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Review Article

Update in Type 2 Diabetes Mellitus Medications: the Many Paths for Control

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Abstract

Diabetes is a growing epidemic worldwide (CDC, 2017). Type 2 diabetes mellitus (T2DM) affects more than 90% of people with diabetes. Because bedside nurses administer and monitor potential side effects of antidiabetic agents, a review of the numerous categories of antidiabetic agents now on the market to treat T2DM is summarized. This discussion is targeted for bedside nurses who are caring for diabetics in acute and transitional care settings, as well as in patient homes. The underlying pathophysiology of T2DM diabetes is reviewed, along with basic mechanisms of action of each category of antidiabetic agent. Safety considerations and common side effects will be presented for each medication category. Discussion will focus on both oral and injectable antidiabetic categories, including concentrated insulin products new to the market.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; ADA: American Diabetes Association

INTRODUCTION

The incidence of diabetes continues to increase across the U.S., with 100 million people now diagnosed with diabetes or pre-diabetes [1,2]. Because of the growing incidence, not only in the U.S. but worldwide, pharmaceutical companies continuously bring to market new products to improve glucose control. The availability of new antidiabetic products makes it challenging for nurses to stay up-to-date and confident in practice. Patients are challenged as well to understand how newer agents work, making patient education a key focus of nursing care.

Standards of care for treatment of diabetes are updated annually by the American Diabetes Association (ADA), and they currently recommend a Hemoglobin A1c level of <7% for non-pregnant patients. A more relaxed goal of <8% is recommended for patients who have experienced frequent episodes of hypoglycemia, have a limited life expectancy, or already have evidence of microvascular or macrovascular complications [3]. Recommendations during pregnancy are more stringent, and outside this discussion. With their most recent update in January 2018, the ADA stresses most persons with diabetes do not meet recommended goals for glucose, blood pressure, or cholesterol control, leaving ample room for improvements in care [4].

Currently there are four major types of diabetes recognized by the ADA: Type 1, Type 2, Gestational, and diabetes secondary to other causes (pancreatic disorders, drug-induced hyperglycemia) [4]. Because more than 90% of diabetes is Type 2, the focus of this article will discuss antidiabetic medications currently marketed to manage Type 2 Diabetes Mellitus (T2DM). The value of exercise and formal diabetic education cannot be overemphasized. While lifestyle recommendations including exercise, nutritional therapy, and caring for mental health needs are vital to holistic care, only pharmaceutical treatment to maintain recommended glucose targets will be addressed.

Pathophysiology of T2DM

Insulin is required to transport glucose into cells in order to effectively use glucose for energy. Insulin resistance develops after years of an obese state with excessive adipose tissue. Hyperglycemia, or T2DM, then develops after years of insulin resistance. Insulin resistance reduces the body's ability to transport glucose inside cells, requiring much higher levels of insulin to effectively use glucose and maintain glucose homeostasis [5]. Newer antidiabetic agents target various pathophysiologic mechanisms of T2DM discussed below [6].

Because obesity is an underlying concern causing cells to become resistant to insulin, obesity is a leading risk factor for T2DM [5]. Additional mechanisms impairing the ability of insulin to be effectively used in tissues contribute to T2DM, including genetic and environmental factors [6]. One result is islet cells of the pancreas work harder to produce higher amounts of insulin to maintain glucose homeostasis. After years of increased

demands to produce larger amounts of insulin, the islet cells of the pancreas can no longer can keep up with higher demands, resulting in hyperglycemia [7-10]. Approximately four years elapse from the time insulin resistance begins to the time hyperglycemia occurs [5,6]. Hyperglycemia may not be actually diagnosed for months or years later, until symptoms develop, or hyperglycemia is recognized incidentally [10,11]. High insulin levels are being used to diagnose pre-diabetes, and oral agents are being prescribed earlier to reduce the progression from pre-diabetes to T2DM [12,13].

Oral antidiabetic agents

Because patients are less fearful of oral medications versus insulin, oral products will be the focus of this discussion. Many products combining two oral antidiabetic agents are available, but this article will focus on the mechanisms of action, common side effects, and patient education appropriate for individual oral antidiabetic products and newer injectable products other than insulin. A table presenting the categories of oral antidiabetic agents, as well as injectable antidiabetic agents other than insulins, is presented in Table 1.

