State of New Jersey
Department of Human Services
Division of Medical Assistance & Health Services
New Jersey Drug Utilization Review Board

NEWSLETTER

Volume 01, No. 08 **November 2013**

TO: Physicians, Advanced Practice Nurses, Midwives, Independent Clinics, Hospital Outpatient Departments **– For Action**
Providers of Pharmaceutical Services, Health Maintenance Organizations **– For Information Only**

SUBJECT: **Clinical News from the New Jersey Drug Utilization Review Board (NJDURB)**

PURPOSE: To provide practitioners useful clinical information that may be helpful for the prescribing of prescription drugs

BACKGROUND: The New Jersey Drug Utilization Review Board (NJDURB) serves as an advisory board to the New Jersey Department of Human Services and the New Jersey Department of Health and Senior Services. The Board's responsibilities include recommending drug utilization review (DUR) standards based, in part, on evaluations of prescription drug use by beneficiaries that participate in the State's pharmacy benefit programs. The Board is also responsible for disseminating information that the Board has determined would encourage appropriate drug utilization.

ACTION: Attached is a bulletin regarding ***Treatment Options for Type 2 Diabetes***. This bulletin may also be viewed on line at http://www.nj.gov/human services/dmahs/durb.html. The NJDURB welcomes your comments regarding the information shared in the bulletin. These comments may be sent to www.state.nj.us/humanservices/dmahs/durb.html. When submitting comments, please include the phrase "DURB Comments" in the subject area of the email.

RETAIN THIS NEWSLETTER FOR FUTURE REFERENCE

TREATMENT OPTIONS FOR TYPE 2 DIABETES

June 2013

BACKGROUND

According to the U.S. Department of Health and Human Services' National Diabetes Statistics, 2011, there are nearly 26 million Americans with diabetes. Every year, 1.9 million are diagnosed with type 2 diabetes.[1] This type of diabetes consists of an array of dysfunctions characterized by hyperglycemia resulting from the combination of resistance to insulin action, inadequate insulin secretion and excessive or inappropriate glucagon secretion.[3] Type 2 diabetes is a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations. It is also associated with obesity, hypertension, and hypercholesterolemia as well as increased risk of cancer, serious psychiatric illness, cognitive decline, chronic liver disease, accelerated arthritis, and other disabling or deadly conditions. Effective management strategies are of obvious importance.[4]

TYPE 2 DIABETES IS A LEADING CAUSE OF CARDIOVASCULAR DISORDERS, BLINDNESS, END-STAGE RENAL FAILURE…

TREATMENT GOALS

The goal of glycemic control is to both prevent acute, symptomatic hyperglycemia and prevent the development of long-term microvascular and macrovascular complications related to chronic hyperglycemia and hypertension.[5] There are several treatment guidelines offered by different organizations for the treatment of type 2 diabetes. One set is published by the American Diabetes Association (ADA) in collaboration with the European Association for the Study of Diabetes (EASD)[4]; the other is by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE).[2,6] While these two sets of guidelines promote similar principles, they differ in some areas. (Table 1). For example, the ADA recommends hemoglobin A1C (A1C) goal of <7 percent or a more stringent target (6.0-6.5%) in certain disease states, if this can be achieved without significant hypoglycemia. The AACE/ACE on the other hand (2013) recommends A1C goal of ≤6.5 for healthy patients without concurrent illness and at low hypoglycemic risk, and A1C >6.5% for patients with concurrent illness and at risk for hypoglycemia.[11]

Table 1: Recommendations for Glycemic Control in Type 2 Diabetes in Adults (**see note for geriatric patients****)

	ADA	**AACE**
A1C (%)	<7*	≤6.5
Fasting (preprandial) plasma glucose	<130 mg/dL	<110 mg/dL
Two-hour postprandial plasma glucose	<180 mg/dL	<140 mg/dL

*6.0 – 6.5 in certain selected patients

**** American Geriatric Society recommends not using medications to achieve A1C <7.5% in adults >65 years olds.**

American Diabetes Association. *Diabetes Care* . 2013;36S1

AACE Diabetes Guidelines – *Endocr Pract. 2011;17S2*

The AACE/ACE and ADA/EASD have published their own algorithm for treating this patient population. The AACE/ACE treatment algorithm (Figure 1) stratifies patients by their current A1C level and approaches treatment on 3 categories: A1C <7.5%, A1C ≥7.5, and A1C > 9% (May 2013).[11] The ADA guideline is divided into two different tiers: tier 1 includes well-validated core therapies, while tier 2 includes less established therapies[4].

TREATMENT OPTIONS

Eleven classes of drugs are approved by the U.S. Food and Drug Administration (FDA), for the treatment of type 2 diabetes. Table 2 provides a summary of some of these products, their mechanisms of action and expected A1C reduction rates.

