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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals

Medical University of South Carolina

Paul Bush
Medical University of South Carolina

Kelli Garrison
Medical University of South Carolina

Jason Cooper
Medical University of South Carolina

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Drug Information Center
Medical University of South Carolina
Department of Pharmacy Services
Charleston, South Carolina

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In This Issue

Pharmacy & Therapeutics

Update

Drug Information for Health Care Professionals

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New Treatment Options for Diabetes

By: Kathryn Noyes, PharmD
Pharmacy Practice Resident

In 2004, an estimated 1.4 million adults were newly diagnosed with diabetes, which represents a nearly 54% increase since 1997.[1] It has been predicted that within approximately 50 years the prevalence of diabetes in the United States will increase by 165% to approximately 29 million.[2] Therefore, health care professionals must continue to educate themselves and others about the prevention and management of diabetes.

Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) promote the early diagnosis and intensive management of diabetes.[3,4] The intensive management of diabetes is described as long-term maintenance of near normal glucose concentrations and also includes the optimization of other related health conditions (eg, dyslipidemia, hypertension, obesity). The goals for intensive management of diabetes have been proven to decrease diabetes-associated complications and reduce mortality.[4] In order for patients with diabetes to achieve these goals, ADA recommends that pre-prandial plasma glucose be maintained between 90 and 130 mg/dL, peak postprandial plasma glucose remain below 180 mg/dL, and hemoglobin A1c (HbA1c) remain below 7%.[3] AACE recommends that diabetic patients follow more strict criteria to include pre-prandial glucose less than 110 mg/dL, postprandial glucose less than 140 mg/dL, and a HbA1c less than or equal to 6.5%.[4]

It is important to remember that these recommendations are guidelines and that treatment should be individualized to each patient in order to optimize management while reducing the occurrence of side effects and adverse reactions.

ADA also recommends a goal blood pressure less than 130/80 mmHg, LDL less than 100 mg/dL, HDL greater than 40 mg/dL, and triglycerides less than 150 mg/dL for all diabetes patients.[3]

The foundation of diabetes treatment begins with proper diet, exercise, and education of the newly diagnosed patients.[2,3] Although type 1 diabetes therapy will require the administration of insulin

upon diagnosis these principles remain critical to their care. On the other hand, patients with type 2 diabetes may begin their treatment and reach target goals strictly with diet and exercise. If significant improvement is not seen or maintained with nonpharmacological therapy, then treatment with oral antidiabetic agents, insulin, or combination of agents can be initiated. There are several classes of antidiabetic agents that have unique mechanisms of action; therefore, treatment can be tailored to the individual patient's needs (Table 1).

Treatment typically begins by adding 1 oral agent to lifestyle modifications. The selection of this agent depends on the clinical picture of disease (ie, insulin resistance versus insulin deficiency) in each individual patient.

Patients with insulin resistance may be characterized by being obese and having elevated fasting blood glucose concentrations. Their diabetes is typically associated with hypertension and hyperlipidemia. Metformin or a thiazolidinedione would be the optimal initial choice for these patients, since these agents act by sensitizing tissue to the insulin that is present and by decreasing the production of glucose by the liver.[4,5] In comparison, patients who are leaner and have elevated post-prandial blood glucose are more likely to have insulin deficiency.[3-5] For these patients, selecting agents that increase the release of insulin from the remaining functioning beta cells (eg, sulfonylurea, nonsulfonylurea secretagouge) would be optimal.[5] Additionally, an alpha glucosidase inhibitor that acts by delaying the absorption of carbohydrates from the gastrointestinal tract would also be beneficial in these patients.[5]

If significant improvement is not seen with the maximum tolerated dose after 3 months, a second agent with a different mechanism of action can be added.[4,5] Combination of oral agents is very common and many are available commercially as combination products. If targets are still not reached within 3 months the addition of insulin can be considered.[4,5] If the patient is within 1 percentage point of reaching their goal, another option would be a combination of 3 agents (eg, metformin + sulfonylurea + thiazolidinedione or metformin + sulfonylurea + exenatide).[3-5]

ADA guidelines do not include the alpha-glucosidase inhibitors (ie, acarbose, miglitol), nonsulfonylurea secretagogues (ie, repaglinide, nateglinide), or newer antidiabetic agents (ie, inhaled insulin, pramilintide, exenatide). These agents are generally less effective in lowering HbA1c, have limited clinical data, or are more expensive than other agents. Therefore, these agents should be considered in patients who are close to their goal HbA1c and continue to have postprandial hyperglycemia.

