by chronic levodopa therapy, which suggests that CB1 receptor blockade might be useful as an adjuvant for the treatment of parkinsonian motor symptoms.[147] High endogenous cannabinoid levels are found in the cerebrospinal fluid of untreated PD patients.[148] Administration of inhibitors of endocannabinoid degradation reduced parkinsonian motor deficits in vivo.[149] Thus, both agonists and antagonists of CB receptors seem to help in some parkinsonian symptoms. In clinical trials, the cannabinoid receptor agonist nabilone significantly reduced levodopa-induced dyskinesia in PD.[150] THC improved motor control in a patient with musician's dystonia.[151] In contrast to these findings, some studies find no effect of cannabinoids on PD: orally administered cannabis extract resulted in no objective or subjective improvement in either dyskinesias or parkinsonism,[152] no significant reduction in dystonia following treatment with nabilone,[153] and rimonabant could not improve parkinsonian motor disability.[154] However, an anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of the respondents had taken cannabis and 45.9% of these described some form of benefit.[155] Thus cannabinoids seem to be able to treat at least some symptoms of neurological diseases.[156-158]

Huntington's disease (HD) or Huntington's chorea ("chorea" meaning "dance" in Greek) is a disorder characterized by a distinctive choretic movement, progressive motor disturbances, dementia, and other cognitive deficits. Neuropathologically, HD is characterized by a degeneration of medium spiny striato-efferent γ-aminobutyric acid (GABA)ergic neurons and by an atrophy of the caudate nucleus. Advanced grades of HD showed an almost total loss of CB1 receptors and a further depletion of D1 receptors in the caudate nucleus, putamen, and globus pallidus internus, and an increase in $GABA_A$ receptor binding in the globus pallidus internus.[159,160] Loss of cannabinoid receptors is also seen in the substantia nigra in HD.[161] These findings suggest a possible therapeutic role of cannabinoid agonists in HD. Indeed, arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of HD generated by bilateral intrastriatal application of 3-nitropropionic acid (3-NP).[162] The reduction in the increased ambulation exhibited by 3NP-lesioned rats in the open-field test caused by AM404 (anandamide's transport inhibitor, which also binds to vanilloid receptor 1) was reversed when the animals had been pretreated with capsazepine (VR1 antagonist), but not with SR141716A, thus suggesting a major role of VR1 receptors in the antihyperkinetic effects of AM404. However, both capsaicin (VR1 agonist) and CP55,940 (an CB1 agonist) had antihyperkinetic activity.[163] Quinolinic acid (QA) is an excitotoxin which, when injected into the rat striatum, reproduces many features of HD by stimulating glutamate outflow. Perfusion with WIN 55,212-2 significantly and dose-dependently prevented the increase in extracellular glutamate induced by QA. Thus, the stimulation of CB1 receptors might lead to neuroprotective effects against excitotoxic striatal toxicity.[164] In a clinical trial CBD was neither symptomatically effective nor toxic in neuroleptic-free HD patients.[165]

Tourette syndrome (TS) is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Anecdotal reports have suggested that the use of cannabis might improve tics and behavioral problems in patients with TS. Indeed, THC reduced tics in TS patients,[166] without causing acute and/or long-term cognitive deficits.[167] In another clinical trial, where tic severity was assessed using a self-rating scale and examiner ratings, patients also rated the severity of associated behavioral disorders. There was a significant improvement of motor tics, vocal tics and obsessive-compulsive behavior after treatment with THC. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration, suggesting a possible role of this THC metabolite on the positive effect of THC.[168] In another, longer clinical trial, THC was also found to be effective and safe in the treatment of tics.[169] In view of the positive effect of CB1 agonists in the treatment of TS, CB1 gene mutations were investigated. However, TS was not found to be caused by mutations in the *CNR1* gene.[170]

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. Many effects of marijuana may be applicable to the management of ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, its strong antioxidative and neuroprotective effects may prolong neuronal cell survival.[171] Indeed, treatment of postsymptomatic, 90-day-old SOD1G93A mice (a model of ALS) with WIN 55,212-2, significantly delayed disease progression. Furthermore, genetic ablation of the FAAH enzyme, which results in raised levels of the endocannabinoid anandamide, prevented the appearance of disease signs in these mice. Surprisingly, elevation of cannabinoid levels with either WIN 55,212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in these mice, but significantly extended life span. Together these results show that cannabinoids have significant neuroprotective effects in this model of ALS, and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms.[172] THC was also found to delay the progression of disease.[173,174] Treatment with AM1241, a CB2-selective agonist, was effective at slowing signs of disease progression, when administered after onset of signs in an ALS mouse model. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls[175]; moreover, AM-1241 prolonged survival in these mice.[176] In a survey among ALS patients, cannabis was reported to be moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, and drooling.[177]
Cannabinoids were also proposed to have a role in the treatment of *Alzheimer's disease (AD)*. THC competitively inhibits acetylcholinesterase (AChE) and prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of AD.[178] THC treatment also decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC.[179] Compared with baseline, THC led to a reduction in nocturnal motor activity. These findings were corroborated by improvements in the Neuropsychiatric Inventory total score, as well as in subscores for agitation, aberrant motor, and nighttime behaviors; no side effects were observed.[180]
Studies on *cannabinoid anticonvulsant activity* began in 1975, when CBD, and four CBD derivatives, (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-tri-acetate and 9-hydroxy-CBD-triacetate) were shown to protect against maximal electroshock convulsions in mice, to potentiate pentobarbital sleeping-time and to reduce spontaneous motor activity.[181] Later additional CBD analogs were shown to be active.[182-184] CBD was found to be an effective anticonvulsant with specificity more comparable to drugs clinically effective in major, but not in minor seizures. Furthermore, it appears that CBD enhances the anticonvulsant effects of drugs in major seizures and reduces their effects in minor seizures.[185,186] Hence, CBD was suggested as a drug for the treatment of children with pharmacoresistant epilepsy.[187]
The application of the CB1 receptor antagonists SR141716A or AM251 to "epileptic" neurons caused the development of continuous epileptiform activity, resembling electrographic status epilepticus. The induction of status epilepticus-like activity by CB1 receptor antagonists was reversible and could be overcome by maximal concentrations of CB1 agonists.[188] Arachidonyl-2'-chloroethylamide (ACEA), a highly selective cannabinoid CB1 receptor agonist, enhances the anticonvulsant action of valproate in a mouse maximal electroshock-induced seizure model.[189] There are currently insufficient data to determine whether occasional or chronic marijuana use influences seizure frequency.[190] In one case report, marijuana smoking was proposed to induce seizures.[191] In another study, patients suffering from secondary generalized epilepsy with temporal focus treated with CBD remained almost free of convulsive crises throughout the experiment; other patients demonstrated partial improvement in their clinical condition.[192]

Bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), depression, anxiety, insomnia

Cannabis use is common in patients with *bipolar disorder*, and anecdotal reports suggest that some patients use marijuana to alleviate symptoms of both mania and depression.[193] In a case report, one female patient found that cannabis curbed her manic rages; others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects.[194]
The effect of cannabinoids on *schizophrenia* is controversial. Neuropsychological results in THC-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schiz-

ophrenic psychoses, as regards disturbances in internal regulation of perceptual processes.[195] In a recent study, it was found that anandamide levels are enhanced in first-episode schizophrenic patients, and that THC downregulates anandamide signaling.[196] This observation possibly means that THC lowers endogenous production of anandamide, which may actually be a defense mechanism—presumably comparable to the known observation that administration of corticosteroids blocks corticosteroid synthesis. Data from experimental-psychological tests show that personality changes generated by schizophrenia progression are comparable to psychopathological phenomenon due to cannabis intoxication.[197] In another study, psychosis, which develops or recurs in the context of cannabis use, did not have a characteristic psychopathology or mode of onset.[198] First-episode schizophrenic patients with long-term cannabis consumption were significantly younger at disease onset, mostly male, and suffered more often from paranoid schizophrenia (with a better prognosis) than those without cannabis consumption.[199] However, a trend towards more insight and of fewer abusive or accusatory hallucinations was seen amongst cannabis users. This argues against a distinct schizophrenia-like psychosis caused by cannabis.[200] Less avolition and fewer apathy symptoms were detected in patients with schizophrenia and cannabis abuse than in those with no abuse.[201] In another clinical trial, the role of CB1 receptors in schizophrenia was studied by administration of CB1 antagonist to patients. The group receiving the CB1 antagonist did not differ from the group receiving placebo on any outcome measure.[202]

CBD causes antipsychotic effects.[203] It was found to be a safe and well-tolerated alternative treatment for schizophrenia.[204] (See, however, also ref 205).

Post-traumatic stress disorder (PTSD) is a term for severe psychological consequences of exposure to, or confrontation with, stressful, highly traumatic events. Cannabinoids are believed to help in such cases. AM404-treated animals showed decreased shock-induced reinstatement of fear.[206] In conditioned fear and Morris water maze experiments, FAAH (-/-) mice and mice treated with the FAAH inhibitor OL-135 did not display any memory impairment or motor disruption, but did exhibit a significant increase in the rate of extinction. SR141716 blocked the effects of OL-135, suggesting that endogenous anandamide plays a facilitator role in extinction through a CB1 receptor mechanism of action. In contrast, THC failed to affect extinction rates, suggesting that FAAH is a more effective target facilitating extinction than a direct-acting CB1 receptor agonist.[207] Acutely, the absence of CB1 receptors reduces the neuroendocrine response and does not affect the behavioral response to moderate stress. However, upon repeated stress or acute severe stress, CB1 receptor deficiency causes persistent behavioral inhibition. Repeated bell stress seemed to cause a cumulative fear in CB1 receptor knockout mice.[208] In self-reports of substance use among help-seeking veterans, PTSD diagnosis was significantly associated with marijuana use.[209] These observations suggest that the endocannabinoid system can be modulated to enhance emotional learning, and that endocannabinoid modulators may be therapeutically useful as adjuncts for exposure-based psychotherapies, such as those used to treat PTSD and other anxiety disorders. CB1 receptor gene polymorphism is known to modify transcription of the gene. In patients with Parkinson's disease, the presence of two long alleles, with more than 16 repeated AAT trinucleotides in the CNR1 gene, was associated with a reduced prevalence of depression.[210]

CBD, and some derivatives, were found to cause a selective anxiolytic effect in the elevated plus-maze, within a limited range of doses.[211,212] A single dose of nabilone produced only mild improvement in anxiety[213]; in a repeated-dose treatment a dramatic improvement in anxiety was noted in the nabilone group.[214]

The effects of marijuana on human sleep patterns were noticed long ago.[215-217] Reduced eye movement density was seen, with some tolerance developing to this effect.[218,219] THC is sedative, while CBD has alerting properties as it increased awake activity and counteracted the residual sedative activity of THC.[220]

Asthma, cardiovascular disorders, glaucoma

Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus. In animal experiments, after methacholine-induced or exercise-induced bronchospasm, marijuana caused a prompt improvement of the bronchospasm and associated hyperinflation.[221] In humans, habitual smoking of marijuana may cause mild, but significant, functional lung impairment[222]; However, a mild and inconstant bronchodilatory action was found for THC.[223] In other clinical trials, smoking marijuana or ingesting THC were found to increase airway conduction.[224,225] Other plant cannabinoids did not provide

effective bronchodilation. The daily use of THC was not associated with clinical tolerance.[226] THC administered in metered volumes by inhalation from an aerosol device to patients judged to be in a steady state, increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) and produced bronchodilatation.[227] In another study, salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were not detected by radioimmunoassay. The mode of action of THC differed from that of sympathomimetic drugs.[228]

In another study, THC induced sympathetic stimulation and parasympathetic inhibition of *cardiovascular control pathways*. The peak heart rate rise after THC was attenuated by atropine and by propranolol, and nearly abolished by atropine-propranolol pretreatment.[229] Acute THC significantly increased heart rate, shortened pre-ejection period (PEP) and prolonged left ventricular ejection time (LVETc) without any change in afterload; it enhanced cardiac performance. Partial inhibition of this effect was achieved with prior β-adrenergic blockade.[230] In contrast, following the smoking of one to three marijuana cigarettes, the heart rate rose, cardiac output rose, stroke volume, ejection fraction, PEP and LVET did not change; thus, in long-term heavy users of cannabis, marijuana has no significant effect on myocardial contractility independent of its effect on heart rate.[231] Cardiovascular effects of acute THC administration included increased sympathetic and reduced parasympathetic tone; supine tachycardia and increased blood pressure with upright hypotension were observed. With repetitive dosing supine bradycardia and decreased blood pressure with tolerance to orthostatic hypotension were observed.[232,233] Rimonabant attenuated the hypotensive effect of smoked marijuana in male smokers, suggesting a role for the CB1 receptor in cannabinoid hypotensive action.[234]

A number of studies suggest that there is a correlative, but not necessarily causal, relationship between *glaucoma* and systemic hypertension. Ocular hypertension (OHT) refers to any situation in which intraocular pressure is higher than normal, and is the most important risk factor for glaucoma. THC, CBN, and nabilone were active in lowering intraocular pressure (IOP) in rabbits, while CBD was inactive.[235] Certain derivatives of THC were more active in lowering IOP than the parent cannabinoid[236]; some topically used soft analogs that have no systemic effects were also active in IOP reduction.[237] The effect on IOP of 2-AG was biphasic (ie, an initial increase in IOP followed by a reduction). In contrast, noladin ether decreased IOP immediately after topical administration, and no initial IOP increase was observed. AM251 blocked the effect on IOP of noladin ether, but did not affect the action of 2-AG.[238] Topical administration of anandamide and arachidonyl propionitrileamide decreased IOP; rimonabant antagonized the IOP reduction, suggesting that cannabinoids lower IOP through CB1 receptors.[239,240] Significantly, higher levels of CB1 mRNA levels were found in the ciliary body than in the iris, retina, and choroid. CB2 mRNA was undetectable. This expression pattern supports a specific role for the CB1 receptor in controlling IOP.[241] When delivered topically to cat eyes with osmotic minipumps, whole marijuana extract, THC and other plant cannabinoids reduced IOP, while cannabichromene was inactive. Ocular toxicity was seen after THC treatment, consisting of conjunctival erythema and chemosis as well as corneal opacification. Although these changes also occurred with marijuana extract, their intensity was much reduced. In contrast, no ocular toxicity was apparent during administration of plant cannabinoids other than THC.[242-244] Marijuana smoking was shown to reduce IOP as early as 1971; the effect was later confirmed.[245-248] The peak effect of THC on the central nervous system coincided well with the reduction in intraocular pressure induced by the drug; However, hypotonia outlasted euphoria. The results indicate that THC may have value as a hypotonizing ocular drug.[249] The functional responses after THC inhalation in sitting normotensive and hypertensive patients included invariable increases in heart rate followed by substantial decreases in systolic pressure, diastolic pressure, and intraocular pressure. The intensity and duration of the arterial and ocular pressure responses to THC were greater in hypertensives than in normotensive patients; the changes in ocular pressure paralleled the changes in blood pressure in glaucoma patients.[250] A single sublingual dose of THC, but not cannabidiol, reduced the IOP temporarily and was well tolerated by most patients.[251]

Cancer

The antiproliferative action of cannabinoids on cancer cells was first noticed in the 1970s. Since then cannabinoids were found to act on various cancer cell lines, through various mechanisms.[252,253] Cannabinoids were

also found to be suppressors of angiogenesis and tumor invasion.[254] Our knowledge on the anticancer activity of cannabinoids is rapidly expanding; hence only results of recent research on this topic are presented here. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner. Moreover, cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo.[255] The nonpsychoactive cannabidiol triggered caspase activation and oxidative stress in human glioma cells.[256] Human melanomas express CB1 and CB2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis, and metastasis, and increased apoptosis, of melanomas in mice.[257] THC, through activation of CB2 cannabinoid receptors, reduced human breast cancer cell proliferation by blocking the progression of the cell cycle and by inducing apoptosis. THC arrested cells in G2→M via downregulation of Cdc2.[258] Cannabinoids induced apoptosis of pancreatic tumor cells via stress protein p8 and endoplasmic reticulum stress-related genes. These effects were prevented by blockade of the CB2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo.[259] THC-induced apoptosis in Jurkat leukemia T cells was found to be regulated by translocation of Bad to mitochondria.[260] Exposure of leukemia cells to CBD led to CB2-mediated reduction in cell viability and induction in apoptosis (although CBD is considered not to bind to either CB1 or CB2 receptors). It is noteworthy that CBD exposure led to an increase in reactive oxygen species (ROS) production as well as an increase in the expression of the NAD(P)H oxidases Nox4 and p22(phox).[261] Cannabinoid-induced apoptosis of human prostate cancer cells LNCaP proceeded through sustained activation of ERK1/2 leading to G1 cell cycle arrest.[262] Rimonabant inhibited human breast cancer cell proliferation through a lipid raft-mediated mechanism.[263] In a pilot phase I trial, nine patients with recurrent glioblastoma multiforme, that had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumour progression, were administered THC intratumorally. THC inhibited tumor-cell proliferation in vitro, decreased tumor-cell Ki67 immunostaining and prolonged the survival time of two of the patients.[264]

Conclusion

Many drugs used today can cause addiction and are misused and abused, for example opiates,[265] cocaine,[266] benzodiazepines,[267] barbiturates,[268] cholinergic agonists,[269] ketamine,[270,271] dopaminergic agonists,[272] amphetamines,[273] and others. Nevertheless they are still an important part of our pharmacopeia. Marijuana was used for centuries as a medicinal plant, but during the last century, because of its abuse and addictive potential it was taken out of clinical practice. Now, we believe that its constituents and related compounds should be brought back to clinical use. The reasons are: (i) the therapeutic potential of CB1 agonists is huge, as described in this review; (ii) for local action, topical CB1 agonists, or agonists that do not penetrate the blood-brain barrier, can be used; (iii) cannabinoids acting specifically on CB2 receptors, which cause no psychoactivity, may be used on peripheral targets (such as osteoporosis,[274,275] which is only one of many examples); (iv) there are additional, new cannabinoid targets distinct from the CB1/CB2 receptors[276-278] which do not cause psychoactivity; (v) there are cannabinoids, such as CBD, which do not cause psychoactivity, but have various therapeutic effects.

The endocannabinoid system is a very complex one and regulates numerous processes, in parallel with other well-known systems, such as the adrenergic, cholinergic, and dopaminergic systems. Neglecting the potential clinical uses of such a system is, in our view, unacceptable; instead we need to work on more selective agonists/antagonists, more selective distribution patterns, and in cases where it is impossible to separate between the desired clinical action and the psychoactivity, to monitor these side effects carefully. ❑

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Clinical research

Cannabinoides en la salud y en la enfermedad

Las preparaciones de Cannabis sativa L. se han empleado en medicina desde hace milenios. Sin embargo, la preocupación acerca de los peligros del abuso condujo a la prohibición de la utilización médica de la marihuana en la mayoría de los países en la década de 1930. Sólo recientemente, los agonistas y antagonistas naturales y sintéticos de los receptores de marihuana, como también compuestos químicamente relacionados, cuyo mecanismo de acción todavía es confuso, han vuelto a reconsiderar el valor terapéutico. Pero su empleo está estrictamente limitado. A pesar de la adicción leve a cannabis y el posible incremento de la adicción a otras sustancias de abuso, cuando se combinan con cannabis, el valor terapéutico de los cannabinoides es muy alto como para no tomarlo en cuenta. Numerosas enfermedades como la anorexia, la emesis, el dolor, la inflamación, la esclerosis múltiple, trastornos neurodegenerativos (Enfermedad de Parkinson, Enfermedad de Huntington, Síndrome de Tourette , Enfermedad de Alzheimer), epilepsia, glaucoma, osteoporosis, esquizofrenia, trastornos cardiovasculares, cáncer, obesidad, y trastornos relacionados con el síndrome metabólico, por nombrar sólo algunas, están siendo tratadas o tienen el potencial de tratarse por agonistas o antagonistas de los cannabinoides o compuestos relacionados con ellos. Dada la muy baja toxicidad y los efectos secundarios generalmente benignos de este grupo de compuestos, desatender o negar su potencial clínico es inaceptable; hay que trabajar en el desarrollo de agonistas y antagonistas, y compuestos relacionados que sean más selectivos para el receptor de cannabinoides, como también de nuevos fármacos de esta familia con mejor selectividad, patrones de distribución y fármaco-cinética, y -en casos donde sea imposible separar la acción clínica deseada y la psicoactividad- igual monitorear estos efectos secundarios cuidadosamente.

Cannabinoïdes: effets chez le sujet sain et utilisation en thérapeutique

Depuis des millénaires, des préparations à base de Cannabis sativa L ont été utilisées en médecine. Dans les années 1930 cependant, des inquiétudes concernant le danger lié à l'abus de cette substance ont conduit à l'interdiction de l'utilisation médicale de la marijuana dans la plupart des pays. Ce n'est que depuis peu que la marijuana et les agonistes et antagonistes des récepteurs cannabinoïdes synthétiques et naturels, ainsi que les composés chimiquement apparentés dont le mécanisme d'action est encore obscur, sont à nouveau considérés comme ayant un intérêt thérapeutique. Leur usage est cependant très limité. Malgré la dépendance modérée au cannabis et la possible stimulation de la dépendance à d'autres drogues lorsqu'elles sont associées au cannabis, la valeur thérapeutique des cannabinoïdes est trop élevée pour être négligée. De nombreuses pathologies, telles que l'anorexie, les vomissements, la douleur, l'inflammation, la sclérose en plaques, les troubles neurodégénératifs (maladie de Parkinson, chorée de Huntington, syndrome de Gilles de la Tourette, maladie d'Alzheimer), l'épilepsie, le glaucome, l'ostéoporose, la schizophrénie, les troubles cardiovasculaires, le cancer, l'obésité et les troubles liés au syndrome métabolique, pour n'en nommer que quelques-unes, sont traitées ou pourraient être traitées par des agonistes/antagonistes des cannabinoïdes, ou substances apparentées. Au regard de la très faible toxicité et des effets secondaires généralement bénins de cette classe de produits, il serait inacceptable de négliger ou de nier leur potentiel clinique. Il faut au contraire travailler au développement de récepteurs agonistes/antagonistes des cannabinoïdes et de composés apparentés sélectifs, ainsi qu'à de nouveaux médicaments de cette famille plus sélectifs, avec un mode de distribution et une pharmacocinétique meilleurs. Et lorsqu'il est impossible de séparer l'action clinique désirée et les effets psychoactifs, il est simplement nécessaire de surveiller attentivement les effets indésirables.