Table 2: Classes of Drugs Used in Type 2 Diabetes

Class	Example(s) of Medication	Mechanism of Action	Common Adverse Effects**	Usual Dosing/route	Expected A1C reduction **
Alpha-Glucose Inhibitors (AGI)	Miglitol (Glyset), acarbose (Precose)	Delays absorption and glucose production	Gas, bloating, diarrhea	3 times daily (oral)	0.5 - 0.8%
Amylin agonists	Pramlintide (Symlin)	Controls postprandial blood glucose	Hypoglycemia, nausea	3 times daily (inj)	0.5 – 1%
Biguanides	Metformin (Glucophage)	Lowers plasma glucose	Nausea, lactic acidosis	2 to 3 times daily, XR once daily (oral)	1 - 2%
Dipeptidyl-peptidase-4 Inhibitors (DPP-4)	Sitagliptin (Januvia), Saxagliptin (Onglyza) Linagliptin (Tradjenta)	Increases insulin secretion	Hypoglycemia (rare), reports of acute pancreatitis with Januvia	Once daily (oral)	0.5 – 0.8%
Glucagon-like peptide-1 (GLP-1) or incretin mimetic	Exenatide (Byetta), liraglutide (Victoza)	Enhances glucose-dependent insulin secretion	Headache, nausea, renal insufficiency, e.t.c.	1 to 2 times daily (inj)	0.5 – 1.1%
Insulin	Various	Insulin replacement therapy	Weight gain, hypoglycemia	Varies (inj)	1.5 - 3.5%
Meglitinides	Repaglinide (Prandin), nateglinide (Starlix)	Increases insulin production	Bloating, abdominal cramps, e.t.c.	Once daily (oral)	0.5 – 1.5%
Sulfonylureas	Glipizide (Glucotrol), glyburide (Diabeta)	Increases insulin secretion	Hypoglycemia	1 to 2 times daily (oral)	1 – 2%
Thiazolidinediones (TZD)	Pioglitazone (Actos), rosiglitazone (Avandia)	Improves insulin sensitivity	Volume retention, heart failure	Once daily (oral)	0.5 – 1.4%
Bile acid sequestrant	Colesevelam (Welchol)	Reduces hepatic production	GI, nausea, bloating, constipation	1 to 2 times daily (oral)	0.5%
Dopamine agonist	Bromocriptine (Cycloset)	May reverse metabolic changes (obesity)	Hypotension, syncope	Once daily (oral)	0.5%

*** Partially adapted from Pharmacist's Letter May 2010:26 No.26050.*[(10)]

Please see products package inserts for details

(From Ref #2)

Fig. 1.

AACE/ACE DIABETES ALGORITHM *For Glycemic Control*

A1C Goal ≤ 6.5%

LIFESTYLE MODIFICATION

A1C 6.5-7.5% **

Monotherapy

MET †	DPP4 [1]	GLP-1	TZD [2]	AGI [3]

↓ *2-3 mos. ****

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

↓ *2-3 mos. ****

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

↓ *2-3 mos. ****

Insulin +/- Other Agent (s) [6]

A1C 7.6-9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1] or TZD [2]
		SU or Glinide [4,5]

↓ *2-3 mos. ****

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

↓ *2-3 mos. ****

Insulin +/- Other Agent (s) [6]

A1C > 9%

Drug Naive | *Under Treatment*

Symptoms

Insulin +/- Other Agent (s) [6]

No Symptoms

MET	+	GLP-1 or DPP4 [1]	+/- SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	+/- TZD [2]

Under Treatment

Insulin +/- Other Agent (s) [6]

Adapted from Glycemic Control Algorithm, *Endocr Pract. 2009; 15 (No.6)*
Available at www.aace.com/pub

* May not be appropriate for all patients
** For patients with diabetes and A1C < 6.5%, Pharmacologic Rx may be considered
*** If A1C goal not achieved safely
† Preferred initial Agent
1 DDP4 if † PPG and † FPG or GLP-1
If ††PPG
2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
3 AGI if † PPG
4 Glinide if †PPG or SU if † FPB
5 Low dose secretagogues recommended
6 a) Discontinue insulin secretagogues with multidose insulin
b) Can use pramlintide with prandial insulin
7 Decrease secretagogues by 50% when added to GLP-1 or DPP-4
8 If A1C <8.5 %, combination Rx with agents that cause hypoglycemia should be used with caution
9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

American Geriatrics Society recommends not using medications to achieve HgA1C <7.5% in most adults age 65 and older; moderate control is generally better for these patients.

One consistency in the guidelines is that in the absence of contraindications, metformin is generally preferred as the first-line agent.[2,4,8,9] According to the ACE/AACE guidelines, its safety and efficacy also makes it the cornerstone of dual and triple therapies for most patients. If the desired goal is not achieved with metformin, addition of a sulfonylurea or thiazolidinedione (TZD) could be considered. Dipeptidyl peptidase-4 (DPP-4) inhibitors are additional alternatives.[9] The glucagon-like peptide-1 (GLP-1) agonists are injectable drugs that reduce A1C more than DPP-4 and could be used as alternative addition to metformin. (see Table 2). Most patients with type 2 diabetes eventually require multi-drug therapy or insulin if A1C remains poorly controlled. A patient with type 2 diabetes can also present later in its course with marked hyperglycemia and even ketosis. In these patients, insulin treatment protocols used in type 1 diabetes are appropriate until the type 2 pattern of glucose homeostasis is recognized.[7]

ROLE OF THE PROVIDER

Several factors come into play when choosing a particular antihyperglycermic agent: glycemic target necessary, ease of use, adverse effects of the medication(s), contraindications, cost, and adherence. Patient education can ease some of the confusion associated with making these choices. The availability of several choices of medications with different mechanisms of action, while a big plus in the fight against type 2 diabetes, could also pose challenges to the patient. Patient compliance is likely to improve with avoidance of complex dosing regimens. When the target A1C is not achieved, long-term complications can be minimized with frequent follow-ups and timely changes in dosing regimens, as appropriate.

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