Biguanides

While not the original oral antidiabetic category, biguanides (metformin) is currently considered the first drug of choice for T2DM. Biguanides reduce glucose production in the liver, reduce glucose absorption in the gut, and help reduce insulin resistance by increasing insulin sensitivity in fat and muscle [14]. Metformin helps reduce the blood viscosity and platelet aggregation. Because metformin is primarily eliminated by the kidneys, metformin is used cautiously in patients with elevated serum creatinine levels (males 1.5 mg/dl or greater, females 1.4 mg/dl or greater). The ADA currently recommends metformin as long as glomerular filtration rate (GFR) remains above 30 ml/min [4,15]. Because of the risk of worsening renal function in the presence of contrast dye, metformin should be held for 48 hours before and after imaging studies requiring contrast [14]. Another indication to hold metformin is pre-existing metabolic acidosis. Lactic acidosis is a rare complication of metformin, yet is associated with a 50% mortality rate. Preventing dehydration is important to reduce acidosis risk. Patients with hepatic and renal dysfunction are at higher risk of drug accumulation leading to lactic acidosis [9,14].

Buguanides are affordable, with availability on low-cost pharmacy lists. Biguanides are rarely associated with hypoglycemia but patients may have gastrointestinal (GI) upset, especially when initiating [9,14]. They are also associated with lower B 12 levels necessitating monitoring of B 12 with prolonged use [14]. Metformin is considered safe in elderly due to low risk for hypoglycemia, but should be used with caution in patients with hepatic and significant renal impairments [3,14]. Because biguanides improve insulin sensitivity and reduce the work of the pancreas, they are used for patients with pre-diabetes as well [13].

Patient teaching should include metformin is not associated with concerns for hypoglycemia. Patients should be warned about the potential for GI upset, including diarrhea. Dosing metformin

Table 1: Oral and Injectable Antidiabetic Agents Other Than Insulins.

CATEGORY	GENERIC Name (examples)	Mechanism of Action	Risk for Hypoglycemia	Comments
Sulfonylureas (Secretagogue)	Glipizide Glyburide Glynase Glimepiride	Stimulate pancreas to produce more insulin	Definite risk, especially if used with rapid or intermediate-acting insulin.	Used with long-acting insulins to improve glucose control. Low cost. Requires multiple daily dosing.
Biguanides	Metformin	Increases glucose uptake in tissues	Small	GI upset initially
DPP-4 Inhibitors	Sitagliptin Saxagliptin	Reduced glucagon secretion	Small	Weight neutral
Thiazolidinedione (TZDs)	Rosiglitazone Pipglitizone	Increased insulin sensitivity in fat and muscle	Small	Edema, wt. gain, worsening heart failure
Alpha-Glucosidase Inhibitors	Acarbose Miglitol	Reduce absorption of carbohydrates from the GI tract	None	GI upset including flatus. Must be taken with meals.
Meglitinides	Repiglinide nateglinide	Stimulates insulin secretion with meals	Yes	Wt. gain and frequent dosing
Injectable Products Other Than Insulins				
GLP-1 Agonists (Incretin Mimetic)	Exenatide Liraglutide Dulaglutide	Reduces glucogon secretion, increases insulin secretion	Small	Nausea. May improve wt. loss. Available in daily or weekly dosing.
Amylin Analogs	Pramlintide	Slows GI emptying and reduces glucogon secretion	Yes	Hypoglycemia should be expected if previous insulin dose not reduced. Nausea

Original table developed from references: 9, 16.]
Abbreviations: DPP-4: **Dipeptidyl peptidase inhibitors**; GLP-1Agonists:**Glucagon-like, Peptide-1 (GLP-1) Agonists**.

with the evening mealhelps patients appreciate the degree of GI upset they may need to deal with when away from home. Patients should also understand food will reduce the absorption/effectiveness of metformin in the immediate release form [14-16]. The rare side effect of lactic acidosis is more common in patients with worsening renal function, including those with recent dehydration. Signs of lactic acidosis include dizziness, muscle pain, and weakness. Patients with T2DM will often appreciate a positive aspect of metformin use is the potential for weight loss [9,14].