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Review

Cannabinoids: New Promising Agents in the Treatment of Neurological Diseases

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Abstract: Nowadays, *Cannabis sativa* is considered the most extensively used narcotic. Nevertheless, this fame obscures its traditional employ in native medicine of South Africa, South America, Turkey, Egypt and in many regions of Asia as a therapeutic drug. In fact, the use of compounds containing *Cannabis* and their introduction in clinical practice is still controversial and strongly limited by unavoidable psychotropic effects. So, overcoming these adverse effects represents the main open question on the utilization of cannabinoids as new drugs for treatment of several pathologies. To date, therapeutic use of cannabinoid extracts is prescribed in patients with glaucoma, in the control of chemotherapy-related vomiting and nausea, for appetite stimulation in patients with anorexia-cachexia syndrome by HIV, and for the treatment of multiple sclerosis symptoms. Recently, researcher efforts are aimed to employ the therapeutic potentials of *Cannabis sativa* in the modulation of cannabinoid receptor activity within the central nervous system, particularly for the treatment of neurodegenerative diseases, as well as psychiatric and non-psychiatric disorders. This review evaluates the most recent available data on cannabinoids utilization in experimental and clinical studies, and highlights their beneficial effects in the prevention of the main neurological diseases and for the clinical treatment of symptoms with them correlated.

Keywords: *Cannabis sativa*; cannabinoids; cannabinoid receptors; neurodegenerative diseases; epilepsy

1. Introduction

Cannabis is probably one of the most ancient non-food crops cultivated by mankind; it belongs to the botanical family of *Cannabaceae*, along with *Humulus*, the cultivated hop. It is an annual, dioecious plant, though monoecious varieties have been bred, and its diploid chromosomic complement is $2n = 20$, with 18 autosomes and a couple of sexual chromosomes (XY for male and XX for female and monoecious plants [1].

The *Cannabis* species originated from Central Asia, where it was probably domesticated over 6000 years ago, but it has since been cultivated at virtually all latitudes for a large number of end-products deriving from the seed (e.g., fatty acids and proteins), the fiber, the wooden core and from the inflorescences, where cannabinoids are produced and secreted [2]. There still is limited agreement on whether *Cannabis sativa* should be considered a single species or a poly-species genus; however, the species boundaries, if existing, are weak, as full intercrossing between the different *Cannabis* accessions can occur, and several molecular markers-based analyses confirmed that *Cannabis* is a highly heterozygous species, with the intra-accession variation as wide as the inter-accession one [3].

In recent years, the debate on *Cannabis* re-introduction in our agricultural landscapes went beyond the agronomical and productive virtues of the plant, and especially focused on the potential of the plant's main metabolites, the cannabinoids, as medicines useful for a number of therapeutical applications [4].

In fact, medications based on *Cannabis* have been used for therapeutic purposes in many cultures for centuries [5], with descriptions of its effects including alterations in mood, cognitive functions, memory and perception of the user [6].

In Europe, they were used at the end of the 19th century to alleviate a wide variety of conditions, including pain, spasms, dysentery, depression, sleep disturbance and loss of appetite [7]. In the first half of the 20th century cannabinoid medications fell into almost complete disuse, partly because scientists were unable to establish the chemical structure of the ingredients of the *Cannabis* plant (*Cannabis sativa* L.).

It was only in 1964 that the psychoactive component of the *Cannabis* resin and flowers, Δ^9-tetrahydrocannabinol (Δ^9-THC) was isolated [8]. Following, numerous non-psychoactive cannabinoids have been identified, such as cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), Δ^9-tetrahydrocannabivarin (Δ^9-THCV) and cannabidivarin (CBDV). These compounds exert multiple actions through mechanisms that are only partially related to modulation of the endocannabinoid system.

In recent years, a growing interest has been dedicated to the study of cannabinoids for their antioxidant, anti-inflammatory and neuroprotective effects [9,10]. Specifically, Δ^9-THC is the most widely studied phytocannabinoid, but also the predominant psychotropic component of *Cannabis*, strongly limiting its therapeutic use as an isolated agent. Therefore, recently research focused to include non-psychotropic compounds, some of which exhibit potential as therapeutic agents in preclinical models of central nervous system (CNS) disease.

The present review focused on the current state of evidence regarding the possible usefulness of cannabinoid agents (psychotropic and non-psychotropic) in prevention of the main neurological disorders and/or in the treatment of symptoms correlated to them, at least in association with existing conventional therapy.

2. Current Cannabinoid-Based Drugs

Despite the illegality of *Cannabis* in most nations, a renewed interest in its medicinal properties has led to development of a number of cannabinoid-based medicines. Currently three drugs are used in clinical practice.

Dronabinol (Marinol®, Solvay Pharmaceuticals, Brussels, Belgium) capsules, a synthetic formulation of Δ^9-THC, was approved by the U.S. Food and Drug Administration in 1986, for the management of nausea and vomiting associated with cancer chemotherapy in patients who have not responded to conventional antiemetic treatments [11]. Dronabinol is also used for the treatment of anorexia with weight loss in patients with HIV/AIDS [12].

Nabilone (Cesamet®, Valeant Pharmaceuticals International Inc, Mississauga, ON, Canada) capsules, is another synthetic derivative of Δ^9-THC that is similar to dronabinol, but appears to be more potent. It was first approved in Canada in 1982 and is now also available in the United States and United Kingdom, still for the treatment of emesis [13].

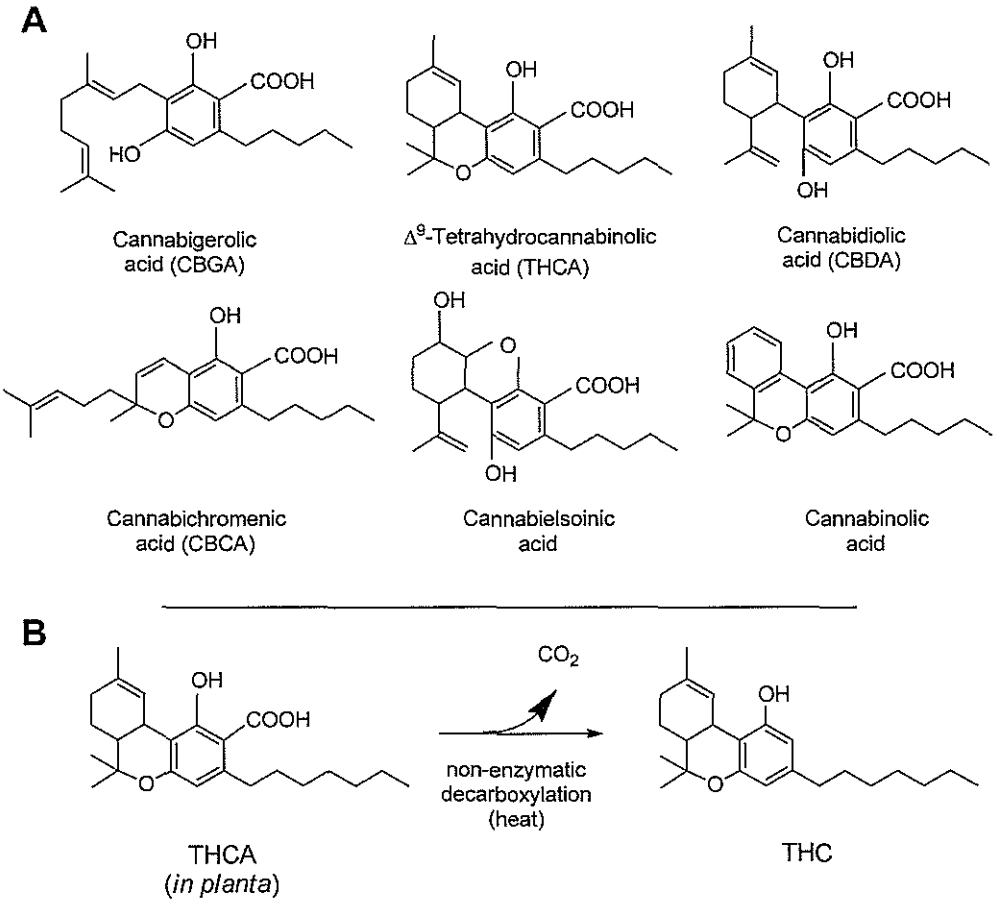
Unlike Dronabinol and Nabilone, Sativex® (GW Pharma, Ltd, Salisbury, Wiltshire, UK) is administered in an oral spray, consisting of a mixture of two extracts in approximately a 1:1 ratio (2.7 mg of Δ^9-THC and 2.5 mg of CBD) in an alcoholic solution (50% ethanol). In Spain, Germany, Denmark as well as in Canada, United Kingdom and Italy, Sativex® is used as treatment to alleviate spasticity in adult multiple sclerosis (MS) patients which did not show an appropriate response to other drugs during an initial trial period of therapy [14,15]. Compared to the oral route, its advantage is a faster plateau of plasma concentration. Also, it has been established that coadministration of CBD and Δ^9-THC can reduce unwanted effects of Δ^9-THC.

3. Synthesis and Production of Phytocannabinoids

Although *Cannabis* plant can be defined as a true "chemical factory" extremely rich in secondary compounds, therapeutic applications essentially rely on the cannabinoids. According to a recent review [16], there are almost 500 different chemical compounds synthesized by the *Cannabis* plant, and about 70 among these are cannabinoids. Cannabinoids are secondary compounds unique to the genus *Cannabis*, and therefore of taxonomic significance; they are terpenophenols, produced by the enzymatic condensation of a terpenic moiety (geranyl diphosphate) with a phenolic one (mainly olivetolic or divarinic acid).

There are two chemical characteristics of the cannabinoid molecule that are particularly relevant (Figure 1). The first is the carboxylic group on the phenolic ring of the cannabinoid; this group is readily lost upon drying or mild heating, leaving the decarboxylated form of the different cannabinoids. It is this decarboxylation that converts the native Δ^9-tetrahydrocannabinolic acid (THCA) into Δ^9-THC, the cannabinoid well known for its intoxicating and psychotropic effects. All cannabinoids in *Cannabis* plants are synthesized and accumulated in their acidic form [17].

Figure 1. (**A**) Structure of the most common cannabinoids found in *Cannabis* plants. All the compounds have been represented in their acidic, native form, and with a pentylic side chain; (**B**) the non-enzymatic decarboxylation of Δ^9-tetrahydrocannabinolic acid (THCA) to THC.



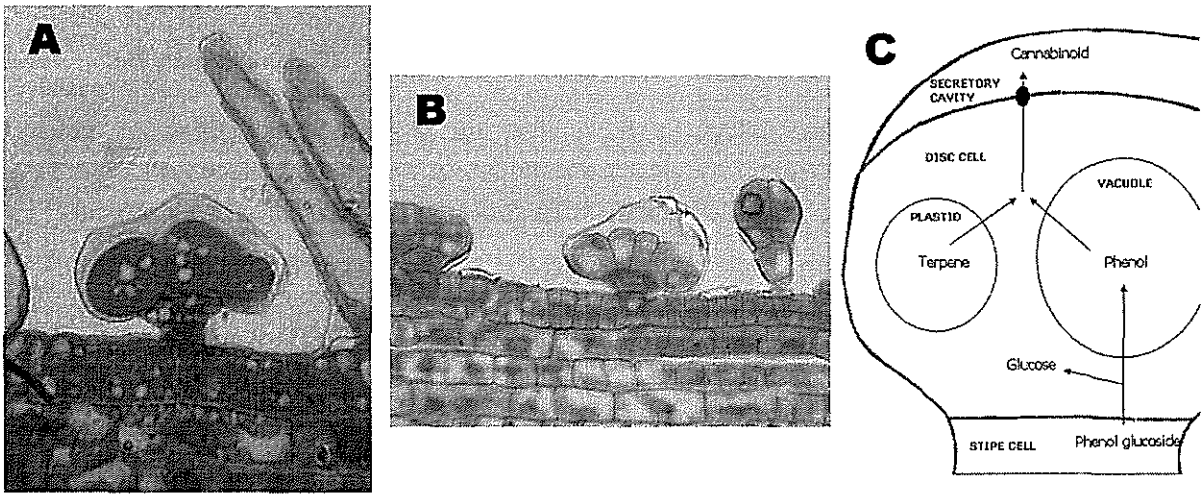
The second relevant characteristic of the cannabinoid molecule is the polyketide chain present in *meta* position to the hydroxylic group of phenolic portion (Figure 1). The most abundant cannabinoids in *Cannabis* have in this position a pentyl chain, but also propyl and even methyl side chain groups have been described [18,19].

Cannabis sativa accessions and varieties have been divided into chemotypes, according to the main cannabinoid they produce at maturity and to their content ratio. Five chemotypes can be recognized as most commonly occurring: chemotype I has a very low cannabidiolic acid (CBDA)/THCA content ratio, and is mainly the chemotype found in drug strains. Chemotype III, on the contrary, is characterized by a very high CBDA/THCA ratio, and is typical of all cultivated fiber varieties. Chemotype II is a mixed chemotype, containing roughly equal amounts of CBDA and THCA, as can be found in hashish strains, but also in some old fiber varieties. Chemotype IV accumulates cannabigerolic acid (CBGA) as the main cannabinoid. Finally, plants showing no cannabinoids upon gas-chromatographic analysis of mature inflorescences have been described, and for these plants the chemotype V has been proposed [20]. Clearly, plants belonging to the different chemotypes have different potentials as sources for the active principles they synthesize, and the breeding of *Cannabis* for pharmaceutical purposes had as its first

target the exploration and exploitation of the variability available in *Cannabis* germplasm for cannabinoid synthesis.

The sites of biosynthesis and accumulation of cannabinoids are the glandular trichomes (Figure 2A,B). Glandular trichomes are particularly dense in inflorescences, especially on the bracts, but also the leaves and, to a minor extent, the stems of *Cannabis* plants carry trichomes. Roots and seeds are devoid of any trichome, and, accordingly, these organs contain no cannabinoids. Glandular trichomes can be capitate-stalked, capitate-sessile, or bulbous, and these different morphologies are associated with a different quantity of cannabinoids accumulated [21].

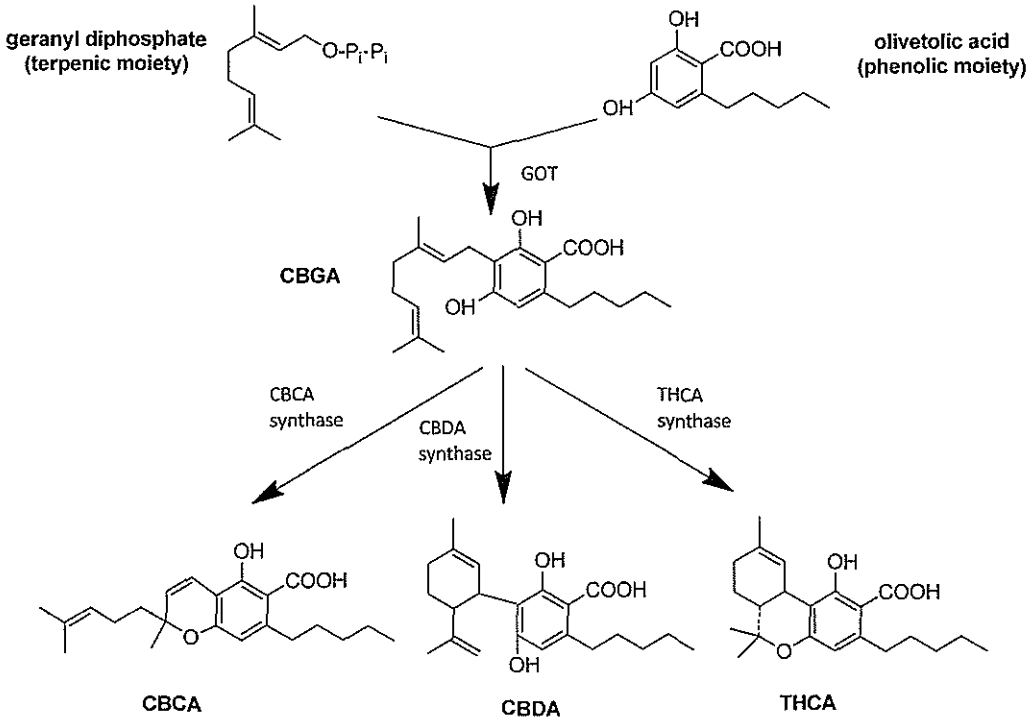
Figure 2. Capitate-sessile (**A**) and bulbous (**B**) glandular trichomes. In (**A**), also some non-glandular trichomes (not secerning) are visible. (**C**), schematic representation of the current model of secretion of cannabinoids from the trichomes.



The glandular trichomes density is a trait especially important when breeding *Cannabis* for pharmaceutical purposes. In nature, the meaning for the plant's fitness of the accumulation of cannabinoids in trichomes is still debated; it has been proposed that the conjugate bonds system characterizing THCA might have helped to protect plant functions from UV, a hypothesis partially supported by the origin of high-THCA *Cannabis* strains in regions with a high UV irradiance.

The first committed step in the biosynthesis of cannabinoids is the prenylation of terpene geranyl diphosphate with olivetolic acid (or, less frequently, divarinic acid), to yield the cannabinoid considered today to be the precursor of all other cannabinoids, the CBGA (Figure 3). This enzymatic step is catalyzed by the enzyme geranylpyrophosphate: olivetolate geranyltransferase (GOT). The length of the side chain (determined by the preferential use of olivetolic or divarinic acid as the phenolic component of the cannabinoid) is a genetically determined trait, though specific genes involved have not yet been identified [22]. From the pharmaceutical point of view, this "variations on the theme" due to the different length of the alkylic side chain has a great potential, as it is likely that each member of the alkyl-homologs series for each cannabinoid could be endowed with different and specific therapeutical properties [23].

Figure 3. The biosynthesis of the main cannabinoids.



CBGA is the precursor of the most abundant cannabinoids deriving from enzymatic transformation, *i.e.*, THCA, CBDA and cannabichromenic acid (CBCA). These three cannabinoids are synthesized through the oxidocyclization of CBGA mediated by three specific enzymes, THCA-synthase (THCAs), CBDA-synthase (CBDAs) and CBCA-synthase (CBCAs) (Figure 3). These enzymes have been isolated from inflorescences of different *Cannabis* strains or growth stages, and biochemically characterized in detail [24].

The hypothesis that the THCAs and CBDAs genes were alleles at the same locus, and that therefore the two proteins were isoenzymes, found confirmation by in-depth genetic analysis. The cross of pure-THCA breeding lines with pure-CBDA ones systematically yields F1 progenies producing equal amounts of both cannabinoids; besides, upon selfing or intercrossing of F1 plants, the F2 offspring obtained showed a perfect 1:2:1 segregation of pure-THC: mixed THC+CBD: pure CBD chemotypes [19], as expected for a single locus (termed *B*) with two codominant alleles, B_T and B_D, respectively, coding for THCAS and CBDAS. These data confirmed that, despite the several environmental factors able to modulate the total amount of cannabinoids, the chemotype (*i.e.*, the THCA/CBDA content ratio) has a simple Mendelian inheritance, while the amount of cannabinoids produced by the plant is a typically quantitative trait. The two aspects of inheritance of cannabinoids had a great impact on breeding of *Cannabis*, mainly for pharmaceutical purposes.

Nowadays, the increased availability of sequence data for several *Cannabis sativa* strains related to genes encoding for the biosynthesis of secondary compounds of therapeutic interest has led to the development of advanced tools for breeding and selection of therapeutic *Cannabis* varieties. For their use in modern pharmaceutical industry, these varieties are highly uniform, and devoted to the production of a specific single cannabinoid, or of a specific blend of different cannabinoids; even the zero-cannabinoid

varieties have been used in clinical tests as *placebo*. The completion of the sequencing of the *Cannabis* genome and the extensive characterization of the alleles encoding for different cannabinoid synthase variants, promises to further widen the portfolio of phytocannabinoids available for therapeutic applications; besides, the recent definition of the tertiary structure of THCAS by X-ray crystallography at the 2.75 Å resolution, with the identification of specific aminoacids crucial for enzyme function, pave the way for several biotechnological applications for synthesis of the cannabinoids *ex planta* [25].

4. Cannabinoid Receptors

In the human body there are specific binding sites for cannabinoids, distributed on the surface of many different cells. To date, two types of receptors have been identified to have different tissue distribution and mechanisms of signaling.

CB1 receptors, of which CB_{1A} and CB_{1B} represent two subtypes [26,27], are localized in the CNS [28]. Particularly, in the brain CB1 receptors are mainly expressed in areas involved in motor coordination and movement (cerebellum, basal ganglia and *substantia nigra*), attention and complex cognitive functions (cerebral cortex), learning, memory and emotions (amygdala and hippocampus) [29,30].In addition, CB1 receptors are present to a lesser extent in some organs and peripheral tissues, including endocrine glands, leukocytes, spleen, heart and part of the reproductive, urinary and gastrointestinal systems [31].

CB1 receptors reduce neuronal cell activity and interfere with the release of some neurotransmitters, such as serotonin, gamma-aminobutyric acid (GABA), acetylcholine, dopamine, histamine, glutamate and noradrenaline, preserving the CNS from overstimulation or over-inhibition that may be caused by other neurotransmitters.

CB2 receptors are expressed predominantly in cells of the immune system [31] and hematopoietic, but more recently their presence has been detected in the brain, in particular microglial cells, though at low concentrations [32]. It is well known that in response to damaging events, such as neuro-inflammation and cerebral hypoxia-ischemia, microglial cells may upregulate CB2 receptors expression in brain. Indeed, CB2 receptors exhibit potent anti-inflammatory effects modulating the release of cytokines [33,34].

Both CB1 and CB2 receptors belong to the family of G-protein coupled receptors (GPCRs) that, after cannabinoid agonist binding and signaling, exert an inhibitory effect on adenylate cyclase activity [35,36]. This inhibits the conversion to cyclic adenosine triphosphate (ATP) to cAMP, an important cellular secondary messenger involved in the mechanisms of signal transduction, which activates kinase protein A (PKA).

CB1 and CB2 receptors signaling leads to the downstream activation of all mitogen-activated protein kinase (MAPK), p44/42, p38 and c-JUN amino terminal kinase, which can regulate nuclear transcription factors. Also, their activation is strictly linked to ion channel regulation by inhibition of calcium channels and activation of potassium channels [37].

There is increasing evidence supporting the existence of additional cannabinoid receptors (no-CB1 and no-CB2) in both central and peripheral system, identified in CB1 and CB2- knockout mice [38,39]. Indeed, some actions of certain cannabinoid ligands seems that are mediated by other receptors like transient receptor potential vanilloid type 1 (TRPV1), G protein-coupled receptor 55 (GPR55), G protein-coupled receptor 18 (GPR18), G protein-coupled receptor 119 (GPR119) and 5-hydroxytryptamine receptor subtype 1A (5-HT1A).