Pramlintide (Symlin®) is an analogue of the exogenous peptide amylin, which is a neurohormone that is secreted from beta cells along with insulin in response to meals. The release of amylin results in a reduction in food intake, slows gastric emptying, and decreases glucagon release resulting in the reduction of postprandial serum glucose concentrations.[8,9]

Pramlintide, indicated for use with meal-time insulin for uncontrolled type 1 and type 2 diabetes, is administered as a subcutaneous injection immediately prior to meals (Table 2). The administration of pramlinitide with mealtime insulin has been shown to approximately reduce hemoglobin A1c by 0.1 to 0.6% in type 1 and 2 diabetes and also reduce 2-hour postprandial glucose concentrations by 3.6 to 4.8 mmol/L.[9] Weight reduction is another beneficial effect seen with the use of pramlinitide compared with the weight gain typically seen with insulin therapy; however, long term data are lacking.[9] The most common adverse effects are hypoglycemia and nausea. In order to reduce risk of hypoglycemia, close monitoring of blood glucose concentrations with initiation of therapy is recommended along with a 50% empiric dose reduction in short-acting premeal insulin.[8,9]

The 2 newest classes of antidiabetic agents are the incretin mimetics and dipeptidyl peptidase IV inhibitors. These agents work through effects on the incretin gut hormone, glucagon-like-peptide-1 (GLP-1). This hormone is secreted within minutes after the ingestion of food and results in the stimulation of glucose-dependent insulin. It is then quickly degraded by the enzyme dipeptidyl peptidase IV.[10]

Patients with type 2 diabetes demonstrate deficiencies in the secretion of incretin hormones. The incretin mimetics act to replace the insufficient endogenous secretion of GLP-1, whereas the dipeptidyl peptidase IV inhibitors act to limit the breakdown of endogenous GLP-1. Therefore, both agents act to increase the amount of GLP-1 that is available in the body.[10] Additionally, GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon secretion, suppresses appetite, regulates gastric emptying, and promotes proliferation and neogenesis of beta cells.[10]

Exenatide (Byetta®) is an incretin mimetic indicated for treatment of type 2 diabetes in patients who have not met their goals with metformin, a sulfonylurea, or combination of a sulfonylurea and metformin.[10,11] Exenatide is administered subcutaneously, twice daily (Table 2).[11] The expected HbA1c reduction is lower than other agents at approximately 0.5 to 1%. Common adverse effects and contraindications are listed in Table 1.[10,11] Currently, exenatide is not approved for the treatment of patients with type 2 diabetes that have failed other therapies or those with type 1 diabetes.

Sitagliptin (Januvia®), is a dipeptidyl peptidase IV inhibitor that is approved for the treatment of type 2 diabetes as monotherapy or in the combination with metformin or a thiazolidinedione.[10-13] Dosing is listed in Table 2, and dose reductions are recommended for those patients with moderate renal impairment.[12] The expected HbA1c reduction is lower than other agents at approximately 0.6 to 0.8%. To date, serious adverse effects have not been reported with sitagliptin; however, minimal hypoglycemia and weight gain have been noted in clinical trails.[10, 13]

The latest development in insulin technology is the recent approval of Exubera®, the first inhaled human insulin.[6] This new insulin is indicated for the treatment type 1 and type 2 diabetes.[6] It has been shown to have a more rapid onset with a similar duration of action compared with regular human insulin.[6] Adverse effects associated with the use of inhaled insulin include hypoglycemia and weight gain; however, these effects were comparable with those seen with subcutaneous regular insulin.[6,7]

It is important to note that the dosing is different compared with injectable insulin products (Table 2). The initial dose of inhaled insulin is 0.05 mg/kg administered just prior to meals.[7] Exubera® is available as 1-mg and 3-mg unit-dose blister cartridges with 1 mg being equivalent to 3 units of regular insulin and 3 mg being equivalent to 8 units of regular insulin.[7] Due to the differences in conversion to units, three 1-mg blister cartridges is not equivalent to one 3-mg blister cartridge. Therefore, it is important to educate patients about their difference if they require both 1- and 3-mg cartridges.

