

New Drugs for Glycemic Control in Type 2 Diabetes Mellitus

Recently-approved and pipeline drugs for treatment of type 2 diabetes

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Current estimates of the prevalence of diabetes reveal 12.9% of the United States population aged 20 or older has diabetes, although approximately 40% of those with diabetes are undiagnosed.¹ In addition, another 29.5% of the United States population has pre-diabetes. Altogether, approximately 40% of the citizens of the United States have a hyperglycemic condition. Based on these estimates and the United States population clock on July 1, 2010,² approximately 40 million Americans have diabetes, and about 90 million Americans have pre-diabetes.

In consideration of diabetes in Wisconsin, 9.6% of adults aged 19 and older (419,870 citizens) were estimated to have diabetes as of 2008; this is an 11% increase from 2005 data.³ The burden of diabetes related to inpatient hospital charges in Wisconsin for 2008 was estimated to be almost \$2 billion, a 48% increase from 2005. Additionally, 1.06 million Wisconsin residents likely have pre-diabetes.

Diabetes Therapy

Trends in United States treatment of diabetes show significant changes from 1994 to 2007.⁴ Medical visits increased from 29 million to 45 million per year and the mean number of medications prescribed increased from 1.06 to 1.45 per patient. Insulin use dropped from 38% to 28% and sulfonylurea use dropped from 67% to 34%. Metformin, thiazolidinediones and sitagliptin were not available for 1994 analysis, yet accounted for 27%, 28%, and 10% (respectively) of therapies prescribed in 2007. Drug expenditures for diabetes were estimated to be \$6.7 billion in 2001 and \$12.5 billion in 2007.

Therapy Quandaries

Despite currently available diabetes pharmacotherapy options, approximately 43% of patients with diabetes have not achieved the established hemoglobin A1c (A1c) goal of 7% or less.⁵ In addition, it is not known if achievement of glycemic goals with currently available therapies, whether newer

or older agents, translates to improvement in long-term patient-oriented outcomes such as prevention of macrovascular events and cardiac risk reduction. Given cardiovascular safety concerns, the FDA released final guidance for industry in December 2008 regarding evaluation of cardiovascular risk for new drugs to treat type 2 diabetes.⁶ Sponsors are required to create committees which prospectively evaluate cardiovascular risk in all phase 2 and 3 trials, and studies are to be designed so that meta-analysis of cardiovascular risk can be assessed across trials. Subgroup evaluation of risk is also expected. In addition, postmarketing studies are required if the cardiovascular outcome risk ratio exceeds 1:3.

CURRENT GUIDELINES FOR GLYCEMIA MANAGEMENT IN TYPE 2 DIABETES

Given the complexity of the treatment algorithms, readers are encouraged to visit the guideline Web sites (see sidebar on page 18) in order to view the flow charts while reading this portion of the article.

Wisconsin Guidelines

The Wisconsin Diabetes Mellitus Essential Care Guidelines were last released in August 2008⁷ and are in the process of being updated in 2010. Section four of the Wisconsin guidelines covers glycemic control and includes a treatment algorithm on pages 4-17. After diagnosis of type 2 diabetes, initial intervention with lifestyle changes and metformin is suggested. If A1c is still 7% or greater and/or the fasting plasma glucose remains above 130 mg/dL after maximizing the initial intervention, three paths may then be considered:

- basal insulin (preferred given efficacy),
- a sulfonylurea (preferred given lower cost), or
- a glitazone, sitagliptin or exenatide (less preferred given less available published data, most expensive as compared to the other two path agents, and more contraindications and precautions to consider prior to and during use).



Objectives

At the conclusion of this activity, the pharmacist should be able to:

1. Explain the epidemiology and burden of diabetes in Wisconsin and the United States.
2. Compare and contrast current glucose control treatment recommendations for patients with type 2 diabetes.
3. Analyze the therapeutic rationale of bromocriptine and colesevelam for diabetes.
4. Summarize the role of incretin-enhancing therapies and their potential impact on patient care.
5. Evaluate emerging diabetes therapies regarding future diabetes management.

Next steps:

- If addition of basal insulin is selected but glycemic goals are not reached, the next suggested step is to intensify basal insulin by targeting fasting plasma glucose.
- If a sulfonylurea is selected but glycemic goals are subsequently not attained, either basal insulin or one of the less preferred agents may then be added.
- If a less preferred agent path is selected as the second step but goals are not reached, addition of a basal insulin or sulfonylurea is then offered for consideration.

Regardless of which paths are chosen, basal plus prandial insulin may eventually be needed in addition to referral to a diabetes specialist.