TRPV1 is a non-selective cation channel for calcium, magnesium and sodium ions. It exhibits various activation and modulatory mechanisms, involving in the stimulation by GPCRs, noxious heat, low pH, and various endogenous cannabinoids such as anandamide (AEA), 12-hydroperoxy-eicosatetraenoic acid (12-HPETE) and N-arachidonoyl dopamine (NADA) [40]. Also, TRPV1 receptors play a role in transmission and modulation of nociception, as well as the integration of diverse painful stimuli [41]. They are found mainly in the nociceptive neurons of the peripheral nervous system, but they have also been described in CNS, specifically, in the hippocampus, cortex, and *substantia nigra* [42,43].

Orphan GPCRs, most notably GPR55, GPR18 and GPR119 have been proposed as potential novel cannabinoid receptors [44]. GPR55 is widely expressed in the brain, especially in the cerebellum. GPR55 can be characterized as a cannabinoid receptor, on the basis of sequence homology at the binding site, in fact the encoded integral membrane protein is a likely CB1 and CB2 cannabinoid receptors [45]. Also, it was demonstrated that GPR55 responds to a variety of both endogenous and exogenous cannabinoid ligands, such as Δ^9-THC, CP55940 (CB1 and CB2 agonist), AEA and virodhamine [46] as do the cannabinoid receptors. These features led to suggest GPR55 as a putative third cannabinoid receptor [46,47]. GPR55 may be involved in several physiological and pathological processes by activating a variety of signal transduction pathways [48]. Combining with an extracellular signal and transmitting the signal across the membrane by activating an associated G-protein, promotes the exchange of GDP for GTP on the alpha subunit of a heterotrimeric G-protein complex. Also its activation promotes activation of the small G proteins rhoA, cdc42 and rac1 and a transduction mediated by the ERK1 and ERK2 cascade [49,50].

Recently a fourth potential receptor GPR18 activated by N-arachidonoylglycine (NAGly), a metabolite of AEA, has also been described [51]. GPR18 is expressed in gastrointestinal, immune and testicular tissues, as well as the striatum, cerebellum and brain stem [52]. Also, GPR18 is found on microglial cells in the brain where it regulates the migration of these cells following CNS damage or inflammation [51].

GPR119 is another orphan receptor originally identified in genome-sequencing efforts and expressed predominantly in the pancreas and gastrointestinal tract [53]. The identification of GPR119 as a putative cannabinoid receptor comes from reports of activation of GPR119 by oleoylethanolamide, a monounsaturated analogue and functional antagonist of AEA [54], although controversy remains on its physiological role.

5-HT1A receptor is a subtype of serotonin receptor expressed both as a presynaptic autoreceptor on raphè neurons, and as a major postsynaptic receptor in several brain regions including cerebral cortex, amygdala and hippocampus involved in mood, memory, emotion and stress response [55]. Activation of both pre- and postsynaptic 5-HT1a receptors decreases neuronal excitability [56,57] Also, 5-HT1A is a GPCR that inhibits adenylate cyclase and activate receptor operated potassium channel, whereas inhibits voltage gated calcium channel [58].

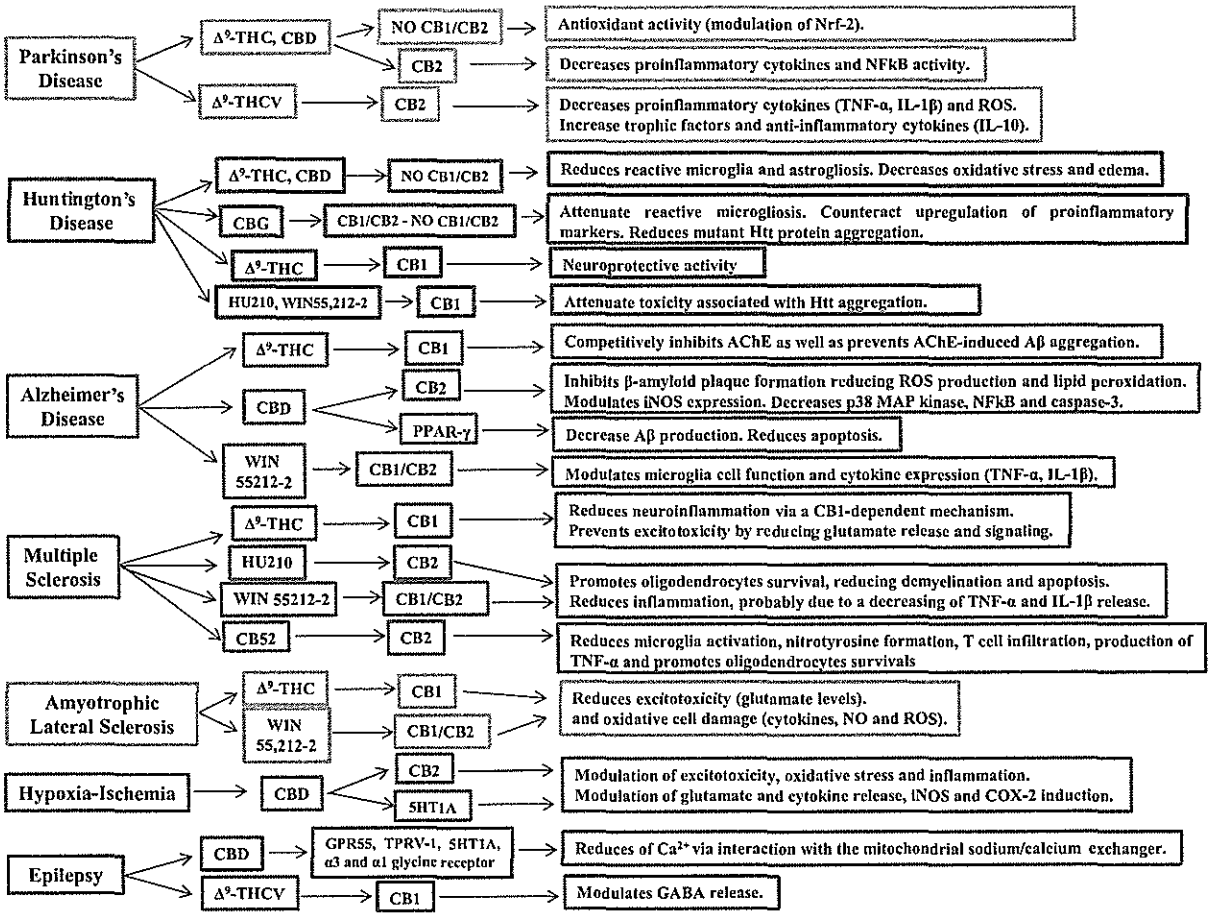
Particularly, it was demonstrated that CBD exerts many of its effects by binding 5-HT1A receptor. Activation of this receptor in key brain areas related to defensive responses, including the dorsal paeriaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex, leads to anxiolytic, antidepressant and antipsychotic effects showed by CBD [59].

Δ^9-THC, of which are well-known psychotropic effects, is believed to perform the majority of its actions in the CNS binding CB1 and CB2 receptors [60]. Non-psychotrophic phytocannabinoids (CBD,

CBG, CBC, Δ^9-THCV and CBDV), exert multiple pharmacological effects via CB1/CB2 receptors as well as no-CB1 and no-CB2 receptors [50] involving intracellular pathways that play a key role in neuronal physiology. These compounds, especially CBD, are able to suppress the production of a wide range of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL-)1β [61,62]. They show also a potent action in inhibiting oxidative and nitrosative stress, modulating the expression of inducibile nitric oxide synthase (iNOS) and reducing the production of reactive oxygen species (ROS) [63]. Moreover, non-psychotrophic phytocannabinoids attenuate high-glucose-induced mitochondrialsuperoxide generation and NF-κB activation, along with the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) [64]. Together, these activities suggest that these compounds can exert neuroprotective, antioxidant and anti-inflammatory effects.

Figure 4 summarizes the mechanisms of action and cannabinoid-induced cellular signaling in the neurological diseases investigated.

Figure 4. Cannabinoid-induced cellular signaling in neurologic disease.



Therapeutic properties of CB receptor agonists and antagonists have been proposed for the treatment of different human disorders by preclinical and clinical observations. Interactions at CB1 and/or CB2 sites appear to affect molecular mechanisms that are responsible for disease onset or progression.

5. Cannabinoids in the Treatment of Neurodegenerative Diseases

Neurodegenerative diseases are chronic and progressive disorders characterized by the gradual loss of neurons in discrete areas of the CNS. Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and cerebral ischemia are considered the disorders with the highest incidence in the population worldwide.

While the etiopathogenesis of these diseases is different, a number of common mechanisms underlying their progressive nature have been elucidated, such as neuro-inflammation, oxidative stress, excitotoxicity, protein misfolding and mitochondrial dysfunction.

Nowadays, for these diseases there is no cure, current therapies have focused on treatment of symptoms and try to delay their progression. It has been demonstrated that endocannabinoid signaling is alterated in many neurodegenerative diseases [65]. Therefore, it is believed that modulation of the endocannabinoid system could be a useful alternative in neurodegeneration treatment. Furthermore, preclinical research from animal models of neurodegeneration and clinical trials have suggested a potential role of cannabinoids in the attenuation of inflammation and the protection of neurons at risk of damage. Below we reported the most significant data regarding the current status of therapeutic effects of cannabinoids in neurodegenerative disease management.

5.1. Cannabinoids in Parkinson's Disease

PD is a chronic, progressive neurodegenerative disorder, characterized by the progressive degeneration of dopaminergic neurons in the *substantia nigra pars compacta* and consequent reduction in dopamine (DA) content in striatum [66]. The enzyme tyrosine hydroxylase (TH) present in all dopaminergic cells, catalyzes the formation of L-DOPA, the rate-limiting step in the biosynthesis of DA, thereby directly linking PD with TH [67]. Thus, a TH deficiency in the striatum is a hallmark of PD [68].

The death of nigral dopaminergic neurons leads to the typical motor symptoms observed in PD, bradykinesia, tremor, and rigidity.

Several experimental and clinical studies have demonstrated that endocannabinoid system undergo evident neurochemical and neurophysiological alterations after dopamine depletion [69–72]. In fact, as consequence of reduction in dopaminergic signaling, endocannabinoids levels as well as CB1 receptor expression result to be up-regulated in basal ganglia [73,74], suggesting that cannabinoids could have a therapeutic role in the treatment of movement disorders associated with PD.

To better understand what is the cannabinoid mechanism of action in PD and their antiglutamatergic effects, it is vital to explain the network of synapses involved in the genesis and in the control of voluntary and involuntary movements. For this purpose, it will be beneficial to summarize and comment on mechanism prospects outlined by many authors [75–77].

At level of basal ganglia, when the prefrontal sensorial cortex receives a stimulus to perform a movement, sensitive cortical neurons send glutamatergic excitatory signals to striatum nucleus (putamen) that, via GABAergic neurons, inhibits the activity of internal globus pallidus. This is known as the direct pathway of movement control. So doing, the GABAergic inhibitory signal of globus pallidus, that normally controls the activity of thalamic nucleus, is lost and thalamus can send an excitatory glutamatergic signal to motor cortex that perform the movement.

There is also an indirect pathway triggered from putamen: GABAergic neurons project to external globus pallidus that is inhibited to send, in turn, its GABAergic inhibitory signal to subthalamic nucleus. Subthalamic nucleus can now activate three pathway trough glutamatergic excitatory signals direct to: (1) *substantia nigra pars reticulate*; (2) internal segment of globus pallidus; (3) *substantia nigra pars compacta*. Among them, *substantia nigra pars compacta* is crucial to release dopamine neurotrasmitter activating striatum that stimulates the triggering of direct pathway via D1 receptors and, parallel, the inhibition of indirect pathway via D2 receptors. In PD, a depletion of dopamine in the striatum causes a cascade that lead to invert the normal balanced functioning of the basal ganglia circuitry. All this cascade of events lead to the blocking of the direct pathway and to the activation of the indirect pathway, so that we have bradykinesia as well as distorted muscle movements characteristic of PD patients.

Overall, the results is a disinhibition of the striatal neurons and therefore a relative glutamatergic overactivity, that antiglutamatergic therapies with cannabinoids counteract, mostly via CB1 receptor sited at level of presynaptic region of glutamatergic terminal [78].

More in detail, since the glutamatergic excitation is mediated by N-methyl-D-aspartate (NMDA) receptors of the neurons sited in the striatum and subthalamic nucleus, antagonists of NMDA receptors could reduce activity through the indirect pathway [77]. The result of cannabinoids action is translated in a reduction of glutamate release, decreasing calcium influx, as well as of local inflammatory events.

Current therapeutic strategies aim to increase dopaminergic transmission in basal ganglia by administration of dopamine precursors, such as L-DOPA [79], however, in a proportion of patients the efficacy of the treatment declines through time.

The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic propose that CB1 receptor antagonists could prove useful in the treatment of both Parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have a role in reducing levodopa-induced dyskinesia (LID) [69].

In reserpine rat model of PD, the dopamine D2 receptor agonist quinpirole led to a significant reduction of akinesia [80]. This effect was substantially reduced by coinjection with the cannabinoid CB1/CB2 receptor agonist WIN 55,212-2. The concomitant administration of the CB1 antagonist rimonabant (SR141716A) with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced reduction of akinesia [80]. This suggests that cannabinoid antagonists might be therapeutically advantageous together with dopamine agonists in reversing the endocannabinoid effects upon inhibitory motor function observed in PD.

In Lastres-Becker *et al.* [81] study, PD was induced in rats injected stereotaxically with a 6-hydroxydopamine (6-OHDA), and then administered for two weeks with Δ^9-THC and CBD.The authors found that both compounds were equally effective in protecting nigrostriatal dopaminergic neurons from the neurotoxin 6-OHDA. Also, it was shown that CBD can attenuate dopamine depletion and TH deficits, which are indicative of the degree of neurodegeneration of nigrostriatal dopaminergic projections [81]. These cannabinoids may function as neuroprotective agents in PD due to their capability to reduce oxidative stress. Δ^9-THC and CBD might restore the balance between the excessive production of ROS and a relative deficiency in antioxidant properties by acting as ROS scavengers as well as improving antioxidant enzymes through the activation of signaling triggered by nuclear factor-erythroid 2 (Nfr-2) [82].

Also, CBD showed anti-inflammatory properties, reducing the generation of pro-inflammatory cytokines, such as TNF-α and IL-1β, as well as ROS and anti-inflammatory cytokines like IL-10 [83].

Moreover, Δ^9-THCV has been shown to have neuroprotective effects, both in rats subjected to injection of 6-OHDA [84] as well as in mice injected with lipopolysaccharide (LPS) [84], possibly mediated through its antioxidant effects as well as through upregulation of CB2 receptors, and can therefore affect microglia activation. Also, in both models of PD, it was demonstrated that administration of Δ^9-THCV delayed disease progression, reducing motor inhibition, presumably through changes in glutamatergic transmission [84].

However, despite the encouraging data achieved on the potential therapeutic utility of cannabinoids in PD rodent models, studies with non human 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates have also produced conflicting results.

It was been demonstrated that the therapy with plant-derived cannabinoid agonists for attenuating hypokinetic signs was useless and did not alleviate motor deficits [85,86]. In MTPT-treated common marmosets, the blockade of CB1 receptors with SR141716A (rimonabant), a cannabinoid CB1 receptor antagonist, reduced LID without affecting the anti-Parkinsonism efficacy of L-DOPA [87]. Similarly, Meschler *et al.* [88] using cynomolgus monkeys (*Macaca fascicularis*), confirmed that SR141716A did not improve motor disability. Also in the same study it was demonstrated that cannabinoid agonist levonantradol produced a decrease in locomotor activity and an increase in bradykinesia in primates. Also, cannabinoid agonists did not induce catalepsy in primates, a property that differs from their effects in rodents [88].

Furthermore, as for the animal studies, drug trials in PD patients have produced conflicting results. In a randomized, double-blind, placebo-controlled study the cannabinoid receptor agonist significantly reduced LID in PD [89]. On the contrary, in a double-blind, cross-over study, *Cannabis* extracts, while well tolerated, did not show effects on LID [90].

5.2. Cannabinoids in Huntington's Disease

Huntington's disease (HD) is an autosomal-dominant inherited disorder characterized by striatal neurodegeneration. Literature reports that the cause of the disease is a mutation in the huntingtin (*HTT*) gene consisting of a CAG triplet repeat expansion translated into an abnormal polyglutamine (polyQ) tract in the amino-terminal portion of huntingtin (Htt) protein [91]. Htt aggregation and its accumulation are extremely toxic for striatal and cortical neuronal subpopulations [92–94]. The loss of motor inhibition that follows results in an evident abnormal and involuntary writhing, commonly defined as "choreiform" movements [95], associated with dementia [96] and cognitive impairment [97].

The brain region to which is ascribed the pathology is the corpus striatum that has the functional role to control both posture and gait via GABA neurons that project to globus pallidus and zona reticulata of the substantia nigra, controlling in turn subthalamic nucleus. So doing, it inhibits or gates inappropriate or uncontrolled movements [98,99].

About neuroprotective effects of cannabinoid compounds in experimental HD, three mechanism of neuroprotection have been hypothesized: CB1-dependent, CB2-dependent and CB1-/CB2-independent [96]. The first hypothesis is corroborated by the fact that CB1 receptor is early down-regulated in ongoing disease, even in asymptomatic phases, so that CB1 receptor loss could have a role in HD pathogenesis [96].

The second hypothesis born from the evidence given by CB2 receptor localization. It was observed that it is poorly expressed in striatal parenchima under healthy condition while it is progressively over-expressed during degenerative events leading to HD. In this circumstance, CB2-activation preserve striatal neurons from inflammatory insults produced by reactive microglial cells, maybe through the release of neurotrophins, anti-inflammatory cytokines and metabolic substrates [100,101].

Finally, the CB1-/CB2-independent pathway, involved in the neuroprotection during experimental models of HD seems related to some cannabinoids with antioxidant properties, such as Δ^9-THC and CBD, since their particular phenolic structures could exert a scavenger action against ROS. Parallel, there is also the assumption of an intracellular signal regulation via the expression control of antioxidant enzymes of phase II (*i.e.*, Nrf-2/ARE signaling) [96]. On this framework, there are conflicting data and the literature about it is very wide.

From a research on MEDLINE about "Huntington's disease and cannabinoids" we got 61 results, extended to 103 when the search was related to "Huntington's disease and cannabinoid receptor".

Among them, noteworthy was a recent preclinical study published on PNAS on January 2014 performed on R6/2 mouse [102]. It is the most commonly used model of HD. R6/2 mouse expresses exon 1 of the human huntingtin gene with around 150 CAG repeats. It also exhibits a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures [103].

The paper reports that a restricted population of CB1 receptors, and more precisely those located on glutamatergic terminals, play a crucial role in the neuroprotective activity of Δ^9-THC and, more in general, of (endo)cannabinoids, so that the authors look at these receptors as a promising target for neuroprotective strategies of therapy during HD [102].

Also, Valdeolivas *et al.*, last September published in Neurotherapeutics, the neuroprotective effects of CBG treatment in two *in vivo* models of HD, such as R6/2 mutant mouse and 3-nitropropionate (3-NP) acid-lesioned mice [104].

Authors ascribe CBG effects both to cannabinoid receptor-dependent and/or independent mechanisms. So, in the toxic model of HD authors show the neuroprotective CBG capability to attenuate the reactive microgliosis and to counteract the upregulation of pro-inflammatory markers, while in genetic model of HD they describe a recovery in the deteriorated rotarod performance typical of R6/2 mice, an expression partially normalized by CBG treatment of genes linked to HD, as well as an up-regulation of BDNF, IGF-1 and PPARγ genes. Finally, CBG-treated animals showed a reduction in the aggregation of mutant Htt protein in striatal parenchyma.

Moreover, a MEDLINE research performed on "Huntington's disease and preclinical study and cannabinoids" gave just two results: "Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease" published in Journal of Neuroscience Research in September 2011 [105] and the other one entitled "Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington's disease: role of CB1 and CB2 receptors" published on ACS Chemical Neuroscience in May 2012 [106].

The first study tests a 1:1 botanical combination of extracts enriched in either Δ^9-THC or CBD (the main constituents of the cannabis-based drug Sativex®) on rats stereotaxically subjected to unilateral injection into left striatum of the complex II inhibitor malonate, inducing HD through: (1) increasing the volume of edema; (2) reducing the number of Nissl-stained cells and enhancing the number of

degenerating cells (3) causing reactive microglia and astrogliosis (4) increasing oxidative stress. According to these authors, the reversion of these effects would be mediated by a CB1 and CB2 receptor-independent mechanism provided by both cannabinoids [106].

Differently by other studies, but in accordance with evidences also reported by Fernández-Ruiz *et al.* [107], the above-reported study ascribes a balanced role to CB1/CB2 receptors with a likely involvement in drug treatment showing an up-regulation of CB2 followed by a down-regulation of CB1 receptors, suggesting that CB2 receptors could play a particularly important role in the protective effect of Sativex®.

Furthermore, about synthetic cannabinoids HU210 and WIN 55,212-2, they seems to work in transgenic R6/1 mice, expressing exon 1 of the human HD gene carrying a 115 CAG repeat, through a mechanism mediated by G-protein alpha subtype i/o (G(i/o))-linked and ERK-dependent signal transduction [108]. This promotes the coupling of CB1 receptors to Gi/o and attenuate toxicity associated with Htt aggregation [108].

Despite the encouraging results obtained by the experimental investigations about the potential therapeutic use of cannabinoids in HD symptoms management, clinical trials have not confirmed these results. Particularly, studies performed using cannabinoids have not shown expected improvement in the hyperkinetic symptoms of HD. Consroe *et al.* [109] published one of the first clinical trials in which CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with HD. Authors demonstrated that CBD, was neither symptomatically effective nor toxic in these patients. Also, in literature, are reported two uncontrolled, single patient studies evaluating efficacy of nabilone, but these studies yielded conflicting results for reducing chorea severity [110,111]. Thus, although nabilone induced signs of improvement in one of these studies, in the other study [110] it made symptoms worse [111]. Nabilone was also used in a double-blind, placebo controlled, cross-over study in which it induced improvements in motor and cognitive indices [112].

The data obtained recently in animal models led to suggest that the combination of different cannabinoids, such as Sativex® may be an interesting tool for developing novel therapies in HD although to date there have been no results.

5.3. Cannabinoids in Alzheimer's Disease

AD is the most frequently form of dementia, with an incidence of about 34 million people worldwide [113]. AD is characterized by lesions in CNS due to the formation of beta-amyloid (Aβ) plaques, neurofibrillary tangles and cortical atrophy [114,115].

It has been demonstrated that in microglia of AD patients, CB1 and CB2 receptor expression is significantly increased, while in basal ganglia and hippocampus neuronal CB1 receptor expression is decreased [116]. Therefore, endocannabinoid system might play an important role in AD pathogenesis.