Sulfonylureas

Sulfonylureas were the first class of oral antidiabetic agents. Because of their age, sulfonylureas have lower cost than other oral medications, making them preferred formulary drugs for insured patients. For patients paying out-of-pocket, sulfonylureas are offered on pharmacy low-cost drug lists. Sulfonylureas (insulin secretagogues) work by stimulating the pancreas to produce more insulin (Secretagogues) [17]. Sulfonylureas help binding between insulin and insulin receptors, but their usefulness over time diminishes as beta cell function diminishes [18]. Insulin resistance has already required islet cells of the pancreas to produce a greater amount of insulin, and sulfonylureas increase the productivity of the islet cells [18,19]. While they will lower Hemoglobin A1c levels approximately 1.5%. Sulfonylureas do place patients with diabetes at risk for hypoglycemia [16,19]. An example of a sulfonylurea is glipizide.

Patients should be aware all sulfonylureas may cause hypoglycemia [16,19]. Patient education should include the signs/symptoms of hypoglycemia, and appropriate actions to take. Verification of the understanding of hypoglycemia should be received verbally by asking the patient to explain how they may feel. Patients should also be able to state appropriate actions to raise their glucose levels.

A second category of secretagogue is a non-sulfonylurea, meglitinides. Meglitinides are an alternative to sulfonylurea for patients with irregular meal times or those who have late post-prandial hypoglycemia episodes with sulfonylureas [20]. Meglitinides also asks the pancreas to produce a greater amount of insulin, their peak effect occurring within an hour of administration, and should be taken just before meals. Meglitinides stimulate insulin production to lower post-prandial glucose levels to provide immediate assistance with glucose spikes due to meals [19]. Meglitinides are rapidly absorbed from the GI tract. They are most often prescribed in combination with other oral antidiabetic agents to achieve glucose goals. Like sulfonylureas, non-sulfonylureas may cause hypoglycemia, and should be held if the patient is not able to eat. Patients should recognize these products work best when taken 20 – 30 minutes before meals to best prevent post-prandial glucose spikes. Meglitinides require multiple daily dosing due to the pre-prandial dosing requirement. An example of a non-sulfonylurea is repaglinide (Prandin) [15,21].

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase inhibitors (DPP-4) help maintain the good work of incretin hormones which stimulate insulin secretion [22]. Incretins also help reduce hunger in many patients [23]. DPP-4 inhibitors target the pathophysiologic dysfunction in T2DM by reducing the rate of decline of beta cells and reducing appetite leading to weight loss [22,23]. DPP-4 inhibitors help lower both pre and post-prandial glucose levels. DPP-4 inhibitors are absorbed from the GI tract and may be taken with or without food. There is little risk of hypoglycemia with DPP-4 inhibitors, but there is some risk of pancreatitis [15,22,24]. An example of a DPP-4 inhibitor is Sitagliptin. Studies are currently targeting the relationship between DPP-4 inhibitors and cardiovascular outcomes [25-27]. DPP-4 inhibitors are not currently available on low-cost pharmacy lists. Patient teaching with DPP-4 inhibitors includes taking the medication daily, and if forgotten, the pill should be taken the same day when remembered. There is no concern for teaching about hypoglycemia with DPP-4 inhibitors when used alone [16, 24].

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors work by delaying carbohydrate absorption form the small intestine. They need to be dosed with meals. Alpha-glucosidase inhibitors are more effective the higher the post-prandial glucose level. They cause a change in carbohydrate digestion into a lower portion of the small intestine. Due to their mechanism of action, alpha-glucosidase inhibitors may cause GI upset including flatulence and abdominal bloating. They are effective in treating pre-diabetes. An example of an alpha-glucosidase inhibitor is miglitol. There is no concern for hypoglycemia with this category [28]. Patient teaching should include the risk of GI upset, including considerable flatus, and the need to dose the medication routinely as they begin eating. Patients should be given hope that the GI side effects will improve often within two weeks [28].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors help control glucose by blocking reabsorption in the kidney and increasing excretion of glucose through the urine [29]. Glucose reabsorption takes place primarily in the proximal tubule via SGLT1, a high-affinity, low-capacity transporter, and SGLT2, a low-affinity high-capacity transporter. SGLT2 contributes to 90% of glucose reabsorption and SGLT1 contributes to 10% of reabsorption respectively [30]. Thus, SGLT2 inhibitors work in the proximal tubules to block up to 90% of glucose reabsorption. This action can lead to osmotic fluid loss and orthostasis, especially in patients already at risk for volume depletion. SGLT2 Inhibitors are contraindicated in patients with GFRs less than 30 ml/min, and dosage reductions are recommended in patients with GFRs of 45 ml/min or less [15,16,29]. Because of changes in fluid volume, renal function should be monitored when patients initially begin a SGLT2 Inhibitor, along with serum potassium levels [15,29]. Other potential concerns with these products include the risk for hypoglycemia if combined with insulin [29].