The incidence of type 2 diabetes continues to grow. Aggressive therapy is required to rapidly achieve and maintain glycemic control. The recent guidelines from ADA emphasize these principles and will assist the clinician in achieving the goals. With the development of new agents possessing various mechanisms of action, a population of diabetes patients that were previously uncontrolled has a better chance of achieving the goal of tight glucose control.

References available upon request.

Did You Know...

Amgen recently informed oncology health care practitioners that results from a large, multicenter, study showed that darbepoetin alfa (Aranesp®) was ineffective in reducing red blood cell (RBC) transfusions in patients with cancer who have anemia that is not due to concurrent chemotherapy. Additionally, this study showed higher mortality in patients receiving darbepoetin.

In the study, darbepoetin alfa was compared with placebo in patients with active malignant disease not receiving or not expected to receive chemotherapy or radiation therapy. This study was designed to establish the effectiveness of darbepoetin alfa in this new indication but failed to meet its primary endpoint of reducing RBC transfusions in the darbepoetin group. This study was not optimal in design to establish the effect on survival, a safety endpoint; however, more deaths occurred in the Aranesp treatment group when compared with the placebo group. This manufacturer-sponsored study was a Phase 3, double-blind,

randomized, placebo-controlled study, monitored by an independent Data Safety Monitoring Board. Patients received treatment for 16 weeks, and additional safety and effectiveness data will be obtained from a 16-week extension study in which randomized treatment was continued. Follow up for survival will continue on patients for a minimum of 2 years.

A total of 989 patients with hemoglobin (Hgb) less than or equal to 11 g/dL, with active cancer, and who were not receiving myelosuppressive chemotherapy or radiotherapy were enrolled. Approximately 60% of patients enrolled had advanced (stage IV) disease. The target Hgb was 12 g/dL.

The final analysis of the initial 16-week treatment period did not show a statistically significant effect on the primary efficacy endpoint (Hazard ratio 0.89; 95% CI: 0.65 to 1.22), with an incidence of RBC transfusions of 24% in the placebo group compared with 18% in the Aranesp group (p=0.15).

In the 16-week treatment phase of the study, more deaths were reported in the darbepoetin group (26%, n=136/515) than the placebo group (20%, n=94/470). With median survival follow-up of 4.3 months the absolute number of deaths was greater in the darbepoetin group (46%, n=216/470) and compared with the placebo group (49%, n=250/515; Hazard Ratio 1.25; 95% CI: 1.04 to 1.51). Details of this study will be presented and published in a peer-reviewed setting as soon as possible.

Darbepoetin is not approved for use in this population. Aranesp is approved for the treatment of patients with anemia, which is caused by chemotherapy treatment of their malignant disease, rather than the underlying malignant disease itself.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the actions listed below.

Additions with Restriction:
Effective February 15, 2007
Varicella virus vaccine (Zostavax®)
Single-dose vial
Prescribing will be restricted to patients in the outpatient clinics.

Conivaptan (Vaprisol®)
4-mL ampule (20 mg)
Prescribing will be restricted to euvolemic patients (ie, syndrome of inappropriate antidiuretic hormone [SIADH]) in an ICU setting who have failed fluid restriction and/or 3% sodium chloride infusions.

Restriction Removed:
Effective March 15, 2007
Meropenem (Merrem®)
The formulary restriction will be removed with the deletion of imipenem/cilastatin.

Automatic Therapeutic Substitution (ATS) Protocol
Effective March 15, 2007
An ATS for meropenem has been developed by the Anti-infective Subcommittee to assist with appropriate dosing due to the formulary changes.