To date, the majority of drugs in use for AD treatment are acetylcholine esterase (AChE) inhibitors. According to Eubanks and colleagues [117], Δ^9-THC competitively inhibits enzyme AChE and prevents Aβ peptide aggregation in the brains of Alzheimer patients.

In rat pheocromocytoma PC12 cells and *in vivo* models, it was shown that CBD also inhibits β-amyloid plaques formation, reducing ROS production and lipid peroxidation [118].

Also, using mice inoculated with human Aβ (1–42) peptide into the right dorsal hippocampus, Esposito *et al.* [119] have demonstrated anti-inflammatory and antioxidant actions of CBD. Indeed, CBD is able to attenuate a β-amyloid plaques formation modulating iNOS expression and also decreasing p38MAP kinase and NF-κB levels. Thus, limiting propagation of neuro-inflammation and oxidative stress.

In addition, Martin-Moreno and colleagues [120] have showed that in Aβ-mice, CBD and synthetic cannabinoid WIN 55,212-2 are able to modulate microglial cell function and cytokine expression, improving learning behavior.

Also, CBD appears able to exert a beneficial effect in the amyloidogenic pathway, through a specific molecular mechanism involving peroxisome proliferator-activated receptor-γ (PPARγ) [121]. Scuderi *et al.* [121] investigated CBD as a possible modulating compound of amyloid precursor protein (APP) in transfected human neuroblastoma SHSY5Y^{APP+} cells. Achieved results indicated the CBD capacity to induce the ubiquitination of APP protein, which led to a substantial decrease in APP full length protein levels in SHSY5Y^{APP+} with the consequent decrease in Aβ production. As consequence, CBD has promoted an increased survival of SHSY5Y^{APP+} cells reducing their apoptotic rate and increasing their survival in long-term period of cell culture. All CBD effects showed were dependent on the selective activation of PPARγ [121].

In a recent paper, Aso and co-workers [122] tested the therapeutic properties of combination of Δ^9-THC + CBD (0.75 mg/kg each) in a AβPP/PS1 transgenic mice, an experimental model of AD, which replicates the most relevant features of disease, including cognitive impairment and several pathological alterations, such as Aβ deposition, dystrophic neurites, synaptic failure, mitochondrial dysfunction, and oxidative stress damage. Authors demonstrated that mixture of the two compounds preserved memory and reduced learning impairment in AβPP/PS1 transgenic mice when chronically administered during the early symptomatic stage [122].

A significant decrease in soluble Aβ (1-42) peptide levels and a change in plaques composition were also observed in Δ^9-THC + CBD-treated AβPP/PS1 transgenic mice, due to a reduced microgliosis and expression of several cytokines and related molecules of neuro-inflammation [122]. In this study authors suggest that combination of Δ^9-THC + CBD exhibits a better beneficial effect than each *Cannabis* component alone and support the consideration of a *Cannabis*-based medicine as potential therapy in AD [122].

Currently, there are only limited data displaying clinical effects of phytocannabinoids on human AD. A single, open-label, non-placebo controlled study [123] performed with AD patients reported that Dronabinol derived from Δ^9-THC has a beneficial role in reducing anorexia and improving behavior, like nocturnal motor activity and agitation.

Despite these encouraging results, the usefulness of cannabinoid based medicines for the treatment of AD awaits the results of severe clinical trials. Also, to date there are no significant data reported in the literature on the use of phytocannabinoids in the treatment of vascular dementia.

5.4. Cannabinoids in Multiple Sclerosis

MS is an autoimmune inflammatory neurodegenerative disease characterized by nerves demyelination in CNS [124]. However its etiology is still unknown. Therefore, in order to better understand the etiopathogenesis of MS and to find new therapeutic strategies, researchers use some experimental

models. The most used is the experimental autoimmune encephalomyelitis (EAE), which mimics the main features of human MS.

Numerous studies have been performed to evaluate the role of cannabinoids on treatment of EAE-associated spasticity as well as on modulation of the neurodegenerative process.

According to a study performed using CB1-knockout mice, it was demonstrated that the mechanism of improvement spasticity was dependent on CB1 receptors, not CB2 [125]. Also, Δ^9-THC was reported to delay or prevent signs of spasticity in EAE mice, as well as increasing survival rates and reducing neuro-inflammation via a CB1-dependent mechanism [126].

Using synthetic cannabinoid agonists of CB1 and CB2 receptors, such as dexanabinol (HU210, (−)-1,1-dimethylheptyl analog of 11-hydroxy-Δ^8-THC) and WIN 55,212-2 in EAE mice, it was demonstrated that they promote oligodendrocytes survival via CB1 and CB2 receptor-mediated effects, potentially reducing demyelination and apoptosis [127,128]. Also, these cannabinoids were able to reduce inflammation, probably by suppression of TNF-α and IL-1β and enhances the release of anti-inflammatory cytokines such as IL-10 in brain and peripheral blood [129]. Same results were confirmed by Arevalo-Martin *et al.* [130], using Theiler's murine encephalomyelitis virus-induced demielinating disease (TMEV-IDD) model of chronic-progressive MS. Indeed, it was demonstrated that systemic treatment with synthetic cannabinoid CB1/CB2 receptor agonist WIN 55,212-2 in TMEV-IDD mice can limit axonal loss and neuro-inflammation in animal models of MS, by modulating microglia and lymphocytre infiltration in spinal cord [130].

Also, it was demonstrated that CB52, a newly developed cannabinoid compound (AEA and Δ^9-THC hybrid), is more effective than other commonly used cannabinoids and its protection on oligodendrocytes is mediated by the activation of the CB2 receptor [131].

Using EAE mice, Ribeiro *et al.* [131], proved that CB52 reduced microglia activation, nitrotyrosine formation, T cell infiltration, production of TNF-α, oligodendrocyte toxicity, myelin loss and axonal damage in the mouse spinal cord white matter and alleviates the clinical scores when given either before or after disease onset.

Moreover, significant alterations of the endocannabinoid system have been found in the brain of EAE and Chronic Relapsing Experimental Allergic Encephalomyelitis (CREAE) mice. Particularly, increased levels of AEA and 2-arachidonoyl glycerol (2-AG), were detected in areas associated with nerve damage in CREAE [4] and in EAE [132], when compared to non-spastic mice.

Also, reduced CB1 expression was showed during acute phases of CREAE [133] and CB2 transcription may be increased in EAE [33]. Administration of SR141716A and SR144528, CB1 and CB2 antagonists, has been shown to worsen tremor and spasticity in CREAE mice, whilst WIN 55,212-2, methanandamide and JWH-133 CB2 agonists reduced both tremor and spasticity in diseased mice [134,135]. In addition, spasticity could also be ameliorated by the inhibition of AEA reuptake and enzymatic hydrolysis, causing a subsequent increase in AEA concentration in the CNS [4].

As well-known endocannabinoids are to be released in response to a wide range of neuronal insults [136], and levels are increased in the CSF and peripheral lymphocytes of patients with MS [137]. Centonze *et al.* [137] indeed reported a relevant increase in AEA, but not 2-AG levels, in the CSF of relapsing-remitting MS patients experiencing current relapse with a strong correlation between AEA levels and the number of inflammatory lesions visible on imaging. AEA concentrations were also higher in peripheral lymphocytes of these patients; an effect associated with increased synthesis and reduced

degradation of this endocannabinoid [137]. Another study also showed elevated AEA levels in MS patients when compared with healthy controls, across the clinical spectrum, this time in the plasma, again suggesting that the peripheral endocannabiboid system ma reflect those occurring centrally [138].

Benefits from cannabinoids use seen in animal studies have also been shown in the treatment of MS patients suffering spasticity, with a significant associated disability and quality of life impairment. It is clear that spasticity results from alterations in the balance, possibly secondary to selective neuronal loss, between excitatory and inhibitory neural circuits. Under physiological conditions, inhibitory signals are sent *via* the corticospinal tract to the spinal cord, but following injury, damage to the corticospinal tract, causes disinhibition of the stretch reflex, leading to reduction in the triggering threshold. This leads to loss of control of neurotransmission between muscles and CNS, resulting in uncontrolled spastic movement [139].

Current therapies for spasticity include GABA receptor agonist, baclofen, tizanidine, benzodiazepine and anxioltyics [140]. Also, local administration of botulinum toxin have also shown efficacy in clinical trials [140]. The use of phytocannabinoids may be useful in MS patients, which show resistance to these conventional therapies, as shown in clinical studies reported in literature.

The Cannabinoids in MS (CAMS) study [141], a double-blind, randomized, placebo-controlled trial, was the first large-scale study designed to test the hypothesis that cannabinoids may have a beneficial effect on spasticity associated with MS. This study involved 630 MS patients treated with dronabinol (a synthetic Δ^9-THC), cannador (2.5 mg of Δ^9-THC, 1.25 mg of CBD, and 5% of elements other than cannabinoids per capsule) and placebo. It did not show any significant improvement in spasticity at 15 weeks [141], but this was evinced with both *Cannabis* compounds after one year of treatment [142]. Also, MS patients perceived a significant improvement in pain and sleep disorders [142]. Other studies performed with smaller numbers of patients and crossover studies [14] have confirmed the same results previously obtained.

Following CAMS study, comes the Cannabinoids Use in Progressive Inflammatory brain Disease (CUPID) study [143], another double-blind, randomized, placebo-controlled trial (duration of three years) in United Kingdom involving 493 patients with progressive MS. The full results from this study are pending, but initial data shows that dronabinol has no overall effect on MS progression, measured with the Expanded Disability Status Scale (EDSS) scale.

Analysis of a subgroup of patients in this study suggested a possible benefit from dronabinol in those who began the trial with milder disability, but not in those who began the trial with more severe disability [143].

A recent randomized, double-blind, placebo-controlled study involving 15 relapsing-remitting MS patients with MS-induced neurophatic pain was conducted to evaluate Nabilone combined with gabapentin. Results suggest that Nabilone as an adjunctive to gabapentin is an effective, well-tolerated combination for MS-induced neurophatic pain and thus can be used as a novel therapeutic combination in MS treatment [144].

In addition, use of Sativex® has been extensively investigated in the management of patients with MS [14,15]. Currently, this spray preparation is used as treatment to alleviate symptoms of spasticity and neurophatic pain in adult MS patients that did not show an appropriate response to other drugs during an initial trial period of therapy. It has also been reported that Sativex® shows efficacy in the treatment of bladder dysfunction, frequent in MS patients, showing a decrease of incontinence episodes and an

increase in bladder retention volume. According to another study [145], MS patients treated with *Cannabis* extract; Δ^9-THC, showed an important reduction in events of urge incontinence compared to placebo. Thus, suggesting that phytocannabinoids might compensate for the bladder neural circuitry disregulation that often accompanies disease progression in MS.

Spasticity, neuropathic pain and uncontrollable bladder and bowel are symptoms observed also in patients affected by spinal cord injury (SCI).

Therefore, use of cannabinoids and mixture of extracts could be useful in treatment of this pathology. Unfortunately, in the literature there are only a few studies that do not report interesting data.

5.5. Cannabinoids in Amyotrophic Lateral Sclerosis

ALS is the most prevalent form of motoneuron disease, characterized by degeneration and death of motor neuron populations in the cerebral cortex, brainstem and spinal cord [146]. Several mechanisms have been involved in ALS pathogenesis, such as neuro-inflammation, mostly mediated by excitotoxicity and oxidative damage on motor neurons [147,148].

There is rapidly emerging evidence that the cannabinoid receptor system has the potential to reduce both excitotoxic and oxidative cell damage.

Numerous studies reported in literature, have been conducted using ALS hSOD(G93A) transgenic mice, the strain predominantly used. Indeed, the disease in these animals closely mimics human ALS.

It was shown that mice treated with Δ^9-THC exhibited an improvement of motor impairment by administration of the molecule, either before or after signs onset, a prolonged survival by 5% [149]. According to Bilsland *et al.* [150], a significant delay was found in disease progression when CB1/CB2 receptor agonist WIN 55,212-2 was administered to ALS hSOD(G93A) mice beginning after onset of motor impairment and tremor (at 90 days old), however, survival was not extended.

Furthermore, using the same experimental model of ALS, it was demonstrated that CB1 deletion, had no effects on disease onset, but extend lifespan by 15 days, a 13% increase in survival [150].

Also, it is important determining CB2 receptor role, since microglia from ALS hSOD(G93A) mice seems to possess increased cytotoxic potential [151]. Indeed, CB2 activation blocks β-amyloid induced microglia activation [152]. On the contrary, with other stimuli, CB2 activation showed increasing microglial migration and proliferation.

Using selective CB2 agonist, AM1241, it was reported that ALS hSOD(G93A) mice showed slowing of disease progression if administered after disease onset [153]. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls. Also, in these mice an increase of 56% in survival interval was shown [153].

In a recent study, Moreno-Martet *et al.* [154] evaluated neuroprotective effects of Sativex® in SOD(G93A) transgenic mice. Sativex® has proven to be effective in delaying ALS progression in the early stages of disease and in animal survival, although the efficacy was decreased during progression of disease. Also, it has been demonstrated that changes occur in endocannabinoid signaling, particularly a marked up-regulation of CB2 receptors in SOD(G93A) transgenic mice. Thus, Sativex® may be used as an adjunctive therapy with only one medicine already approved, Rilutek®, which shows modest efficacy on disease progression.

To date, there have been few studies on human ALS. According to Yiangou *et al.* [155], in human ALS patients, spinal cord demonstrates motor neurons damages marked by CB2-positive microglia/macrophages. Moreover, a recent study analyzing activated microglia from spinal cord in human ALS patients demonstrated a CB2 increase. So all these data show how editing CB2-mediated processes could change ALS progression and how much the endocannabinoid system is potentially involved in reducing neuro-inflammation, excitotoxic, and oxidative cell damage [156].

Finally, in literature it has been reported in a single case study of patients with ALS, the 10% who admitted consuming *Cannabis*, have reported moderate relief of several symptoms, including appetite loss, depression, spasticity and drooling [157].

5.6. Cannabinoids in Cerebral Ischemia and Hypoxia

Ischemia is the result of a transient or permanent reduction in cerebral blood flow caused by occlusion of a cerebral artery via an embolus or local thrombosis, sufficient to alter cerebral functions. This causes a complex sequence of events, including mechanisms of excitotoxicity, release of neurotransmitters, breakdown of blood-brain barrier, inflammation, cytokines production, adhesion molecules upregulation, oxidative and nitrosative stress and programmed neuronal cell death [158–160].

Recently, cannabinoids have emerged as promising neuroprotective agents in several experimental model of brain damage. It seems that the endocannabinoid signaling system has various features for which appears to be involved in ischemic damage. Among these, endocannabinoids and related lipids accumulate in ischemic tissues and play a role in maintaining metabolic homeostasis and responsiveness of the brain to stress [161].

It was demonstrated that CBD can invert brain damage following cerebral ischemia in mice, decreasing brain edema and seizures associated with temporary occlusion of carotid arteries [162]. CBD was able to reduce cerebral hemodynamic impairment and ameliorate brain metabolic activity post-injury [162]. Also, it seems that CBD exerts a neuroprotective effect toward brain ischemia, causing an increase in cerebral blood flow mediated by 5-HT1A receptor and/or be secondary to its cannabinoid receptor-independent anti-inflammatory activity [163].

To date, few studies were carried out in patients with cerebral ischemia, because the limiting factor seems to be that only some compounds results are useful, and only if taken shortly before or within a few hours after cerebral damage. Clinical trials using dexabinol a synthetic Δ^9-THC, showed no efficacy in cerebral ischemia treatment [164].

Similarly, the same mechanisms involved in cerebral ischemia, were found in hypoxic-ischemic brain injury events. Frequently, this devastating condition is one of the most important causes of neonatal brain injury and also results in adverse developmental outcomes [165].

To date, there are few reports on the possible neuroprotective effect of cannabinoids in newborns and existing publications consider their beneficial effects against excitotoxicity. CBD demonstrated neuroprotective effects in the brain of newborn Wistar rats following hypoxia-ischemia, associated with the modulation of excitotoxicity, oxidative stress and inflammation [166]. Indeed, CBD modulates glutamate and cytokines release, as well as the induction of iNOS and type 2 cyclooxygenase (COX2) [167]. Also, using a hypoxic-ischemic brain injury model in newborn pigs, Pazos *et al.* [168] confirmed that CBD modulates these mechanisms acting on CB2 and 5HT1A receptors.

Moreover, CBD activity was tested in newborn piglets, subjected to temporary occlusion of both carotid arteries plus hypoxia [162]. CBD administration reduced short-term brain damage, in a manner that can be attributed to a CBD-induced reduction of cerebral hemodynamic impairment, improvement of brain metabolic activity post-insult, reduction of brain edema, and reduction of seizures. These neuroprotective effects were not only free from side effects but also associated with some cardiac, hemodynamic, and ventilatory benefits [162].

Therefore, CBD may be considered an important candidate for future clinical trials with hypoxic newborns.

6. Other Therapeutic Applications of Cannabinoids

The use of *Cannabis* has been shown in the treatment of many diseases through time. Among these, treatment of epilepsy seems to be one of the most ancient.

Epilepsy is a chronic neurological disease that affects 50 million people worldwide, characterized by recurrent seizures and often accompanied by cognitive deficits and mood disorders [169]. The targeting of neuronal ion channels and both GABA and glutamate receptors has been the primary approach to eliminate convulsions. Despite the availability of a wide range of antiepileptic drugs, about one-third of individuals with epilepsy still experience seizures that do not to respond to medications [170].

The biological reason to believe that cannabinoids could suppress epileptic seizures is the abundance of CB1 receptors in some areas of the brain (hippocampus and amygdala) where partial seizures originate [171].

Various cannabinoids have been show in several clinical studies to have significant anticonvulsive properties, especially CBD and more recently CBDV and Δ^9-THCV [172–174].

The antiepileptic mechanisms of CBD are not well known, since CBD has low affinity for CB1 and CB2 receptors [23], it seems that CBD may exert its effects through different mechanisms, including effects on the equilibrative nucleoside transporter, GPR55, TPRV-1, 5-HT1A, and the α3 and α1 glycine receptors. Also, antiepileptic mechanism of action of CBD might involve a reduction of Ca^{2+}, via interaction with the mitochondrial Na^{2+}/Ca^{2+} exchanger [175].

Likewise CBDV and, to a far smaller extent, Δ^9-THCV produces anticonvulsant effects in animal models of epilepsy. Scutt and Williamson [176] reported that CBDV acts via CB2 cannabinoid receptor-dependent mechanisms but direct CB2 receptor effects were not shown. Recently, it was also demonstrated by other studies that CBDV acts via non-CB1/CB2 mechanisms. These compounds in fact interact with TRPV1, TRPV2, TRPA1, and TRPM8 channels, but their molecular pharmacology and mechanisms of action are less well known [177].

Additionally, CBDV has been shown to inhibit the primary synthetic enzyme of the endocannabinoid, 2-arachidonoylglycerol, diacylglycerol lipase α *in vitro* [178]. While the pharmacological significance of these effects remains unconfirmed *in vivo* and the targets identified have not yet been linked to epilepsy, they support the emergent role of multiple non-CB receptor targets [179].

Moreover, Δ^9-THCV has demonstrated interesting potential use in treatment of convulsions. Δ^9-THCV increases, in a GABA antagonist sensitive manner, inhibitory neurotransmission in mouse cerebellum and also exhibits anticonvulsant activity in a rat piriform cortical (PC) model of epilepsy [180]. Possible mechanisms underlying cannabinoid actions in the CNS include CB1 receptor antagonism or inverse agonism at constitutively active CB1 receptors [180].

Also, Hill *et al.* [173] have shown that Δ^9-THCV reduced Purkinje cell firing via an increase in inhibitory neurotransmission at interneuron-Purkinje cell synapses in mouse acute parasagittal cerebellar brain slices, most likely by reducing CB1 receptor-mediated, endocannabinoid-induced inhibition of GABA release. Interestingly, Δ^9-THCV was shown to modulate GABA release onto Purkinje cells at a network level, as it did not affect Purkinje cell spike firing following GABA-receptor blockade [181].

It is well know that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric diseases, such as anxiety, depression, bipolar disorder, psychosis and sleep disorders.

Although pharmacological effects of CBD in several biological systems have been widely investigated, mechanisms responsible for its therapeutic potential are still not clear. From studies on different animal models, it seems that CBD exerts anxiolytic-like effects by activating post-synaptic 5-HT1A receptors in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex [59,182].

Other effects, such as anti-compulsive, blockade of the anxiogenic consequences of chronic unpredictable stress, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis may depend on potentiation of anandamide-mediated neurotransmission. Activation of TRPV1 channels may be invoked to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD [59].

In addition to these mechanisms, CBD can interfere in different other important biological processes (inhibition of adenosine uptake, inverse agonism at CB2, CB1 antagonism, GPR55 antagonist, intracellular Ca^{2+} increase). Therefore, further studies are needed to investigate their possible involvement on CBD behavioral effects.

Russo *et al.* [183], reviewed the effects of *Cannabis*, and highlighted the benefits that can accrue in this regard, particularly with respect to symptom reduction permitting better sleep, as opposed to a mere hypnotic effect. In several clinical studies, it has been found that low doses of *Cannabis* improve mood, in particular, Δ^9-THC increase serotonin levels in the brain, interacting with CB1 receptors.

Therefore, non-psychotropic compounds require further studies to propose these as a potentially useful drug in the treatment of a variety of intractable conditions, at least in association with current conventional therapy.

Finally, cannabinoids have been shown to be potent analgesics in animal models of hyperlgesia and thus might be useful in the treatment of inflammatory pain as well as neuropathic pain [184].

Neuropathic pain is a debilitating form of chronic pain resulting from peripheral nerve injury, toxic insults, and disease states, such as diabetes, cancer, human immunodeficiency virus, MS, and herpes zoster infection [185–187]. Neuropathic pain remains a significant clinical problem because it responds poorly to available therapies, needing validation of novel analgesic drugs. More recently, CBD was shown to be effective in well-established experimental models of neuropathic pain. It is believed that the analgesic effect of CBD is mediated, at least in part, by TRPV1 [188]. There is also evidence to suggest that cannabinoids can induce antinociception via supraspinal mechanisms and peripheral CB2 receptors [189]. Also, the analgesic effects may be mediated in part at the level of spinal cord via CB1 receptors activation [190].

Table 1 summarizes cannabinoid therapeutic targets for each disorder considered.

Table 1. Therapeutic targets for cannabinoid medicines.