An example of a SGLT2 inhibitor is empagliflozin a "flozin." Current recommendations suggest adding a "flozin" to the treatment regimen after metformin to improve outcomes for patients with arteriosclerotic heart disease [3]. Adverse effects associated with "flozins" include candidiasis in males and females, urinary tract infections (UTIs), a decrease in bone

mineral densities, and amputation [16,29]. SGLT2 inhibitors are safest when used in patients with little or no renal impairments (GFR>60 ml/min). Hypoglycemia is rare, but dizziness can be an adverse effect as well. SGLT2 inhibitors are approximately $300.00 monthly [15,16,29]. Patient teaching should encourage patients to take their medication at the same time daily, preferably before the first meal. Patients should be warned to be cautious when going from supine to upright due to lower fluid volumes and risk for hypotension. Signs and symptoms of Candidiasis should be reviewed [29].

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs) reduce glucose by increasing insulin sensitivity in fat and muscle [15,16,31].TZDs target nuclear receptors to boost the level of proteins that improve insulin action on cells [31]. This improves insulin action in the liver, muscle, and adipose tissue [9]. TZDs do not ask the pancreas to produce more insulin, nor do they place patients at risk for hypoglycemia. Although TZDs work on the root cause of T2DM, they are associated with the adverse effects of weight gain, edema, worsening heart failure, and fracture risk [31]. TZDs are to be avoided in patients with symptomatic heart failure. TZDs may be recognized in the generic format with the suffix "zone." This category offers more sustained glucose control than sulfonylureas or metformin [3].

Patient teaching important to include with TZDs should focus on remembering the medication daily in the morning. Side effects from TZDs are rare, including the risk for hypoglycemia. Because of the risk for fluid retention, patients should understand to report concerns with edema or shortness of breath [31].

Insulins

While the foundation of treatment is focusing on lifestyle changes recommended with T2DM, glucose control is used as a decision point for when to initially begin insulin therapy. Insulin will be considered as first line therapy in patients presenting with a fasting glucose of 250 mg/dl or higher, a random level of > 300 mg/dl, a Hemoglobin A1c level of 9.5% or higher, or weight loss with ketonuria associated with uncontrolled diabetes [3,11]. Insulin will be considered as an add-on therapy to oral agents when the pancreas continues to tire, and glucose levels persist with Hemoglobin A1c levels of > 8.5% [32,33,34].

The disadvantages of insulin therapy include risk of hypoglycemia and weight gain, with hypoglycemia the most life-threatening risk for any age patient [32,34]. Patients should explain verbally how to recognize the signs of low glucose levels, and voice the activities placing them at higher risk for hypoglycemia (increased physical activity).

Oral antidiabetic agents may be continued with the addition of insulin. This decision is based on the mechanism of action of the oral agent, with agents helping to increase insulin sensitivity as priority. Continuing these oral agents helps minimize the amount of supplemental insulin required for adequate glucose control [3, 32, 34]. A table summarizing current insulins with newer high-concentration products is presented in Table 2.

Additional parenteral therapies for glucose control

Amylin analogs: Amylin analogs are Injectable products that slow GI emptying and reduce glucogon secretion after meals [15,16,35]. Amylin analogs are injected twice a day prior to the largest meals. Amylin analogs may be used with metformin and a sulfonylurea. An example of an Amylin analogs includes pramlintide. Amylin analogs are associated with nausea, weight loss, and rare incidence of pancreatitis or thyroid tumors [35].