Deletions:
Effective February 15, 2007
Atropine 0.5% ophthalmic solution

Effective March 15, 2007
Imipenem/cilastatin (Primaxin®)

Line extension:
Effective February 15, 2 007
Vitamin D emulsion
(Bio-D-Mulsion® Forte)
2000-unit/drop emulsion

Med•U•Way to Focus on Macular Degeneration

The next MED•U•WAY Conference will focus on macular degeneration. The program will be held on Thursday, February 18, 2006, at 12:00 PM, in 2 West Amphitheater.

The featured speakers will be Esther Bowie, MD, Storm Eye Institute, Patrick Kelty, MD, Resident, Third-Year Resident, Ophthalmology, and Jim Oates, MD, Division of Rheumatology and Immunology.

Attendees will receive 1 credit hour of continuing education, and lunch is provided.

MED•U•WAY is sponsored by the Pharmacy and Therapeutics Committee.

Table 1. Available Medications for the Treatment of Diabetes

Medication Class	Mechanism of Action	Advantages	Disadvantages
Sulfonylureas ▪ Glyburide (DiaBeta®, Micronase®) ▪ Micronized glyburide (Glynase®)* ▪ Glipizide (Gluctrol®, Gluctrol XL®) ▪ Glimepiride (Amaryl®)*	Stimulates insulin secretion from functioning beta cells	▪ Convenient daily dosing ▪ Decreases microvascular risk	▪ AE: hypoglycemia, weight gain
Nonsulfonylurea Secretagogues ▪ Repaglinide (Prandin®)* ▪ Nateglinide (Starlix®)*	Stimulates insulin secretion from functioning beta cells	▪ Targets postprandial glycemic control ▪ Less hypoglycemia and weight gain than with sulfonylureas	▪ TID dosing ▪ AE: hypoglycemia, weight gain ▪ Cannot be combined with sulfonylurea
Biguanides ▪ Metformin (Glucophage®) ▪ Metformin extended release (Glucophage XR®)*	Reduces hepatic glucose production and enhances peripheral glucose uptake	▪ Less risk of weight gain and potential weight loss ▪ Less risk of hypoglycemia ▪ Decreases microvascular and macrovascular risk ▪ Decreases LDL and TG ▪ Increased fibrinolysis	▪ AE: lactic acidosis and GI effects ▪ CI: renal impairment, hepatic dysfunction, CHF, metabolic acidosis, dehydration, alcoholism, radio contrast studies
Thiazolidinediones ▪ Rosiglitazone (Avandia®) ▪ Pioglitazone (Actos®)	Increases tissue sensitivity to insulin and reduces hepatic glucose production	▪ Less risk of hypoglycemia ▪ Possible preservation of beta cell function ▪ Convenient daily dosing ▪ Decreases TG; Increase HDL ▪ Increases fibrinolysis ▪ Decreases blood pressure	▪ AE: weight gain, edema ▪ Required LFT monitoring ▪ Avoid in hepatic impairment and CHF ▪ Cost
Alpha-glycosidase Inhibitors ▪ Acarbose (Precose®)* ▪ Miglitol (Glyset®)*	Delays absorption of carbohydrates from GI tract	▪ Targets PPG ▪ Less risk of hypoglycemia ▪ Less risk of weight gain ▪ Decreases triglycerides	▪ AE: GI effects ▪ TID dosing
Incretin Mimetic ▪ Exenatide (Byetta®)*	Increase insulin synthesis and release by activating GLP-1 receptors, suppresses glucagon secretion, slows gastric emptying and regulates growth of beta cells	▪ Additional reduction in HbA1c and PPG ▪ Promotes proliferation and neogenesis of beta cells ▪ May promote weight loss	▪ Subcutaneous injection ▪ Must be refrigerated ▪ AE: hypoglycemia, GI effects ▪ CI: severe GI disease, severe renal impairment
Amylin Analogues ▪ Pramlinitide (Symlin®)*	Suppresses postprandial glucagon secretion, slows carbohydrate absorption	▪ Weight loss ▪ Decreases insulin use ▪ Modest decrease in HbA1c and PPG	▪ Subcutaneous injection with meals ▪ Unable to mix with insulin ▪ AE: hypoglycemia, nausea
Dipeptidyl Peptidase IV Inhibitors ▪ Sitagliptin (Januvia®)*	Inhibits breakdown of GLP-1 and prolongs GLP-1 activity	▪ Additional reduction in HbA1c and PPG ▪ Once daily dosing ▪ Promotes proliferation and neogenesis of beta cells	▪ Renal dose adjustment ▪ Patient cost