Disease	Therapeutic Cannabinoids	Therapeutic Targets	Ref.
PD	Δ^9-THC	Tremor	Lastres-Becker *et al.* [81]
	CBD	Dystonia and discinesia	Lastres-Becker *et al.* [81]
	WIN 55,212-2 + SR141716A (RIMONABANT)	Akinesia	Maneuf *et al.* [80]
	Δ^9-THCV	Diskinesia	Garcia *et al.* [84]
HD	Δ^9-THC	Hyperkinesia and choreic movements	Chiarlone *et al.* [102]
	CBG	Hyperkinesia	Valdeolivas *et al.* [104]
	Δ^9-THC+ CBD (SATIVEX®)	Hyperkinesia and choreic movements	Sagredo *et al.* [106]
	HU210 and WIN55,212-2	Hyperkinesia	Scotter *et al.* [108]
AD	Δ^9-THC	Behavior disorders and motor impairment	Eubanks *et al.* [117]
	CBD	Learning behavior	Esposito *et al.* [119]; Martin-Moreno *et al.* [120]
	WIN 55,212-2	Cognitive impairment	Martin-Moreno *et al* [120]
	Δ^9-THC + CBD	Memory and learning impairment	Aso *et al.* [122]
	SYNTHETIC Δ^9-THC (Dronabinol)	Nocturnal motor activity, agitation and anorexia	Walther *et al.* [123]
MS	Δ^9-THC	Spasticity	Lyman *et al.* [126]
	HU210 and WIN 55,212-2	Tremor and spasticity	Molina-Holgado *et al.* [127]; Cabral *et al.* [128]; Arevalo-Martin *et al.* [130]
	JWH-133	Tremor and spasticity	Baker *et al.* [134]; Buccellato *et al.* [135]
	CB52	Motor impairment	Ribeiro *et al.* [131]
	SYNTHETIC Δ^9-THC (NABILONE)	Neuropathic pain	Turcotte *et al.* [144]
	Δ^9-THC+ CBD (SATIVEX®)	Spasticity, neuropathic pain and bladder dysfunction	Vaney *et al.* [14]; Wilkinson *et al.* [15]; Freeman *et al.* [145]
ALS	Δ^9-THC	Motor impairment and spasticity	Raman *et al.* [149]
	WIN 55,212-2	Tremor and motor impairment	Bilsland *et al.* [150]
	AM1241	Tremor and motor impairment	Kim *et al.* [153]
	Δ^9-THC + CBD (SATIVEX®)	Motor impairment	Moreno-Martet *et al.* [154]
Cerebral Ischemia and Hypoxia	CBD	Reduction of brain edema, cerebral hemodynamic impairment and seizures	Alvarez *et al.* [162]; Pazos *et al.* [166,168]
Epilepsy	CBD	Convulsions	Jones *et al.* [172]
	CBDV	Convulsions	Scutt *et al.* [176]; de Petrocellis *et al.* [177]
	Δ^9-THCV	Convulsions	Dennis *et al.* [180]; Ma *et al.* [181]

7. Conclusions

In this review, we showed how the *Cannabis* plant, an ancient industrial crop, is drawing increasing attention as a pharmaceutical plant, and is today considered a true "bioreactor" source of botanical raw material from which high amounts of potentially valuable cannabinoids can be extracted. In the future, these molecules will be increasingly used in clinical trials necessary to assess the potential of each phytocannabinoid for the treatment of several diseases, among which CNS disorders.

Whereas, current treatments for CNS diseases are partially effective and have risks of side effects that are not easily tolerated by patients, the development of new synthetic cannabinoids or cannabinoid-derived drugs may represent an alternative strategy to pursue.

The observations from experimental models of neurological diseases, and now increasingly from clinical trials, underline the therapeutic usefulness of cannabinoids-based medicines for treatment of symptoms associated to these. In addition, there is growing evidence from experimental studies that Δ^9-THC and other cannabinoids, notably CBD, have neuroprotective effects as a result of their antioxidant, anti-inflammatory and anticytotoxic properties which may prove disease modifying in CNS disorders.

Despite emerging evidence regarding putative therapeutic activities of cannabinoids, their effective introduction in the clinical use is still controversial and strongly limited by unavoidable psychotropic effects, exhibited by many of them.

The possibility of overcoming these side effects and developing novel approaches represents the main open question about the use of cannabinoids as new therapeutic drugs for the treatment of neurological disorders.

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Author Contributions

Sabrina Giacoppo performed bibliographic research and drafted and reviewed the manuscript. Giuseppe Mandolino contributed to the manuscript drafting. Galuppo Maria performed bibliographic research and supported manuscript correction. Emanuela Mazzon and Placido Bramanti designed the paper and supervised manuscript drafting.

Conflicts of Interest

The authors declare no conflict of interest.

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Cannabinoids in the management of difficult to treat pain

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Abstract: This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol®) and nabilone (Cesamet®) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex®, a cannabis derived oromucosal spray containing equal proportions of THC (partial CB_1 receptor agonist) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with CB_1 receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

Keywords: cannabinoids, tetrahydrocannabinol, cannabidiol, analgesia, pain management, multiple sclerosis

Introduction

Chronic pain represents an emerging public health issue of massive proportions, particularly in view of aging populations in industrialized nations. Associated facts and figures are daunting: In Europe, chronic musculoskeletal pain of a disabling nature affects over one in four elderly people (Frondini et al 2007), while figures from Australia note that older half of older people suffer persistent pain, and up to 80% in nursing home populations (Gibson 2007). Responses to an ABC News poll in the USA indicated that 19% of adults (38 million) have chronic pain, and 6% (or 12 million) have utilized cannabis in attempts to treat it (ABC News et al 2005).

Particular difficulties face the clinician managing intractable patients afflicted with cancer-associated pain, neuropathic pain, and central pain states (eg, pain associated with multiple sclerosis) that are often inadequately treated with available opiates, antidepressants and anticonvulsant drugs. Physicians are seeking new approaches to treatment of these conditions but many remain concerned about increasing governmental scrutiny of their prescribing practices (Fishman 2006), prescription drug abuse or diversion. The entry of cannabinoid medicines to the pharmacopoeia offers a novel approach to the issue of chronic pain management, offering new hope to many, but also stoking the flames of controversy among politicians and the public alike.

This article will attempt to present information concerning cannabinoid mechanisms of analgesia, review randomized clinical trials (RCTs) of available and emerging

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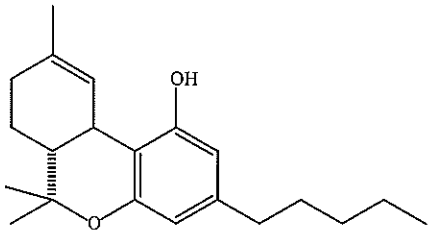
cannabinoid agents, and address the many thorny issues that have arisen with clinical usage of herbal cannabis itself ("medical marijuana"). An effort will be made to place the issues in context and suggest rational approaches that may mitigate concerns and indicate how standardized pharmaceutical cannabinoids may offer a welcome addition to the pharmacotherapeutic armamentarium in chronic pain treatment.

Cannabinoids and analgesic mechanisms

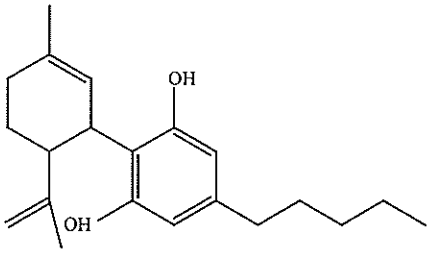
Cannabinoids are divided into three groups. The first are naturally occurring 21-carbon terpenophenolic compounds found to date solely in plants of the *Cannabis* genus, currently termed phytocannabinoids (Pate 1994). The best known analgesic of these is Δ^9-tetrahydrocannabinol (henceforth, THC)(Figure 1), first isolated and synthesized in 1964 (Gaoni and Mechoulam 1964). In plant preparations and whole extracts, its activity is complemented by other "minor" phytocannabinoids such as cannabidiol (CBD) (Figure 1), cannabis terpenoids and flavonoids, as will be discussed subsequently.

Long before mechanisms of cannabinoid analgesia were understood, structure activity relationships were investigated and a number of synthetic cannabinoids have been developed and utilized in clinical trials, notably nabilone (Cesamet®, Valeant Pharmaceuticals), and ajulemic acid (CT3, IP-751, Indevus Pharmaceuticals) (Figure 1).

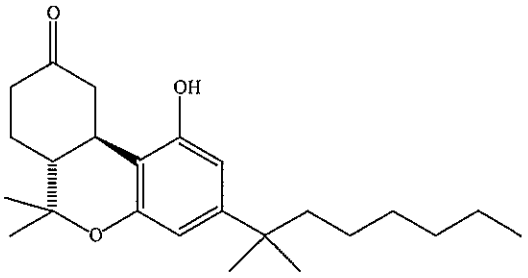
In 1988, the first cannabinoid receptor was identified (CB_1) (Howlett et al 1988) and in 1993, a second was described (CB_2) (Munro et al 1993). Both are 7-domain G-protein coupled receptors affecting cyclic-AMP, but CB_1 is more pervasive throughout the body, with particular predilection to nociceptive areas of the central nervous system and spinal cord (Herkenham et al 1990; Hohmann et al 1999), as well as the peripheral nervous system (Fox et al 2001; Dogrul et al 2003) wherein synergy of activity between peripheral and central cannabinoid receptor function has been demonstrated (Dogrul et al 2003). CB_2, while commonly reported as confined to lymphoid and immune tissues, is also proving to be an important mediator for suppressing both pain and inflammatory processes (Mackie 2006). Following the description of cannabinoid receptors, endogenous ligands for these were discovered: anandamide (arachidonylethanolamide, AEA) in 1992 in porcine brain (Devane et al 1992), and 2-arachidonylglycerol (2-AG) in 1995 in canine gut tissue (Mechoulam et al 1995) (Figure 1). These endocannabinoids both act as retrograde messengers on G-protein coupled receptors, are synthesized on demand,



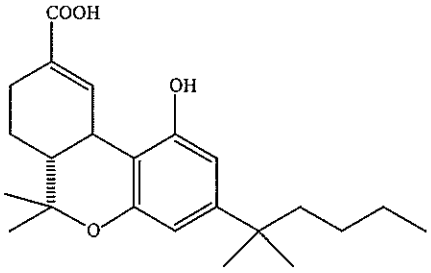
delta-9-tetrahydrocannabinol (THC)



cannabidiol



nabilone (Cesamet)



ajulemic acid

Figure 1 Molecular structures of four cannabinoids employed in pain treatment.

and are especially active on glutamatergic and GABA-ergic synapses. Together, the cannabinoid receptors, their endogenous ligands ("endocannabinoids") and metabolizing enzymes comprise the endocannabinoid system (ECS) (Di Marzo et al 1998), whose functions have been prosaically termed to be "relax, eat, sleep, forget and protect" (p. 528). The endocannabinoid system parallels and interacts at many points with the other major endogenous pain control systems:

endorphin/enkephalin, vanilloid/transient receptor potential (TRPV), and inflammatory. Interestingly, our first knowledge of each pain system has derived from investigation of natural origin analgesic plants, respectively: cannabis (*Cannabis sativa*, *C. indica*) (THC, CBD and others), opium poppy (*Papaver somniferun*) (morphine, codeine), chile peppers (eg, *Capsicum annuum*, *C. frutescens*, *C. chinense*) (capsaicin) and willow bark (*Salix* spp.) (salicylic acid, leading to acetylsalicylic acid, or aspirin). Interestingly, THC along with AEA and 2-AG, are all partial agonists at the CB_1 receptor. Notably, no endocannabinoid has ever been administered to humans, possibly due to issues of patentability and lack of commercial feasibility (Raphael Mechoulam, pers comm 2007). For an excellent comprehensive review of the endocannabinoid system, see Pacher et al (2006), while Walker and Huang have provided a key review of antinociceptive effects of cannabinoids in models of acute and persistent pain (Walker and Huang 2002).

A clinical endocannabinoid deficiency has been postulated to be operative in certain treatment-resistant conditions (Russo 2004), and has received recent support in findings that anandamide levels are reduced over controls in migraineurs (Sarchielli et al 2006), that a subset of fibromyalgia patients reported significant decreased pain after THC treatment (Schley et al 2006), and the active role of the ECS in intestinal pain and motility in irritable bowel syndrome (Massa and Monory 2006) wherein anecdotal efficacy of cannabinoid treatments have also been claimed.

The endocannabinoid system is tonically active in control of pain, as demonstrated by the ability of SR141716A (rimonabant), a CB_1 antagonist, to produce hyperalgesia upon administration to mice (Richardson et al 1997). As mentioned above, the ECS is active throughout the neuraxis, including integrative functions in the periacqueductal gray (Walker et al 1999a; Walker et al 1999b), and in the ventroposterolateral nucleus of the thalamus, in which cannabinoids proved to be 10-fold more potent than morphine in wide dynamic range neurons mediating pain (Martin et al 1996). The ECS also mediates central stress-induced analgesia (Hohmann et al 2005), and is active in nociceptive spinal areas (Hohmann et al 1995; Richardson et al 1998a) including mechanisms of wind-up (Strangman and Walker 1999) and N-methyl-D-aspartate (NMDA) receptors (Richardson et al 1998b). It was recently demonstrated that cannabinoid agonists suppress the maintenance of vincristine-induced allodynia through activation of CB_1 and CB_2 receptors in the spinal cord (Rahn et al 2007). The ECS is also active peripherally (Richardson et al 1998c) where CB_1 stimulation reduces pain, inflammation and hyperalgesia. These mechanisms were also proven to include mediation of contact dermatitis via CB_1 and CB_2 with benefits of THC noted systemically and locally on inflammation and itch (Karsak et al 2007). Recent experiments in mice have even suggested the paramount importance of peripheral over central CB_1 receptors in nociception of pain (Agarwal et al 2007)

Cannabinoid agonists produce many effects beyond those mediated directly on receptors, including anti-inflammatory effects and interactions with various other neurotransmitter systems (previously reviewed (Russo 2006a)). Briefly stated, THC effects in serotonergic systems are widespread, including its ability to decrease 5-hydroxytryptamine (5-HT) release from platelets (Volfe et al 1985), increase its cerebral production and decrease synaptosomal uptake (Spadone 1991). THC may affect many mechanisms of the trigeminovascular system in migraine (Akerman et al 2003; Akerman et al 2004; Akerman et al 2007; Russo 1998; Russo 2001). Dopaminergic blocking actions of THC (Müller-Vahl et al 1999) may also contribute to analgesic benefits.

The glutamatergic system is integral to development and maintenance of neuropathic pain, and is responsible for generating secondary and tertiary hyperalgesia in migraine and fibromyalgia via NMDA mechanisms (Nicolodi et al 1998). Thus, it is important to note that cannabinoids presynaptically inhibit glutamate release (Shen et al 1996), THC produces 30%–40% reduction in NMDA responses, and THC is a neuroprotective antioxidant (Hampson et al 1998). Additionally, cannabinoids reduce hyperalgesia via inhibition of calcitonin gene-related peptide (Richardson et al 1998a). As for Substance P mechanisms, cannabinoids block capsaicin-induced hyperalgesia (Li et al 1999), and THC will do so at sub-psychoactive doses in experimental animals (Ko and Woods 1999). Among the noteworthy interactions with opiates and the endorphin/enkephalin system, THC has been shown to stimulate beta-endorphin production (Manzanares et al 1998), may allow opiate sparing in clinical application (Cichewicz et al 1999), prevents development of tolerance to and withdrawal from opiates (Cichewicz and Welch 2003), and rekindles opiate analgesia after a prior dosage has worn off (Cichewicz and McCarthy 2003). These are all promising attributes for an adjunctive agent in treatment of clinical chronic pain states.

The anti-inflammatory contributions of THC are also extensive, including inhibition of PGE-2 synthesis (Burstein et al 1973), decreased platelet aggregation (Schaefer et al 1979), and stimulation of lipooxygenase (Fimiani et al 1999). THC has twenty times the anti-inflammatory potency

of aspirin and twice that of hydrocortisone (Evans 1991), but in contrast to all nonsteroidal anti-inflammatory drugs (NSAIDs), demonstrates no cyclo-oxygenase (COX) inhibition at physiological concentrations (Stott et al 2005a).

Cannabidiol, a non-euphoriant phytocannabinoid common in certain strains, shares neuroprotective effects with THC, inhibits glutamate neurotoxicity, and displays antioxidant activity greater than ascorbic acid (vitamin C) or tocopherol (vitamin E) (Hampson et al 1998). While THC has no activity at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist that inhibits fatty acid amidohydrolase (FAAH), AEA's hydrolytic enzyme, and also weakly inhibits AEA reuptake (Bisogno et al 2001). These activities reinforce the conception of CBD as an endocannabinoid modulator, the first clinically available (Russo and Guy 2006). CBD additionally affects THC function by inhibiting first pass hepatic metabolism to the possibly more psychoactive 11-hydroxy-THC, prolonging its half-life, and reducing associated intoxication, panic, anxiety and tachycardia (Russo and Guy 2006). Additionally, CBD is able to inhibit tumor necrosis factor-alpha (TNF-α) in its own right in a rodent model of rheumatoid arthritis (Malfait et al 2000). At a time when great concern is accruing in relation to NSAIDs in relation to COX-1 inhibition (gastrointestinal ulcers and bleeding) and COX-2 inhibition (myocardial infarction and cerebrovascular accidents), CBD, like THC, inhibits neither enzyme at pharmacologically relevant doses (Stott et al 2005a). A new explanation of inflammatory and analgesic effects of CBD has recently come to light with the discovery that it is able to promote signaling of the adenosine receptor A2A by inhibiting the adenosine transporter (Carrier et al 2006).

Other "minor phytocannabinoids" in cannabis may also contribute relevant activity (McPartland and Russo 2001). Cannabichromene (CBC) is the third most prevalent cannabinoid in cannabis, and is also anti-inflammatory (Wirth et al 1980), and analgesic, if weaker than THC (Davis and Hatoum 1983). Cannabigerol (CBG) displays sub-micromolar affinity for CB_1 and CB_2 (Gauson et al 2007). It also exhibits GABA uptake inhibition to a greater extent than THC or CBD (Banerjee et al 1975), suggesting possible utilization as a muscle relaxant in spasticity. Furthermore, CBG has more potent analgesic, anti-erythema and lipooxygenase blocking activity than THC (Evans 1991), mechanisms that merit further investigation. It requires emphasis that drug stains of North American (ElSohly et al 2000; Mehmedic et al 2005), and European (King et al 2005) cannabis display relatively high concentrations of THC, but are virtually lacking in CBD or other phytocannabinoid content.

Cannabis terpenoids also display numerous attributes that may be germane to pain treatment (McPartland and Russo 2001). Myrcene is analgesic, and such activity, in contrast to cannabinoids, is blocked by naloxone (Rao et al 1990), suggesting an opioid-like mechanism. It also blocks inflammation via PGE-2 (Lorenzetti et al 1991). The cannabis sesquiterpenoid β-caryophyllene shows increasing promise in this regard. It is anti-inflammatory comparable to phenylbutazone via PGE-1 (Basile et al 1988), but simultaneously acts as a gastric cytoprotective (Tambe et al 1996). The analgesic attributes of β-caryophyllene are increasingly credible with the discovery that it is a selective CB_2 agonist (Gertsch et al 2007), with possibly broad clinical applications. α-Pinene also inhibits PGE-1 (Gil et al 1989), while linalool displays local anesthetic effects (Re et al 2000).

Cannabis flavonoids in whole cannabis extracts may also contribute useful activity (McPartland and Russo 2001). Apigenin inhibits TNF-α (Gerritsen et al 1995), a mechanism germane to multiple sclerosis and rheumatoid arthritis. Cannflavin A, a flavone unique to cannabis, inhibits PGE-2 thirty times more potently than aspirin (Barrett et al 1986), but has not been subsequently investigated.

Finally, β-sitosterol, a phytosterol found in cannabis, reduced topical inflammation 65% and chronic edema 41% in skin models (Gomez et al 1999).

Available cannabinoid analgesic agents and those in development

Very few randomized controlled trials (RCTs) have been conducted using smoked cannabis (Campbell et al 2001) despite many anecdotal claims (Grinspoon and Bakalar 1997). One such study documented slight weight gain in HIV/AIDS subjects with no significant immunological sequelae (Abrams et al 2003). A recent brief trial of smoked cannabis (3.56% THC cigarettes 3 times daily) in HIV-associated neuropathy showed positive results on daily pain, hyperalgesia and 30% pain reduction (vs 15% in placebo) in 50 subjects over a treatment course of only 5 days (Abrams et al 2007) (Table 1). This short clinical trial also demonstrated prominent adverse events associated with intoxication. In Canada, 21 subjects with chronic pain sequentially smoked single inhalations of 25 mg of cannabis (0, 2.5, 6.0, 9.5% THC) via a pipe three times a day for 5 days to assess effects on pain (Ware et al 2007) with results the authors termed "modest": no changes were observed in acute neuropathic pain scores, and a very low number of subjects noted 30% pain relief at the end of the study (Table 1). Even after political and legal considerations, it remains extremely unlikely that crude cannabis could

Table 1 Results RCTs of cannabinoids in treatment of pain syndromes ()

Drug	Subject number N =	RCT indication	Trial duration	Results/Reference
Ajulemic Acid	21	Neuropathic pain	7 day crossover	VAS improved over placebo ($p = 0.02$) (Karst et al 2003)
Cannabis, smoked	50	HIV neuropathy	5 days	Decreased daily pain ($p = 0.03$) and hyperalgesia ($p = 0.05$), 52% with >30% pain reduction vs placebo ($p = 0.04$) (Abrams et al 2007)
Cannabis, Smoked	21	Chronic neuropathic pain	5 days	No acute benefit on pain, average daily pain lower on high THC cannabis vs placebo ($p = 0.02$) (Ware et al 2007)
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p = 0.003$) (Zajicek et al 2003)
Cannador	65	Post-herpetic neuralgia	4 weeks	No benefit observed (Ernst et al 2005)
Cannador	30	Post-operative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p = 0.01$)(Holdcroft et al 2006)
Marinol	24	Neuropathic pain in MS	15–21 days, crossover	Median numerical pain ($p = 0.02$), median pain relief improved ($p = 0.035$) over placebo (Svendsen et al 2004)
Marinol	40	Post-operative pain	Single dose	No benefit observed over placebo (Buggy et al 2003)
Nabilone	41	Post-operative pain	3 doses in 24 hours	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg (Beaulieu 2006)
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs placebo ($p < 0.05$), symptom control best with Sativex ($p < 0.0001$) (Wade et al 2003)
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p < 0.001$) especially in MS ($p < 0.0042$) (Notcutt et al 2004)
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p = 0.002$) and Sativex ($p = 0.005$) over placebo (Berman et al 2004)
Sativex	66	Central neuropathic pain in MS	5 weeks	NRS analgesia improved over placebo ($p = 0.009$) (Rog et al 2005)
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels ($p = 0.004$), dynamic allodynia ($p = 0.042$), and punctuate allodynia ($p = 0.021$) vs placebo (Nurmikko et al 2007)
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement ($p = 0.044$), morning pain at rest ($p = 0.018$), DAS-28

(Continued)

Table 1 *(Continued)*

Drug	Subject number	RCT indication	Trial duration	Results/Reference
				(p = 0.002), and SF-MPQ pain at present (p = 0.016) (Blake et al 2006)
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain socres, but improved Brief Pain Inventory (p = 0.032), and Patients Global Impression of Change (p = 0.001) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs placebo (p = 0.0142), Tetranabinex NSD (Johnson and Potts 2005)
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo (p = 0.001) (unpublished)

Abbreviations: MS, multiple sclerosis; NRS, numerical rating scale; NSD, no significant difference; RCTs, randomized clinical trials; VAS, visual analogue pain scales.

ever be approved by the FDA as a prescription medicine as outlined in the FDA Botanical Guidance document (Food and Drug Administration 2004; Russo 2006b), due to a lack of rigorous standardization of the drug, an absence of Phase III clinical trials, and pulmonary sequelae (bronchial irritation and cough) associated with smoking (Tashkin 2005). Although cannabis vaporizers reduce potentially carcinogenic polyaromatic hydrocarbons, they have not been totally eliminated by this technology (Gieringer et al 2004; Hazekamp et al 2006).