Glucagon-like, Peptide-1 (GLP-1) Agonists (Incretin Mimetic): GLP-1 agonists are daily or weekly injectable products that work by slowing GI emptying, decreasing glucogon secretion, and improving insulin production in response to glucose spikes [16,36]. An example of a GLP-1 **agonist is**exenatide or liraglutide. GLP-1 agonists are associated with nausea, and rarely pancreatitis or gall bladder dysfunction [15,36]. There is low risk for hypoglycemia with GLP-1 agonist and a rare risk of thyroid cancers. GLP-1 agonists may be combined with insulin for more effective glucose control [36]. Patients with atherosclerotic heart disease have been shown to benefit from the addition of liraglutide as an additional treatment following metformin [3].

DISCUSSION AND CONCLUSION

Helping Patients Understand Their Diabetes Diagnosis and Medications

The ADA provides an interactive diabetes education website focusing on medication therapy [4]. Their website located at http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/ is comprehensive and includes up to date medication information, explaining the diagnosis and pharmacotherapeutics for T2DM. The site may be used to augment patient education and to verify patient comprehension about their medications, including safety teaching. Because T2DM is an ongoing chronic illness changes in therapy will be expected. The ADA updates their treatment recommendations annually based on current evidence. Nurses can anticipate changes in individual patient care based upon the ADA's annual updates. Patients can anticipate changes through the ADA as well through Diabetes Forecast located at: http://www.diabetesforecast.org/2014/apr/why-so-many-meds-for-type-2.html Encouraging patients to participate in face-to-face diabetic education sessions leads to improved patient outcomes [37,38].

CONCLUSION

Because there are numerous ways to approach glucose control in T2DM, it is challenging to remember each antidiabetic category. A mnemonic to assist in remembering categories of antidiabetic agents is presented below: **B**ig **A**ppetites **S**tart **S**mall **A**nd **G**row **D**angerous **I**n **T**ime

Big: Biguanides

Appetites: Alpha- Glucosidase Inhibitors

Start: Sulfonylureas

Small: Sodium Glucose Co-Transporter Inhibitors

And: Amylin Agonists

Grow: Glucagon-Like Peptide Agonists

Dangerous: Dipeptidyl Peptidase-4 Inhibitors

Table 2: Insulins.

Rapid-Acting Insulins	Example of Brand Name	Onset of Action	Peak Action	Duration of Action	Concentrations Available
Insulin lispro	Humalog	15 minutes	0.5 – 1.5 hours	U 100: Up to 5 hours U 200: Up to 6 hours	U 100 U 200
Insulin aspart	NovoLog	5 minutes	0.5-2 hours	Up to 5 hours	U 100
Insulin glulisine	Apidra	15 minutes	0.5 – 2 hours	Over 5 hours	U 100
Short-Acting Insulins (Regular)					
Regular 'R'	Humulin R	30 minutes	2 – 3 hours	U 100 up to 12 hours U 500 up to 24 hours	U 100 U 500
Intermediate Acting Insulins (NPH)					
Insulin isophane Suspension (NPH)	Humulin N	1-2 hours	4-10 hours	Up to 24 hours	U 100
Long-Acting Insulins					
Insulin glargine	Lantus	1 hour	None	Up to 32 hours	U 100
Insulin glargine	Basaglar	1 hour	None	Up to 32 hours	U 100
Insulin glargine	Toujeo	6 hours	None	Up to 120 hours	U 300
Insulin detemir	Levemir	1 hour	None	24 hours	U 100
Ultra Long-Acting Insulin					
Insulin degludec	Tresiba	1 hour	None	Up to 42 hours	U 100 U 200

Reference: 16, 38
Abbreviations: U: Unit, NPH: Insulin isophane Suspension

In: Insulins

Time: Thiazolidinediones

Diabetes is often the primary reason nursing care is required, if not a frequently encountered co-morbidity during hospitalization. Feeling confident in understanding the mechanism or action of antidiabetics, and the benefits and concerns of high-concentrated insulin products lead to confident nursing care. Understanding antidiabetic agents can also lead to improved patient understanding and safer medication experiences during hospitalization and in the home.

References

References in the text should be in square brackets, e.g. [1-3], for multiple references e.g., [1,2-5] and figures/tables are in parenthesis, e.g. (Figure 1) or (Table 1).

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