*Nonformulary agents; CI = contraindications; AE = common adverse effects; GI = gastrointestinal; HbA1c = hemoglobin A1c; PPG = post prandial glucose

Table 2. Doses and Average Costs of Antidiabetic Agents

Medication	Dose	Average Patient Cost (30-day supply)+
Glyburide (DiaBeta®, Micronase®)	1.25 -20 mg daily to twice daily (Max: 20 mg/day)	$11
Micronized glyburide (Glynase®)*	0.75-12 mg daily to twice daily (Max: 12 mg/day)	$19
Glipizide (Glucotrol®, Glucotrol XL®)	*Immediate release*: 5 mg daily to BID (Max: 40 mg/day) *Extended release*: 5 to 10 mg daily (Max: 20 mg/day)	$4 $24
Glimepiride (Amaryl®)*	1 to 4 mg daily (Max: 8 mg daily)	$7
Repaglinide (Prandin®)*	0.5 to 4 mg BID to QID with meals (Max: 16 mg/day)	$125
Nateglinide (Starlix®)*	60 to 120 mg TID with meals (Max: 360 mg/day)	$120
Metformin (Glucophage®) Metformin extended release (Glucophage XR®)*	*Immediate release*:1000 to 2550 mg divided BID to TID (Max: 2550 mg/day) *Extended release*: 1000 to 2000 mg daily (Max: 200 mg/day)	$80 $82
Rosiglitazone (Avandia®)	4 mg daily to BID (Max: 8 mg/day)	$139
Pioglitazone (Actos®)*	15 to 30 mg daily (Max: 45 mg daily)	$181
Acarbose (Precose®)*	50 to 100 mg TID with meals (Max ≤ 60 kg: 150 mg/day) (Max > 60 kg: 300 mg/day)	$81
Miglitol (Glyset®)*	50 to 100 mg TID with meals (Max: 300 mg/day)	$74
Glyburide/metformin (Glucovance®)*	2.5/500 to 5/500 mg BID (Max: 20 mg/2000 mg)	$70
Glipizide/metformin (Metaglip®)*	2.5/500 to 5/500 mg BID (Max: 20 mg/2000 mg)	$63
Pioglitazone/metformin (Actoplus Met®)*	15/500 to 15/850 mg daily to BID (Max: 45/2550 mg/day)	$166
Rosiglitazone/metformin (Avandamet®)*	1/500 to 4/1000 mg daily to BID (Max: 8/2000 mg daily)	$230
Rosiglitazone/glimepiride (Avandaryl®)*	4/1 to 4/2 mg daily (Max: 8/4 mg/day)	$116
Sitagliptin (Januvia®)*	100 mg daily	$120
Exenatide (Byetta®)*	5 to 10 micrograms, SC, BID (Max: 20 micrograms/day)	$176
Pramlinitide (Symlin®)*	30 to 60 micrograms, SC, with major meals *Type 1 DM:* initial dose - 15 to 30 micrograms, increased to 45 to 60 micrograms, as tolerated *Type 2 DM:* initial dose - 60 micrograms, increased to 120 micrograms, as tolerated	$95
Inhaled human insulin (Exubera®)*	0.05 mg/kg with meals 1 mg = 3 units of regular insulin 3 mg = 8 units of regular insulin	$180 (Exubera® kit: w/inh chamber) $134 (Exubera® combination kit: 1 mg & 3 mg, 2 release units)

*Nonformulary agents; + Cost based on average wholesale price