Oral dronabinol (THC) is marketed in synthetic form as Marinol® (Solvay Pharmaceuticals) in various countries, and was approved in the USA for nausea associated with chemotherapy in 1985, and in 1992 for appetite stimulation in HIV/AIDS. Oral dronabinol's expense, variability of action, and attendant intoxication and dysphoria have limited its adoption by clinicians (Calhoun et al 1998). Two open label studies in France of oral dronabinol for chronic neuropathic pain in 7 subjects (Clermont-Gnamien et al 2002) and 8 subjects (Attal et al 2004), respectively, failed to show significant benefit on pain or other parameters, and showed adverse event frequently requiring discontinuation with doses averaging 15–16.6 mg THC. Dronabinol did demonstrate positive results in a clinical trial of multiple sclerosis pain in two measures (Svendsen et al 2004), but negative results in post-operative pain (Buggy et al 2003) (Table 1). Another uncontrolled case report in three subjects noted relief of intractable pruritus associated with cholestatic jaundice employing oral dronabinol (Neff et al 2002). Some authors have noted patient preference for whole cannabis preparations over oral THC (Joy et al 1999), and the contribution of other components beyond THC to therapeutic benefits (McPartland and Russo 2001). Inhaled THC leads to peak plasma concentration within 3–10 minutes, followed by a rapid fall while levels of intoxication are still rising, and with systemic bioavailability of 10%–35% (Grotenhermen 2004). THC absorption orally is slow and erratic with peak serum levels in 45–120 minutes or longer. Systemic bioavailability is also quite low due to rapid hepatic metabolism on first pass to 11-hydroxy-THC. A rectal suppository of THC-hemisuccinate is under investigation (Broom et al 2001), as are transdermal delivery techniques (Challapalli and Stinchcomb 2002). The terminal half-life of THC is quite prolonged due to storage in body lipids (Grotenhermen 2004).

Nabilone (Cesamet) (Figure 1), is a synthetic dimethylheptyl analogue of THC (British Medical Association 1997) that displays greater potency and prolonged half-life. Serum levels peak in 1–4 hours (Lemberger et al 1982). It was also primarily developed as an anti-emetic in chemotherapy, and was recently re-approved for this indication in the USA. Prior case reports have noted analgesic effects in case reports in neuropathic pain (Notcutt et al 1997) and other pain disorders (Berlach et al 2006). Sedation and dysphoria were prominent sequelae. An RCT of nabilone in 41 post-operative subjects actually documented exacerbation of pain scores after thrice daily dosing (Beaulieu 2006) (Table 1). An abstract of a study

of 82 cancer patients on nabilone claimed improvement in pain levels after varying periods of follow-up compared to patients treated without this agent (Maida 2007). However, 17 subjects dropped out, and the study was neither randomized nor controlled, and therefore is not included in Table 1.

Ajulemic acid (CT3, IP-751) (Figure 1), another synthetic dimethylheptyl analogue, was employed in a Phase II RCT in 21 subjects with improvement in peripheral neuropathic pain (Karst et al 2003) (Table 1). Part of its analgesic activity may relate to binding to intracellular peroxisome proliferator-activator receptor gamma (Liu et al 2003). Peak plasma concentrations have generally been attained in 1–2 hours, but with delays up to 4–5 hours is some subjects (Karst et al 2003). Debate surrounds the degree of psychoactivity associated with the drug (Dyson et al 2005). Current research is confined to the indication of interstitial cystitis.

Cannador® (IKF-Berlin) is a cannabis extract administered in oral capsules, with differing figures as to THC:CBD ratios (reviewed in (Russo and Guy 2006)), generally approximately 2:1. Two pharmacokinetic studies on possibly related material have been reported (Nadulski et al 2005a; Nadulski et al 2005b). In a Phase III RCT employing Cannador in spasticity in multiple sclerosis (MS) (CAMS) (Zajicek et al 2003) (Table 1), no improvement was noted in the Ashworth Scale, but benefit was observed in spasm-associated pain on subjective measures. Both Marinol and Cannador produced reductions in pain scores in long-term follow-up (Zajicek et al 2005). Cannador was assayed in postherpetic neuralgia in 65 subjects with no observed benefit (Ernst et al 2005) (Table 1), and in 30 post-operative pain subjects (CANPOP) without opiates, with slight benefits, but prominent psychoactive sequelae (Holdcroft et al 2006) (Table 1).

Sativex® (GW Pharmaceuticals) is an oromucosal whole cannabis-based spray combining a CB_1 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring (McPartland and Russo 2001; Russo and Guy 2006). It was approved by Health Canada in June 2005 for prescription for central neuropathic pain in multiple sclerosis, and in August 2007, it was additionally approved for treatment of cancer pain unresponsive to optimized opioid therapy. Sativex is a highly standardized pharmaceutical product derived from two *Cannabis sativa* chemovars following Good Agricultural Practice (GAP) (de Meijer 2004), yielding Tetranabinex® (predominantly-THC extract) and Nabidiolex® (predominantly-CBD extract) in a 1:1 ratio. Each 100 μL pump-action oromucosal Sativex spray actuation provides 2.7 mg of THC and 2.5 mg of CBD. Pharmacokinetic data are available, and indicate plasma half lives of 85 minutes for THC, 130 minutes for 11-hydroxy-THC and 100 minutes for CBD (Guy and Robson 2003). Sativex effects commence in 15–40 minutes, an interval that permits symptomatic dose titration. A very favorable adverse event profile has been observed in over 2500 patient years of exposure in over 2000 experimental subjects. Patients most often ascertain an individual stable dosage within 7–10 days that provides therapeutic relief without unwanted psychotropic effects (often in the range of 8–10 sprays per day). In all RCTs, Sativex was adjunctively added to optimal drug regimens in subjects with intractable symptoms, those often termed "untreatable." Sativex is also available by named patient prescription in the UK and the Catalonia region of Spain. An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain.

The clinical trials performed with Sativex have recently been assessed in two independent review articles (Barnes 2006; Pérez 2006). In a Phase II clinical trial in 20 patients with neurogenic symptoms (Wade et al 2003), Tetranabinex, Nabidiolex, and Sativex were tested in a double-blind RCT vs placebo (Table 1). Significant improvement was seen with both Tetranabinex and Sativex on pain (especially neuropathic), but post-hoc analysis showed symptom control was best with Sativex ($p < 0.0001$), with less intoxication than with THC-predominant extract.

In a Phase II double-blind crossover study of intractable chronic pain (Notcutt et al 2004) in 24 subjects, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for Nabidiolex, 4.63 for Tetranabinex and 4.4 for Sativex extracts ($p < 0.001$). Sativex produced best results for pain in MS subjects ($p < 0.0042$) (Table 1).

In a Phase III study of pain associated due to brachial plexus avulsion ($N = 48$) (Berman et al 2004), fairly comparable benefits were noted in Box Scale-11 pain scores with Tetranabinex and Sativex extracts (Table 1).

In a controlled double-blind RCT of central neuropathic pain, 66 MS subjects showed mean Numerical Rating Scale (NRS) analgesia favoring Sativex over placebo (Rog et al 2005) (Table 1).

In a Phase III double-blind, placebo-controlled trial ($N = 125$) of peripheral neuropathic pain with allodynia (Nurmikko et al 2007), Sativex produced highly statistically significant improvements in pain levels, dynamic and punctate allodynia (Table 1).

In a SAFEX study of Phase III double-blind RCT in 160 subjects with various symptoms of MS (Wade et al 2004), 137 patients elected to continue on Sativex after the initial study (Wade et al 2006). Rapid declines were noted in the first twelve weeks in pain VAS (N = 47) with slower sustained improvements for more than one year. During that time, there was no escalation of dose indicating an absence of tolerance to the preparation. Similarly, no withdrawal effects were noted in a subset of patients who voluntarily stopped the medicine abruptly. Upon resumption, benefits resumed at the prior established dosages.

In a Phase II double-blind, randomized, placebo-controlled, 5-week study of 56 rheumatoid arthritis patients with Sativex (Blake et al 2006), employed nocturnal treatment only to a maximum of 6 sprays per evening (16.2 mg THC + 15 mg CBD). In the final treatment week, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain at present all favored Sativex over placebo (Table 1).

Results of a Phase III study (N = 177) comparing Sativex, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates (Johnson and Potts 2005) demonstrated that Sativex produced highly statistically significant improvements in analgesia (Table 1), while the THC-predominant extract failed to produce statistical demarcation from placebo, suggesting the presence of CBD in the Sativex preparation was crucial to attain significant pain relief.

In a study of spinal injury pain, NRS of pain were not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were clearly positive (Table 1). Finally, in an RCT of intractable lower urinary tract symptoms in MS, accompanying pain in affected patients was prominently alleviated (Table 1).

Highly statistically significant improvements have been observed in sleep parameters in virtually all RCTs performed with Sativex in chronic pain conditions leading to reduced "symptomatic insomnia" due to symptom reduction rather than sedative effects (Russo et al 2007).

Common adverse events (AE) of Sativex acutely in RCTs have included complaints of bad taste, oral stinging, dry mouth, dizziness, nausea or fatigue, but do not generally necessitate discontinuation, and prove less common over time. While there have been no head-to-head comparative RCTs of Sativex with other cannabinoid agents, certain contrasts can be drawn. Sativex (Rog et al 2005) and Marinol (Svendsen et al 2004) have both been examined in treatment of central neuropathic pain in MS, with comparable results (Table 1). However, adverse events were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher due to the presence of accompanying CBD (Russo 2006b; Russo and Guy 2006).

Similarly, while Sativex and smoked cannabis have not been employed in the same clinical trial, comparisons of side effect profiles can be made on the basis of SAFEX studies of Sativex for over a year and up to several years in MS and other types of neuropathic pain (Russo 2006b; Wade et al 2006), and government-approved research programs employing standardized herbal cannabis from Canada for chronic pain (Lynch et al 2006) and the Netherlands for general conditions (Janse et al 2004; Gorter et al 2005) over a period of several months or more. As is evident in Figure 2 (Figure 2), all adverse events are more frequently reported with herbal cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex (see (Russo 2006b) for additional discussion).

Practical issues with cannabinoid medicines

Phytocannabinoids are lipid soluble with slow and erratic oral absorption. While cannabis users claim that the smoking of cannabis allows easy dose titration as a function of rapid onset, high serum levels in a short interval inevitably result. This quick onset is desirable for recreational purposes, wherein intoxication is the ultimate goal, but aside from paroxysmal disorders (eg, episodic trigeminal neuralgia or cluster headache attack), such rapid onset of activity is not usually necessary for therapeutic purposes in chronic pain states. As more thoroughly reviewed elsewhere (Russo 2006b), cannabis smoking produces peak levels of serum THC above 140 ng/mL (Grotenhermen 2003; Huestis et al 1992), while comparable amounts of THC in Sativex administered oromucosally remained below 2 ng/mL (Guy and Robson 2003).

The vast majority of subjects in Sativex clinical trials do not experience psychotropic effects outside of initial dose titration intervals (Figure 2) and most often report subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 (Wade et al 2006). Thus, it is now longer tenable to claim that psychoactive effects are a necessary prerequisite to symptom relief in the therapeutic setting with a standardized intermediate onset cannabis-based preparation. Intoxication has remained a persistent issue in Marinol usage (Calhoun et al 1998), in contrast.

Recent controversies have arisen in relation to non-steroidal anti-inflammatory drugs (NSAID), with concerns

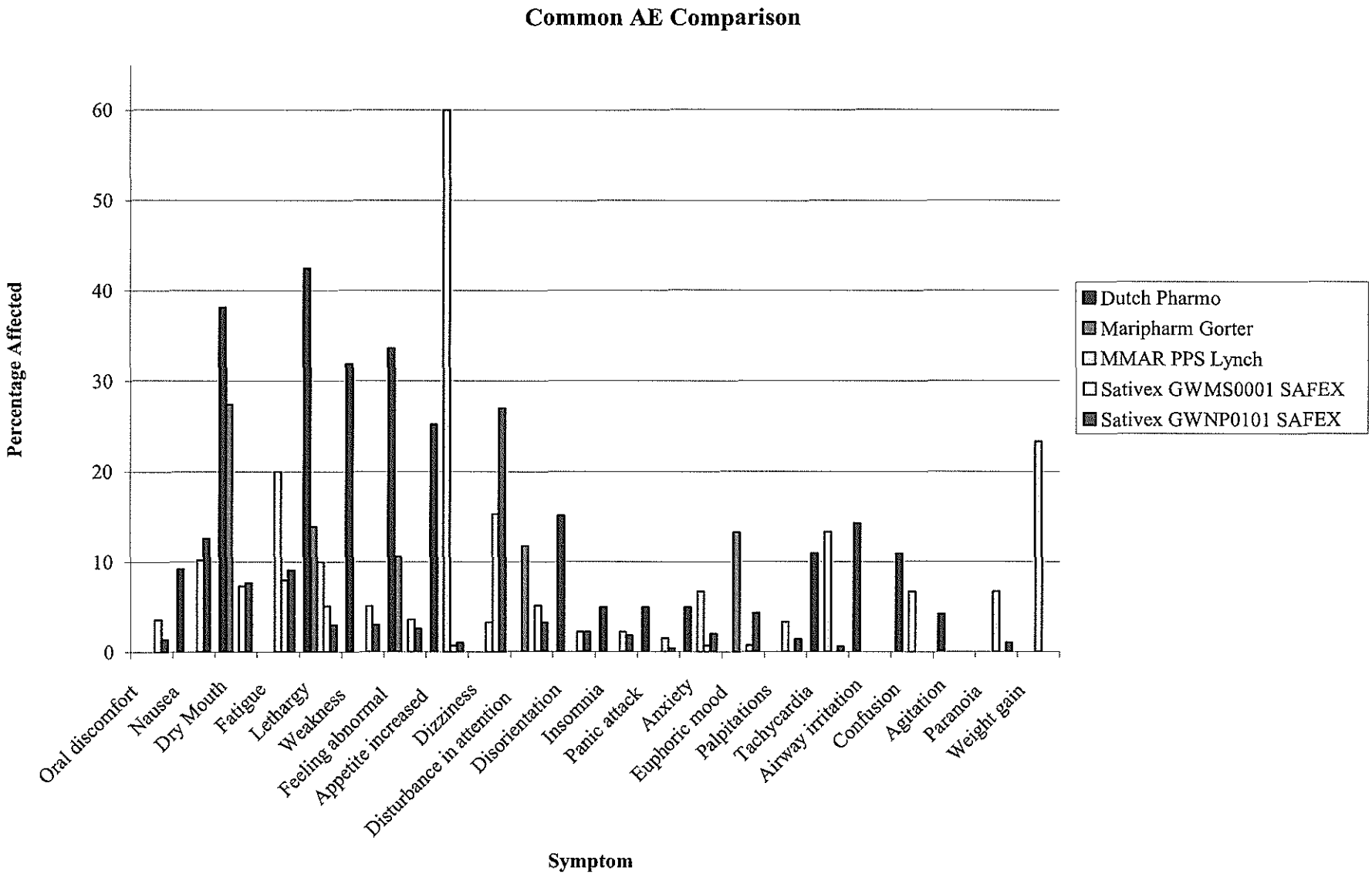


Figure 2 Comparison of adverse events (AE) encountered with long term therapeutic use of herbal cannabis in the Netherlands (Janse et al 2004; Gorter et al 2005) and Canada (Lynch et al 2006), vs that observed in safety-extension (SAFEX) studies of Sativex oromucosal spray (Russo 2006; Wade et al 2006).

that COX-1 agents may provoke gastrointestinal ulceration and bleeding, and COX-2 drugs may increase incidents of myocardial infarction and cerebrovascular accidents (Fitzgerald 2004; Topol 2004). In contrast, neither THC nor CBD produce significant COX inhibition at normal dosage levels (Stott et al 2005a).

Frequent questions have been raised as to whether psychoactive drugs may be adequately blinded (masked) in randomized clinical trials. Internal review and outside analysis have confirmed that blinding in Sativex spasticity studies has been effective (Clark and Altman 2006; Wright 2005). Sativex and its placebo are prepared to appear identical in taste and color. About half of clinical trial subjects reported previous cannabis exposure, but results of two studies (Rog et al 2005; Nurmikko et al 2007) support the fact that cannabis-experienced and naïve patients were identical in observed efficacy and adverse event reporting

Great public concern attends recreational cannabis usage and risks of dependency. The addictive potential of a drug is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal and dependency. Drug abuse liability (DAL) is also assessed by examining a drug's rates of abuse and diversion. US Congress placed cannabis in Schedule I of the Controlled Substances Act in 1970, with drugs categorized as addictive, dangerous, possessing severe abuse potential and no recognized medical value. Marinol was placed in Schedule II, the category for drugs with high abuse potential and liability to produce dependency, but certain recognized medical uses, after its FDA approval in 1985. Marinol was reassigned to Schedule III in 1999, a category denoting a lesser potential for abuse or lower dependency risk after documentation that little abuse or diversion (Calhoun et al 1998) had occurred. Nabilone was placed and has remained in Schedule II since 1985.

The degree to which a drug is reinforcing is determined partly by the by the rate of its delivery to the brain (Samaha and Robinson 2005). Sativex has effect onset in 15–40 minutes, peaking in a few hours, quite a bit slower than drugs of high abuse potential. It has been claimed that inclusion of CBD diminishes psychoactive effects of THC, and may lower potential drug abuse liability of the preparation (see Russo (2006b)) for discussion). Prior studies from Sativex clinical trials do not support the presence reinforcement or euphoria as problems in administration (Wade et al 2006).

Certain facets of acute cannabinoid exposure, including tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, intraocular pressure decreases, etc. are subject to rapid tachyphylaxis upon continued administration (Jones et al 1976). No dose tolerance to the therapeutic effects of Sativex has been observed in clinical trials in over 1500 patient-years of administration. Additionally, therapeutic efficacy has been sustained for several years in a wide variety of symptoms; SAFEX studies in MS and peripheral neuropathic pain, confirm that Sativex doses remain stable or even decreased after prolonged usage (Wade et al 2006), with maintenance of therapeutic benefit and even continued improvement.

Debate continues as to the existence of a clinically significant cannabis withdrawal syndrome with proponents (Budney et al 2004), and questioners (Smith 2002). While withdrawal effects have been reported in recreational cannabis smokers (Solowij et al 2002), 24 volunteers with MS who abruptly stopped Sativex after more than a year of continuous usage displayed no withdrawal symptoms meeting Budney's criteria. While symptoms recurred after 7–10 days of abstinence from Sativex, prior levels of symptom control were readily re-established upon re-titration of the agent (Wade et al 2006).

Overall, Sativex appears to pose less risk of dependency than smoked cannabis based on its slower onset, lower dosage utilized in therapy, almost total absence of intoxication in regular usage, and minimal withdrawal symptomatology even after chronic administration. No known abuse or diversion incidents have been reported with Sativex to date (as of November 2007). Sativex is expected to be placed in Schedule IV of the Misuse of Drugs Act in the United Kingdom once approved.

Cognitive effects of cannabis have been reviewed (Russo et al 2002; Fride and Russo 2006), but less study has occurred in therapeutic contexts. Effects of chronic heavy recreational cannabis usage on memory abate without sequelae after a few weeks of abstinence (Pope et al 2001). Studies of components of the Halstead-Reitan battery with Sativex in neuropathic pain with allodynia have revealed no changes vs placebo (Nurmikko et al 2007), and in central neuropathic pain in MS (Rog et al 2005), 4 of 5 tests showed no significant differences. While the Selective Reminding Test did not change significantly on Sativex, placebo patients displayed unexpected improvement.

Slight improvements were observed in Hospital Anxiety and Depression Scales depression and anxiety scores were noted with Sativex in MS patients with central neuropathic pain (Rog et al 2005), although not quite statistically significant. No long-term mood disorders have been associated with Sativex administration.

Debate continues with regard to the relationship between cannabis usage and schizophrenia (reviewed (Fride and

Russo 2006)). An etiological relationship is not supported by epidemiological data (Degenhardt et al 2003), but if present, should bear relation to dose and length of high exposure. It is likely that lower serum levels of Sativex in therapeutic usage, in conjunction with anti-psychotic properties of CBD (Zuardi and Guimaraes 1997), would minimize risks. Children and adolescents have been excluded from Sativex RCTs to date. SAFEX studies of Sativex have yielded few incidents of thought disorder, paranoia or related complaints.

Adverse effects of cannabinoids on immune function have been observed in experimental animals at doses 50–100 times the psychoactive level (Cabral 2001). In four patients using herbal cannabis therapeutically for over 20 years, no abnormalities were observed in leukocyte, CD4 or CD8 cell counts (Russo et al 2002). Investigation of MS patients on Cannador revealed no major immune changes (Katona et al 2005), and similarly, none occurred with smoked cannabis in a short-term study of HIV patients (Abrams et al 2003). Hematological measures have been normal in all Sativex RCTs without clinical signs of immune dysfunction.

Concerns are frequently noted with new drug-drug interactions, but few have resulted in Sativex RCTs despite its adjunctive use with opiates, many other psychoactive analgesic, antidepressant and anticonvulsant drugs (Russo 2006a), possibly due to CBD ability to counteract sedative effects of THC (Nicholson et al 2004). No effects of THC extract, CBD extract or Sativex were observed in a study of effects on the hepatic cytochrome P450 complex (Stott et al 2005b). On additional study, at 314 ng/ml cannabinoid concentration, Sativex and components produced no significant induction on human CYP450 (Stott et al 2007). Thus, Sativex should be safe to use in conjunction with other drugs metabolized via this pathway.

The Marinol patient monograph cautions that patients should not drive, operate machinery or engage in hazardous activities until accustomed to the drug's effects (http://www.solvaypharmaceuticals-us.com/static/wma/pdf/1/3/1/9/Marinol5000124ERev52003.pdf). The Sativex product monograph in Canada (http://www.bayerhealth.ca/display.cfm?Object_ID=272&Article_ID=121&expandMenu_ID=53&prevSubItem=5_52) suggests that patients taking it should not drive automobiles. Given that THC is the most active component affecting such abilities, and the low serum levels produced in Sativex therapy (vide supra), it would be logical that that patients may be able to safely engage in such activities after early dose titration and according to individual circumstances, much as suggested for oral dronabinol. This is particularly the case in view of a report by an expert panel (Grotenhermen et al 2005) that comprehensively analyzed cannabinoids and driving. It suggested scientific standards such as roadside sobriety tests, and THC serum levels of 7–10 ng/mL or less, as reasonable approaches to determine relative impairment. No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/mL of THC. Prior studies document that 4 rapid oromucosal sprays of Sativex (greater than the average single dose employed in therapy) produced serum levels well below this threshold (Russo 2006b). Sativex is now well established as a cannabinoid agent with minimal psychotropic effect.

Cannabinoids may offer significant "side benefits" beyond analgesia. These include anti-emetic effects, well established with THC, but additionally demonstrated for CBD (Pertwee 2005), the ability of THC and CBD to produce apoptosis in malignant cells and inhibit cancer-induced angiogenesis (Kogan 2005; Ligresti et al 2006), as well as the neuroprotective antioxidant properties of the two substances (Hampson et al 1998), and improvements in symptomatic insomnia (Russo et al 2007).

The degree to which cannabinoid analgesics will be adopted into adjunctive pain management practices currently remains to be determined. Data on Sativex use in Canada for the last reported 6-month period (January-July 2007) indicated that 81% of prescriptions issued for patients in that interval were refills (data on file, from Brogan Inc Rx Dynamics), thus indicating in some degree an acceptance of, and a desire to, continue such treatment. Given their multi-modality effects upon various nociceptive pathways, their adjunctive side benefits, the efficacy and safety profiles to date of specific preparations in advanced clinical trials, and the complementary mechanisms and advantages of their combination with opioid therapy, the future for cannabinoid therapeutics appears very bright, indeed.

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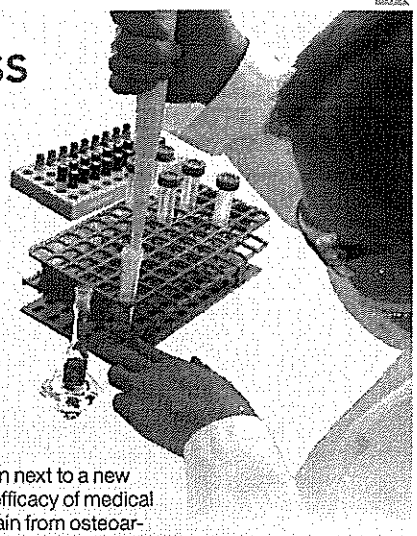
COMMERCIAL FEATURE

Scientific research shows the effectiveness of medical cannabis on pain



A growing body of scientific research is helping the medical community understand the effect of medical cannabis and cannabinoids (an active compound found in cannabis) on pain management. Dr. Mark Ware, director of clinical research, Alan Edwards Pain Management Unit, McGill University Health Centre, has been studying them since 1999.

While working at a pain clinic, a patient of the physician casually mentioned that he thought cannabis was helping manage his achiness. The doctor became interested in knowing more. He found from all the papers he read that they seemed to conclude with the same observation — clinical trials are needed.

The search for answers

"I was a researcher and clinician interested in pain research and complementary therapies that were patient-driven ways to treat pain outside the classic pharmacological model," he says. That provided the inspiration to study medical cannabis. "I'm interested in providing the data to assist physicians make informed decisions about its role in patient treatment."

In December 2015, the findings of researchers, including Dr. Ware, now an internationally acclaimed expert, were published in *The Journal of Pain*. In a large-scale study, 215 patients with chronic pain from seven clinics across Canada were dispensed cannabis with a standardized amount of delta-9-tetrahydrocannabinol or THC (12.5 percent) and monitored for a one-year period. It was the first and largest study of the long-term safety of cannabis. The data showed daily users had no greater risk of serious adverse effects than non-users.

In an earlier study designed by Dr. Ware and his team, published the *Canadian Medical Association Journal* in October 2010, the effectiveness of cannabis on patients with neuropathic pain was examined. The results supported claims that inhaled and properly dosed cannabis reduced pain, improved mood, and helped sleep.

This type of research is important for both patients and the medical community to have and to consider. "We need this data to make decisions. We believe that science can help," says Dr. Ware.

Some old attitudes and myths still prevail. Having scientific information is needed to address them. "It will take a generation or two for attitudes about cannabis to change. We've been so entrenched in the thinking that cannabis is a drug and it's bad. As we begin to know it more, we are realizing that it is a lot more nuanced and it has a wealth of potentially beneficial properties."

Dr. Ware is turning his attention next to a new study, looking at the safety and efficacy of medical cannabis among patients with pain from osteoarthritis of the knee. The CAPRI Trial will explore the effect of varying levels of THC and CBD, two active compounds in cannabis, on pain management in vaporized form. Currently, patients are being recruited for it in Montréal and Halifax. Results are expected in 2017.

It will take a generation or two for attitudes about cannabis to change.

How science helps

Studies like this will advance medical cannabis research in Canada and that's critical, according to Brent Zetti, President and CEO of Prairie Plant Systems Inc. and CanniMed Ltd., the first cannabis producer to be licensed under the new Marihuana for Medical Purposes Regulations (MMPR) enacted by the federal government in 2013.

"We've had an abundance of anecdotal evidence about the effectiveness of medical cannabis, but that's not enough, says Zetti. "Clinical research is critical because it gives the information needed to healthcare professionals so they can assess whether their patients would benefit from medical cannabis." He adds, "There is still so much we don't know about how it works. There are so many discoveries yet to come."

Clearly, the growing body of scientific evidence on medical cannabis is positive for physicians and patients alike.

SUPPORTED BY CANNIMED

Dr. Peter Fisher
Clinical Director, Royal London Hospital

A World-Renowned Doctor Battles for Freedom of Choice in Medicine

Dr. Peter Fisher, Clinical Director at the Royal London Hospital for Integrated Medicine and physician to Her Majesty, Queen Elizabeth II, discusses how patients can benefit from integrating homeopathic medicines into traditional healthcare.

Mediaplanet Where did your interest in homeopathy begin?

Dr. Peter Fisher I first got interested in homeopathy while I was a medical student at Cambridge University. I went to China and I remember being in the operating theatre of a small Chinese provincial town. They were practicing traditional medicine and I remember thinking: "They didn't tell us about that at Cambridge!" Soon after that, I was ill myself and I sent to see a distinguished professor at Cambridge who said: "Tough, nothing can be done." A friend suggested I try homeopathy, so I did. I treated myself initially and it worked.

MP What is homeopathy?

PF Homeopathy is a system of medicine that's based on the idea the body has powerful self-healing powers, but those powers don't always react appropriately. Homeopathic remedies inform the body's self-healing processes by giving the body information. About 60 percent of homeopathic medicine uses plants, but also uses other things, such as minerals and animal products.

MP How can patients benefit from integrating homeopathic medicines into traditional healthcare?

PF It's not uncommon to see patients who are on seven or eight drugs, and it's well-established that when you're on that many drugs, your chances of getting an adverse reaction are close to 100 percent, especially if you're older. So one thing is safety — homeopathy offers safer treatments.

MP What are your thoughts on freedom of choice in medicine?

PF As I wrote recently in a letter to the Canadian Minister of Health, Dr. Jane Philpott, there's plenty of evidence that homeopathy works, and it's safer and less expensive than conventional medicine. The fact is that people should be able to make their own decisions. Why assume the state knows best?

MP How is homeopathy used in other countries?

PF It's fantastically popular in India, and it's very widely used in many parts of Western Europe.

In the United States, 50 percent of plastic surgeons use homeopathic Arnica in nose jobs because it improves the rate of healing. It has no side-effects and no drug interactions. ●

sleep (hours) and quality of sleep (Good, Fair, Poor) were recorded for each night. Appetite, bowel function, bladder function and activity levels were also monitored.

Patients were fully briefed on the possible psychoactive side-effects and the likely seven most common were identified in the diary. These were presented in the form of the question: "Throughout the day have you experienced any of the following (please tick): Dry mouth, Time distortion, Dizziness, Panic/anxiety attacks, Drowsiness, 'High'/'Strange' feeling, Hallucinations". Patients were also asked to record any other side-effects or new symptoms that they experienced whether or not they felt this was associated with the medication. No attempt was made to investigate tolerance, dependency or other longer-term psychiatric effects.

The use of concomitant medication was monitored. Patients were asked not to change their regular medication without prior discussion with the research team. The maintenance of a constant pharmacological background was considered important. Non-cannabinoid medication for breakthrough pain was allowed and documented. However, by definition, most patients were getting very little benefit from their previously prescribed medication.

Cannabinoid administration

The patients underwent 4-h dosing sessions at the hospital (Fig. 1) whenever a new CBME was introduced. Initially, one spray was given every 15 min. This interval had been determined from studies of the use of the spray in healthy volunteers. This interval was changed to 30 min after the first six patients had been studied.

Throughout these titrations, vital signs and side-effects were monitored at regular intervals. Tests of psychomotor and cognitive function were performed before the start and after 3 h (Trail Making Tests A & B [17], Adult Memory and Information Processing Battery (AMIPB) [18]).

At the end of 4 h, patients had received between two and four sprays (two and eight sprays for the first six patients), depending on their response (effects and side-effects). The patients were then discharged home with a relative if in a clinically satisfactory state. They were given a supply of the test CBME. During the initial 2-week run-in period patients were contacted daily for 7 days or longer (as necessary). At all times, a member of the team was available for contact in an emergency, to answer questions, etc.

Data analysis

This study was primarily observational and each patient's data were evaluated individually. The use of placebo and blinding was to provide greater rigour to the observational data. Data from the individual 'N of 1' studies have been aggregated to give an indication of the scale of the benefits seen, the occurrence of side-effects, etc. Similarly a comparison of the effectiveness of the three CBMEs and placebo was undertaken.

Where clinical benefit could be shown for individual patients, they were offered the opportunity to continue into a long-term safety extension study (CBME SAFEX). It had been a requirement of the Local Research Ethics Committee for the patients to be able to continue treatment unless clinical, pharmaceutical or regulatory requirements deemed otherwise.

Results

Patients

A total of 34 patients were studied. Demographic details, underlying diagnosis, main problem symptoms, and previous medicinal use of cannabis are shown in Table 1. The high number of female patients reflected the prevalence of multiple sclerosis. The patients have been grouped for analysis (Fig. 2).

Only seven patients used THC : CBD as rescue medication during the crossover part of the study (Group CRM). Therefore data from these patients have only been included for the assessment of the run-in periods. The first two patients had inadequate data from the baseline period.

Out of the total of 34, 24 patients completed the crossover period without cannabinoid rescue medication (Group NoRM) (Fig. 2). They provide the comparative information on effects and side-effects.

One patient, who experienced a vasovagal episode, continued single-blind without the THC periods for the remainder of the crossover period. Therefore only data on dosage used are included (Table 2).

Two patients were withdrawn from the study (Table 2). One failed to tolerate the THC : CBD at the lowest dose during the run-in and the other could not cope with the study requirements.

Dose titration sessions

The initial rate of titration was too rapid for two of the first six patients who developed dysphoria and lightheadedness. Both recovered fully over the following 2 h. Subsequently, the interval between sprays was changed from 15 to 30 min. This gave the patients adequate opportunity to terminate their titration safely if they started to experience side-effects.

The tests of psychomotor and cognitive function (Trail Tests and AMIPB) yielded unexpectedly equivocal results, requiring a more detailed analysis than planned. There were often improvements in performance after CBME [19]. Therefore the results will be presented separately.

Table 1 Patient details.

No.	Sex	Age	Diagnosis	Years	Site of pain/ symptom (S1)	Site of pain/ symptom (S2)	Prev cann. use*	Rescue CBME**	Global outcome***
1	M	51	MS	12	Lumbar pain	Leg spasms	3	CRM	2
2	M	43	Spinal cord tethering, laminectomy	13	Low lumbar pain	Posterior leg pain (L)	3	CRM	3
3	F	58	MS	6	Thigh pain (L) & spasms	Hip pain (L)	2	CRM	3
4	M	55	Low back, sciatica, post laminectomy	36	Lumbar pain	Posterior leg pain (B)	3	CRM	2
5	F	53	MS	11	Whole leg pain	Neck, arm (L) pain	2	CRM	2
6	F	52	MS	15	Knee pain (B)	Head, face (L)pain	1	CRM	0
7	F	33	Disc degeneration, laminotomy × 2	3.5	Posterior thigh (R)	Low back pain	0	NoRM	1
8	F	44	MS, post cystectomy, ileostomy	18	Urethral pain	Pelvic floor pain	1	NoRM	3
9	F	51	MS	7	Thigh (L), lower legs pain	Chest tightness	N	None	X
10	F	50	MS	1.5	Leg pain (R)	Right leg spasm	1	None	X
11	F	53	Spinal fusion	18	Posterior leg pain (B)	Low back pain	2	NoRM	3
12	F	55	MS	10	Lower leg pain	Lumbar pain	0	NoRM	0
13	F	32	Degenerative Disc, post laminotomy	6	Leg (B) pain	Back pain	0	NoRM	2
14	M	64	Paraplegia, AV malformation of cord	10	Leg pain (B)	Foot (R) stabbing pain	1	NoRM	2
15	F	46	MS	13	Leg pain	Sacro-iliac pain	0	None	3
16	M	41	MS	10	Leg spasms	Bladder urgency	1	NoRM	3
17	F	41	MS	23	Leg spasms	Hip pain (R)	1	NoRM	2
18	M	50	Brachial Plexus Avulsion injury	14	Arm (R) aching pain	Arm, shooting pains	0	NoRM	1
19	M	48	Femoral Plexopathy from phenol inj.	7	Lumbar pain	Leg, scrotum (L) pain	2	NoRM	2
20	F	30	Laminectomy L1-5 × 2	9	Lumbar pain	Leg (L) pain	0	NoRM	1
21	F	46	MS	3	Retro-orbital pain (B)	Arm (R) pain	1	NoRM	3
22	M	53	MS	4	Legs spasticity	Leg (B) pain	1	NoRM	1
23	M	48	Myopathy	4	Leg (B) pain	Upper arms	3	NoRM	2
24	F	35	CRPS1 post ankle trauma	9	Ankle (R) aching pain	Ankle (R) stabbing pain	0	NoRM	1
25	F	26	CRPS1	4	Neck, arm ache	Neck, scapula shooting pain	N	NoRM	1
26	F	41	Polyarthralgia	20	Spinal pain	Knee pain (B)	2	NoRM	0
27	F	26	Disc degeneration, post discectomy	5.5	Lumbar pain	Posterior leg pain (L)	0	NoRM	1
28	F	47	MS	7	Neck, thorax pain	Arm pain (R)	0	NoRM	2
29	F	56	Radiculopathy, cervical fusion	11	Arms, C5-8 pain	Inter-scapular pain	0	NoRM	2
30	F	44	Diffuse systemic Atrophy	11	Jaw pain	Tremor in limbs	2	NoRM	2
31	F	50	MS	10	Neck pain	Lower leg pain (B)	0	NoRM	2
32	F	66	MS	3	Leg pain (B)	Hand pain (B)	0	NoRM	0
33	M	62	Massive Trauma Left Arm	26	Lateral forearm pain (L)	Wrist allodynia (L)	1	NoRM	1
34	M	38	Stiff Man Syndrome	15	Hands, wrists pain	Buttocks, hips pain	3	CRM	2

MS = Multiple Sclerosis; CRPS = Complex Regional Pain Syndrome; R = Right; L = Left; B = Bilateral.
*Previous medicinal cannabis use: 3 = frequent, 2 = sometimes, 1 = occasional, 0 = none, N = nabilone.
**Rescue CBME: CRM = Rescue CBME group; NoRM = No Rescue CBME group; None = others.
***Global Outcome: 3 – Substantial; 2 – Moderate; 1 – Some; 0 – No Benefit; X – Didn't complete.

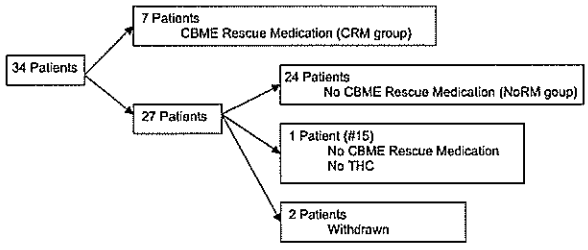


Figure 2 The progress of the 34 patients through the study.

Run-in period symptom control

The two main symptoms (S1, S2) were measured (VAS) at the start and at completion of the 2-week run-in period for all 34 patients. The scores were aggregated and the median and interquartile ranges are shown (Fig. 3). Sixteen of the 34 patients had a decrease in VAS of greater than 50% for either S1 or S2. Of these, 10 patients had a greater than 50% reduction in VAS for both S1 and S2.

Of the 34 patients, 32 recorded the VAS of S1 and S2 at midday on each day of the baseline and run-in periods (2 weeks each). The results have been aggregated (Fig. 4) and the median and interquartile range presented.

Crossover period symptom control

During the crossover period, the cumulative S1 scores for 24 patients in group NoRM measured three times/day (median (interquartile range)) were placebo 5.9 (2.8–7.3), CBD 5.45 (3.6–7.4), THC 4.63 (1.74–6.06) and THC : CBD 4.4 (2.6–5.8). ($p < 0.001$, overall test for significance, Friedman). THC : CBD and THC were

Table 2 Details of the patients who either failed to complete the study or for whom the randomization code was broken.

Patient ID	Reason
#9	Very frail from MS. Could not tolerate the lowest dose of the spray during the open-label period and became too sedated. She was withdrawn at this point.
#10	Travel to the study centre was too distressing for her. 3 weeks into the crossover part of the study she was withdrawn. The randomization was broken. There had been no evidence of benefit during the crossover period.
#15	She experienced a vasovagal episode during titration with THC. Her vital signs had been checked 10 min previously and reflected the pre-dosing results. She recovered uneventfully and was able to return home about 2 h later. The THC periods of the crossover period were omitted and she continued single-blind.
#19	He became very depressed and distressed towards the end of the crossover period having had no benefit for 5 weeks following initial success. Breaking the randomization code it was discovered that only the THC : CBD period had been beneficial. He continued the last 2 weeks single-blind, which included the second THC : CBD period. Later we learned that he was on the verge of divorcing his wife who had a psychiatric disorder, coincidental to the study.
#32	She had an episode of abdominal pain and vomiting in week 2 of the crossover period. Randomization was broken. A diagnosis of gastroenteritis was made. A break from the medication was allowed and she then continued single-blind.

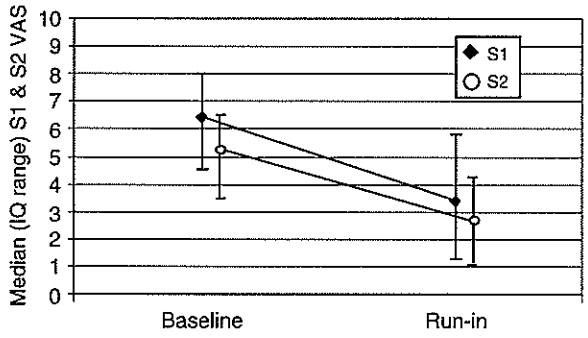


Figure 3 Change in median (interquartile range) VAS for symptom S1 & S2 recorded at the start (baseline) and at completion of the 2-week run-in period for 34 patients with open-label THC : CBD.

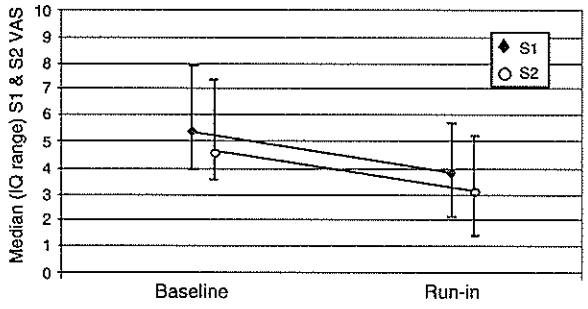


Figure 4 Change in median VAS recorded in the daily diaries at noon for symptom (S1 & S2) & (interquartile range) during 2 weeks base-line period and 2 weeks open-label THC : CBD (Patients #3 to #34).

both significantly better than placebo ($p < 0.05$ and $p < 0.01$, Wilcoxon with Bonferroni correction) (Fig. 5).

Similarly, the S2 scores (median (interquartile range)) for placebo, CBD, THC and THC : CBD were 4.98 (2.61–7.50), 5.03 (3.16–6.88), 4.08 (1.33–5.43) and 4.28 (2.33–5.51), respectively ($p < 0.001$ overall test for significance, Friedman). THC and THC : CBD were significantly better than placebo ($p < 0.001$ and $p = 0.054$, Wilcoxon with Bonferroni correction).

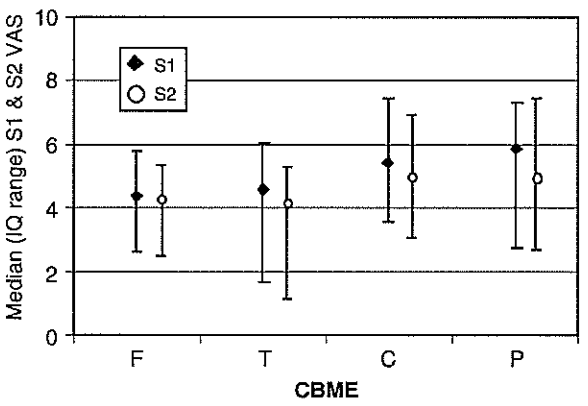


Figure 5 Crossover period aggregated symptom S1 and S2 VAS measured 3 times/day (median, (interquartile range)) for the four pairs of weeks for each CBME and placebo. F = THC : CBD; T = THC; C = CBD; P = Placebo.

Of these 24 patients, nine had a decrease in VAS of more than 50% for either S1 or S2 when using one of the three active preparations, compared with placebo. All nine experienced this with THC and/or THC : CBD. Of these, three patients also achieved this reduction with CBD.

Effectiveness of medication in comparison with run-in THC : CBD

At the weekly visit the patients were asked to compare their current test medication with the THC : CBD received during the initial run-in period of the study. Fourteen of 24 patients in group NoRM found the

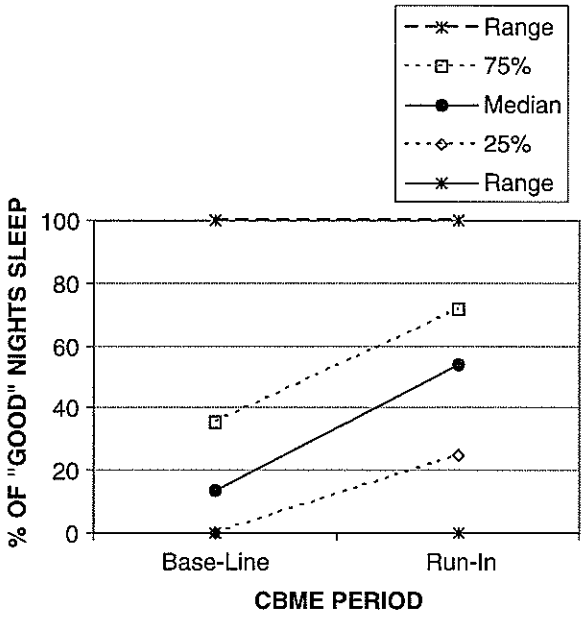


Figure 6 Percentage of nights when sleep was of "good" quality for 32 patients (#3 to #34) comparing the 14-day baseline and run-in periods (median, interquartile range, range).

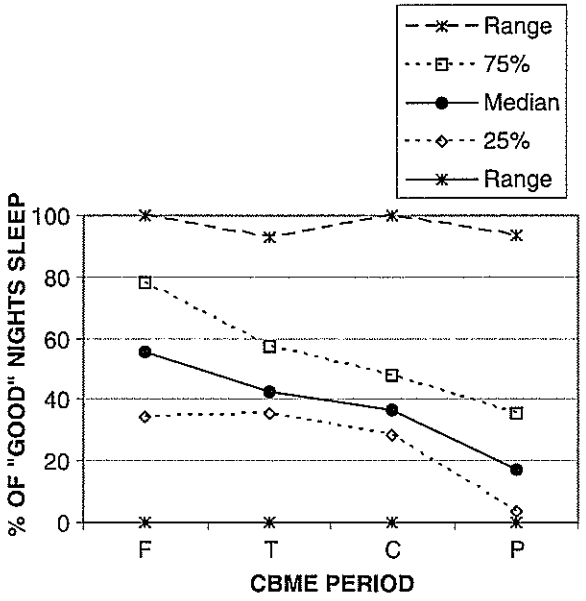


Figure 7 Percentage of nights when sleep was of "good" quality for 24 patients (Group NoRM) comparing the 14 days of each CBME used during the crossover periods (median, interquartile range, range).

THC : CBD (nine patients) and/or the THC (eight patients) as equal or more effective for symptom control. Four of these patients also found CBD as effective as the original medication. No patient found the placebo as effective as the original medication.

Quality of sleep

The percentage of nights that each patient described as 'good quality sleep' were compared for the baseline and the run-in periods. The results from 32 of 34 patients are presented (median, IQR, range). The median (IQR) rose from 13.4% (35.7, 0) to 53.5% (71.4, 25) (Fig. 6).

Similarly. the percentage of 'good' nights was calculated for the 24 patients of group NoRM for the crossover part of the study, comparing the three different CBMEs and placebo (median, IQR, range). (Fig. 7). The median (IQR) for THC : CBD was 55.4% (78, 34.5), for THC was 42.9% (57.2, 35.7), for CBD was 36.9% (47.9, 28.6), and for placebo 17.0% (35.7, 3.6). ($p < 0.001$ overall test for significance, Friedman). THC : CBD, THC and CBD were all significantly better than placebo ($p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively, Wilcoxon with Bonferroni correction).

Duration of sleep

The duration of sleep for each of the 24 patients in group NoRM for each of the CBMEs and placebo during the crossover part of the study was calculated. The mean (SD)

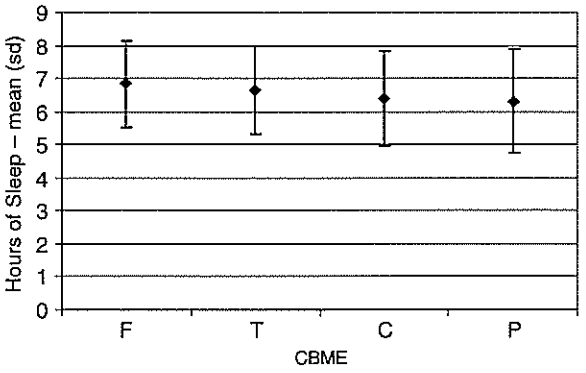


Figure 8 Duration of sleep in hours (mean, SD) for 24 patients (Group NoRM) comparing the 14 days of each CBME used during the crossover periods. F = THC : CBD; T = THC; C = CBD; P = Placebo.

sleep duration in hours for THC : CBD, THC, CBD and placebo were 6.8 (1.3), 6.7 (1.3), 6.4 (1.4) and 6.3 (1.6), respectively (Fig. 8).

General Health Questionnaire 28 (GHQ28)

The GHQ28 assesses the patient's health in general over the preceding few weeks. It has four components (Somatic Symptoms, Anxiety & Insomnia, Social Dysfunction, Severe Depression) and it is recognised that these are not independent of each other. The lower the

Table 3 Median values (interquartile range [range]) of the four elements, the total score and the caseness of the GHQ28 and of the BDI at the start, the end of the run-in and at the end of the study.

General Health Questionnaire (GHQ28)							
Period	Somatic Symptoms	Anxiety & Insomnia	Social Dysfunction	Severe Depression	Total (Maximum 84)	Caseness	BDI
Baseline	8.5 (13,4.5 [19,2])	9 (11.5,5.5 [18,1])	9 (13.5,7.5 [18,1])	3 (12,1 [20,0])	36 (44,23 [69,11])	13 (17,5 [25,0])	16 (26.7,9.7 [42,3])
End of Run-In	5 (6,4 [10,0])	5 (8,2 [9,0])	7 (8,5.5 [11,1])	1 (6.5,0 [10,0])	18 (26,13 [36,8])	2 (6,1 [9,0])	7 (16.25,5 [43,0])
End of Study	6 (7.5,5 [14,1])	7 (8,4 [13,0])	7 (9.5,5.5 [17,0])	1.5 (6.5,0 [12,0])	24.5 (31.5,16.5 [41,2])	4 (10,0.5 [14,0])	8 (20,4.75 [42,0])

score, the 'healthier' the patient. The median scores (interquartile range [range]) for the 24 patients in group NoRM measured at the start, at the end of the run-in period and at the end of the study are shown (Table 3). The 'Caseness', derived from the patient's score, is an indication of psychological/psychiatric disturbance.

Depression

For the 24 patients in group NoRM, the median (IQR) of the BDI score measured at the start, at the end of the run-in period and at completion of the study are shown (Table 3). Fourteen patients changed the severity of their depression between the start and the end of the study. Seven patients moderate → mild; three patients moderate → minimal; two patients severe → moderate; one patient severe → mild; one patient minimal → mild. [BDI score: Minimal 0–9, Mild 10–16, Moderate 17–29, Severe 30–63].

Daily intake of CBME

At the start of the run-in period each of the patients titrated themselves to their optimum dose over a period of several days. The amount was partly determined by the onset of side-effects and partly the improvement in symptoms. During the crossover period the patients reached their optimum dose more quickly.

The two patients who used six or more sprays as a single dose found it difficult to retain sublingually because of salivation. This caused some of the CBME to be swallowed, theoretically altering the absorption profile. Across the 34 patients there was a range of use of between one and eight sprays as a single dose.

For 25 patients (Group NoRM + patient #15), the average daily intake of CBME for the last 4 days of the run-in and each pair of CBME treatment weeks during the crossover period was calculated (median, IQR, range) (Fig. 9). This assumed a level of stability in the dose used towards the end of each week.

Side-effects

In their daily diaries the patients recorded episodes of the seven specified side-effects. For 24 patients (Group NoRM) the number of days on which the three commonest side-effects occurred during the run-in period and the 2 weeks of use of each CBME and placebo during crossover are shown (Fig. 10). Unfortunately data on the incidence of the designated side-effects (e.g. dry mouth, drowsiness) during the baseline period was substantially incomplete due to an error in data collection and is not presented.

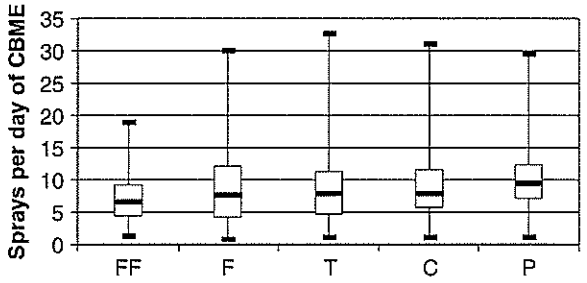


Figure 9 Box and whisker plot of the median (interquartile range, range) number of sprays/day used by 25 patients (Group NoRM + patient #15). The last 4 days of the run-in period and the last 4 days of each of the pairs of weeks of each CBME were averaged. FF = Run-In THC:CBD; F = THC : CBD; T = THC; C = CBD; P = Placebo.

Drowsiness and euphoria/dysphoria ('high') were common in the first 2 weeks of the run-in period while patients tried to find an appropriate dose and were more frequent with CBMEs containing THC. Dizziness followed a similar pattern but was less of a problem. Episodes of panic and anxiety were infrequent. They were commonest during the run-in period and not exclusive to those who were cannabinoid naïve. Time distortion was infrequent but occurred with CBMEs containing THC. Hallucination was recorded by only one patient and was not reported as severe.

The most common symptom that patients complained of was a dry mouth (Fig. 10). However, most patients were taking other medications which could contribute to this, indicated by the high occurrence when using placebo.

Some patients experienced a stinging sensation on use of the spray, particularly with the initial formulation. Many did not like the taste. No sublingual mucosal changes were observed.

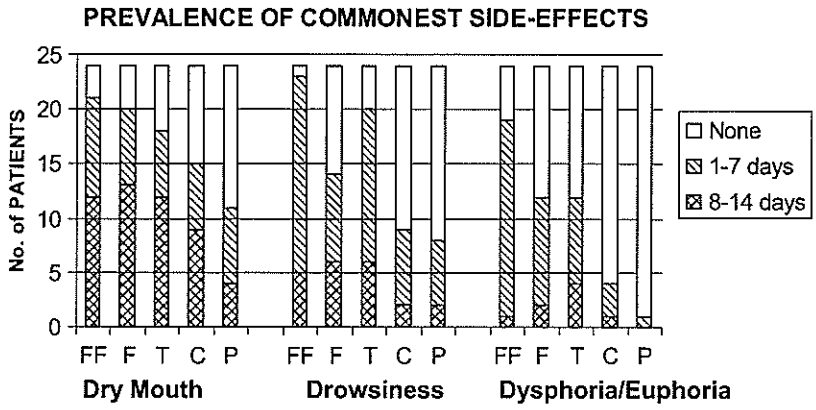


Figure 10 Prevalence of daily episodes of dry mouth, drowsiness and dysphoria/euphoria ("high") during run-in (14 days) and crossover periods (7 + 7 days). None = No episodes. 1–7 days = Episodes on <51% of days. 8–14 days = Episodes on >50% of days. FF = Run-In THC : CBD; F = THC : CBD; T = THC; C = CBD; P = Placebo.

Patient #15 had a vasovagal episode during a dosing session. It occurred 1 h after the third spray when using THC for the first time (as revealed on immediate unblinding) (Table 2). The reaction was probably due to a combination of prolonged sitting and excessive dosing. No other cardiovascular side-effects were observed for any patients.

A change in neural function was observed in two patients who had had previous spinal surgery. One had a return of an absent ankle reflex (patient #11). The second (patient #2) discovered that touch sensation reappeared in a previously anaesthetic fifth lumbar dermatome. He also found that his ability to maintain an erection was dramatically improved, leading to the accidental pregnancy of his partner and birth of a daughter.

No other side-effects related to the use of CBME emerged during the study.

The patients were weighed at the beginning and the end of the study in normal clothing. The median change in weight for 27 of 34 patients (interquartile range [range]) was 0.5 kg (−2 to 0.6 kg [−5.6 to 4 kg]). Of the remaining seven, two patients terminated the study early, one patient was paraplegic and unweighable, and data were unrecorded on four.

Full blood count, urea and electrolytes and liver function tests remained within normal limits for 33 patients. One patient had transient changes in alanine transaminase and alkaline phosphatase which may have been related to the use of erythromycin for a vaginal abscess.

During the 3 months of the study, other events occurred which were unassociated with CBME but would be likely to have an effect on outcomes (significant marital disharmony (two), husband made redundant (one), wife undergoing chemotherapy (one), pregnancy and misdiagnosis of a major genetic abnormality (one), flare up of MS (one), other (two)). The randomization was broken for two patients and both continued single-blind (Table 2).

Preferences

The 28 patients who obtained benefit were asked which CBME they had preferred. Eleven preferred THC : CBD; 14 found THC and THC : CBD equally satisfactory; two preferred THC; and one found THC and CBD equally satisfactory.

At the end of each individual study the senior clinician made a clinical assessment of the overall benefit for each patient to decide on progression to the safety extension study. This subjective assessment included the control of symptoms S1 and S2 and other identified symptoms, sleep, mood and GHQ28 (Table 1).

Discussion

This was the first clinical study of both the use of CBMEs and of their delivery via the sublingual route. The objectives were to obtain an initial indication of the efficacy, safety and tolerability. We had no firm knowledge of the extent of the therapeutic effect, the likely dose range, the frequency and pattern of administration, the incidence of and threshold for side-effects or the tolerability of the CBME spray.

Designing the study

In designing the study six major factors were taken into consideration.

1 Chronic pain is a heterogeneous problem with multiple and variable pathophysiological mechanisms coexisting in the patient and varying over time. Different mechanisms for pain genesis probably exist within a single clinical diagnostic group, leading to the need for different treatment strategies [20,21].

2 There has been a pressure to use cannabinoids in patients for whom all other therapy has failed. These are usually the most difficult and complex patients to study.

3 The effect of cannabinoids on pain is likely to be at variable sites in the nervous system ranging from the peripheral neurone to the cerebral cortex.
4 Previous and current therapy is usually heterogeneous.
5 Differences between healthy volunteers and patients in side-effect profile were anticipated.
6 Differences in therapeutic dose, effect and in side-effect profile between patients were expected, as seen with morphine and many other psycho-active drugs.

For multiple sclerosis (MS), the aetiology of the pain may be central neuropathic, somatic muscle spasm and spasticity, visceral muscle spasm (e.g. bladder), mechanical (spinal), mechanical (immobility) or even unrelated to MS. The pain may be markedly aggravated by psycho-social factors such as depression, immobility, employment loss, burden on the family and variable progression of the disease. To these must be added the effects of a variety of other problems including defects of vision, co-ordination, strength, sensation, bladder control, and sexual function.

There were three specific reasons for focussing on patients with MS. Firstly, there is extensive anecdotal evidence of the benefits of illicit cannabis for symptom control in this disease. Secondly, there is a perception that cannabinoids should be used for treating neuropathic pain, although there is no strong evidence to support this opinion. We therefore saw no reason to exclude others with a variety of other intractable pain problems. All patients exhibited multiple pains of nociceptive, neuropathic and/or uncertain pathophysiology. Two patients nominated a symptom that was not specifically painful (tremor, bladder urgency). Third, it was expedient to focus on this group to obtain agreement to initiate studies of CBMEs. However, choosing the most intractable problems for the clinical trial of a new drug for pain is far from ideal.

With all these difficulties we decided that a classical parallel or crossover group study was inappropriate [22]. We opted to use an 'N of 1' approach, which has been described as a developer's tool and has been recommended for studying new therapy in chronic pain [23,24] and cannabinoids [7]. The method has already been used by others for the study of the medicinal use of cannabinoids in individuals [25,26].

The patients are studied as individuals but with the rigour of double-blind placebo controlled crossover techniques. Each individual patient study stands by itself and indeed is much closer to everyday clinical practice than is the classical parallel trial of a new pharmacological treatment. It allows both for the heterogeneity of patients and their varied responses. The capture of data can be individualised, allowing a variety of endpoints. Variable dosing patterns are acceptable, enabling the patients to individually customise their usage to different endpoints.

Comparisons of results across groups of patients cannot reach the same level of statistical significance as with homogeneous, parallel group studies. Therefore the analyses undertaken are an attempt to summarise some of the data from the 34 individual studies. Furthermore, the patients were desperate to participate in the study because of the failure of past symptom control. The attention from the study team further complicates the evaluation. It was not surprising that all but one patient could show some benefit at the end of the run-in period. Therefore the data only allows for generalizations to be drawn, thereby providing information for individual clinical practice and for the design of future and more focussed studies.

The progress of patients in a 'steady state' in the subsequent extension study will complement the information given here (paper in preparation). Future studies might give tighter indications of the likely success of CBMEs in treating the specific symptoms of specific diseases, although we are still far from being able to predict accurately the outcome of most therapy in chronic pain.

The 1-week periods of the crossover part were too short. However, periods of 2 weeks or more would have extended this study unacceptably. Alternatively, we could have eliminated one or more CBMEs. However, as we had no hard evidence on the optimum CBME, we compromised. We did not include washout periods, as cannabinoids have a long half-life in the body even though their clinical effect may only last a few hours.

Dosing

Although healthy volunteers in the Phase 1 studies could tolerate titration at 15-min intervals, our patients proved different. This vindicated our use, at the beginning of the study, of patients who had previous experience of medicinal cannabis use.

In general, patients initially titrated to the limit of tolerability (drowsiness, dysphoria) rather than benefit. The tests of psychomotor and cognitive function served mainly as a reassurance for discharging the patients home (19). The wide range of dosage parallels that seen with morphine and many other psycho-active drugs.

As the study progressed, the instructions for home usage of the CBMEs evolved. Because of our concerns over safety, we instructed patients to initially use, as a single dose, 30–50% less than they had received during the titration session. They were allowed to use the CBME up to 6 times per day, as required. Over the days, the patients' dosage and pattern of use was customised to their need from their response. For example, some might

prefer a higher dose at night. With experience and confidence, the patients quickly moved to their optimum dosing schedule.

Pain and other symptoms

No attempt has been made to analyse effects of the CBME on specific pain symptoms. The VAS scores do not differentiate between improvements due to direct effects on neural pathways, effects on sleep and mood, and the benefit of the supportive environment of the study. Equally some patients found the study tiring, tedious and frustrating, whilst others experienced domestic upheavals etc.

The overall trends seen with the use of THC and THC : CBD were encouraging. We anticipated that CBD would have little effect by itself in this study, but it may have other therapeutic roles, particularly in inflammatory pain [14,27].

All eight patients with residual pain associated with the failure of spinal surgery obtained benefit and this is an exciting prospect for further study in this notoriously difficult group to treat.

Sleep and mood

The CBME seemed to have little effect on the recorded number of hours of sleep. However, the change in quality from 'poor' or 'fair' to 'good' was unexpectedly high. The quality of sleep is a subjective global assessment and includes duration, depth and disturbance. It is more important for the patient than duration alone. Others have analysed nocturia [15] and shown a reduction in its frequency with the use of THC. The effects of CBMEs on sleep may prove to be one of the major benefits of the use of cannabinoids in chronic pain and MS.

The GHQ28 indicated that the use of CBME had had a broad effect even though it was only applied on three occasions across the study. The changes in the 'Caseness' of the GHQ28 and in the BDI show valuable improvement in mood.

Side-effects

The psycho-active side-effects of cannabinoids are the main focus of objection to this group of drugs. We specifically targetted the common acute side-effects by recording their daily occurrence. Whilst we did not measure intensity or duration directly, the daily occurrence gives an indication of prevalence (Fig. 10).

Patients were free to record any other perceived effects. However, except for the oral effects of the spray itself, no other side-effects emerged.

In general, the side-effects were manageable, tolerable and similar to those seen clinically with most other psycho-active drugs used in pain management. They were most prevalent during the run-in period as patients learnt to titrate themselves to an appropriate level. Realistically, the weekly periods of the study were too short to allow time for the patients to fully customise their use and their side-effect management.

Drowsiness and dizziness induced by the CBMEs were common, but manageable for all but one patient (Table 2). It was used to positive advantage at night time to improve sleep (as with tricyclic antidepressants, morphine, etc.).

Dysphoria and mild euphoria were common during the run-in period. Some patients were pleased to experience a feeling of relaxation and well-being, especially if they had had a bad day with pain. Some found the distancing effect beneficial. However, no patient wanted to exchange the disabling effect of chronic pain for that of immobility from being dysphoric/euphoric.

At the start of the study and before the dose titration sessions, the patients were briefed about the possibility of panic attacks. We had no information about their incidence or at what point they might appear. No severe panic attacks occurred, although some became anxious at the onset of dysphoria. It may be that these are primarily a feature of uncontrolled dosing, particularly in the novice recreational user.

A dry mouth was a common oral problem. However, many patients were using other drugs which could contribute to this effect. No specific oral lesions were seen, although they have occurred in patients in other studies (GW Pharmaceuticals).

Cannabis is known to stimulate appetite. However, only one patient showed a substantial increase in weight. The loss of 5.6 kg by another probably reflected substantial marital disharmony.

Preferences

The initial open-label titration with THC : CBD proved to be a guide to the optimum dose of THC. Although CBD and placebo had limited effect, patients did not titrate themselves much further than they had with the original THC : CBD. Prior to the study we had expected to find that the THC : CBD mixture would be optimal, that we would see more side-effects with THC, and that CBD alone would be almost ineffective. Whilst there was a preference for THC:CBD, the differences were not as marked as we anticipated. The lack of effect of CBD by itself may just reflect either the narrow range of pain problems studied and/or the need for a substantially higher dose of CBD.

In conclusion, this study has been a first step in gaining confidence in the use of CBMEs. THC and THC : CBD were effective in relieving pain and improving sleep in a

small group of patients. As experience was gained in dosing, the spray proved easy and convenient for the patients to use. They were able to medicate in public without attracting unwelcome attention from others. Side-effects were not substantially different to those seen with most other psycho-active drugs used in pain management.

Studying CBMEs in patients with a wider variety of pain problems, exploring specific areas, and deepening the clinical experience are the next steps. The potential uses in a variety of other, non-pain areas (neuro-protection, psychiatric disease, tumour therapy, inflammation, AIDS, etc.) are exciting prospects for the future now that we have some confidence and experience in the use of these materials.

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