American/European Diabetes Consensus Guideline

In January 2009, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a consensus guideline for management of glycemia in type 2 diabetes. The guideline was published simultaneously in three journals, *Clinical Diabetes*, *Diabetes Care* and *Diabetologia*.⁸⁻¹⁰ This consensus guideline may be sectioned in two ways: by tier and by step. Two tiers are offered: tier 1 includes therapies with more literature support/validation and tier 2 includes therapies with less literature support/validation. The three steps are presented in Table 1.

American Endocrine Consensus Guideline

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a consensus statement in the September/October

2009 issue of *Endocrine Practice*.¹¹ This guideline recommends lifestyle modification for all patients with drug therapy recommendations allocated according to patient A1c. Therapy suggestions are provided for single, double and triple-drug therapies and are given for A1c ranges of 6.5-7.5%, 7.6-9% and greater than 9%. The guideline may best be understood by visiting the algorithm online.

NEW DRUG THERAPY FOR TYPE 2 DIABETES MELLITUS

New Diabetes Indication for Established Drugs

An alternative to finding new agents to treat diabetes is to examine existing drug therapies that could benefit patients. Recently, drugs such as colesevelam and bromocriptine have been granted the indication for treatment of type 2 diabetes mellitus.¹²⁻¹³

COLESEVELAM

Colesevelam, a nonabsorbed bile acid

sequestrant, was granted approval in January 2008 as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes in addition to its current indication for reduction of low-density lipoprotein-cholesterol (LDL-cholesterol).¹²

Efficacy

Several trials show that colesevelam improves glycemic control and reduces A1c by 0.4 to 0.8% in patients poorly controlled on metformin, sulfonylurea and/or insulin, although the exact mechanism is unknown.¹⁴⁻¹⁷ It is thought to be related to several mechanisms: reduction of hepatic insulin resistance with subsequent decrease in hepatic glucose production, effects on molecular mediators of glucose metabolism, and effects on intestinal glucose absorption.¹⁸ There is an ongoing clinical trial to assess the use of colesevelam in combination with metformin for pre-diabetes and as a first line agent for diabetes.¹⁹

Concerns

Data from clinical experience with colesevelam for LDL-cholesterol reduction indicates a low incidence of adverse effects, mostly mild gastrointestinal effects.¹² The recommended dose is 6 tablets (625 mg each) once daily or 3 tablets twice daily, which could affect adherence. Also, it can reduce absorption of medications and fat soluble vitamins, requiring that it be spaced at least 4 hours after drugs such as glyburide, levothyroxine, oral contraceptives or anything with a narrow therapeutic index.

Place in Therapy

Colesevelam is an adjunctive therapy with benefits of no hypoglycemia or weight gain, although the decrease in A1c is modest. It is an agent that could be considered in a patient with an A1c near goal and in need of a second LDL-cholesterol reducing agent in addition to

TABLE 1: AMERICAN/EUROPEAN DIABETES CONSENSUS GUIDELINE

At Diagnosis: STEP 1: Lifestyle changes and metformin (if not contraindicated)					
If A1c >7% in 3 months, choices include Tier 1 therapies or Tier 2 therapies					
STEP 2:					
Tier 1: well-validated core therapies	Add basal insulin	OR	Add sulfonylurea (NOT glyburide)	OR	If sulfonylurea insufficient, add basal insulin
Tier 2: NOT well validated, but still an option	Add pioglitazone	OR	Add GLP-1 agonist	OR	If pioglitazone alone is insufficient, add sulfonylurea (NOT glyburide) or add basal insulin
STEP 3:					
Lifestyle changes + metformin + intensive insulin (and discontinue any other agents)					

DIABETES GUIDELINES ONLINE

- Wisconsin Guidelines, Section 4 (glycemic control)
<http://dhs.wisconsin.gov/health/diabetes/PDFs/GL04.pdf>
- American/European Diabetes Consensus Guideline
<http://care.diabetesjournals.org/content/32/1/193.long>
- American Endocrine Consensus Guideline
<http://www.aace.com/pub/pdf/GlycemicControlAlgorithmPPT.pdf>

a statin. The AACE/ACE algorithm does include colesevalam as a choice for dual therapy in combination with metformin for patients with an A1c 6.5 -7.5%.¹¹ It is not recommended for use in patients with hypertriglyceridemia (triglycerides more than 300 mg/dL). There is no outcome data in terms of reduction in diabetes complications or mortality at this time.

BROMOCRIPTINE

Bromocriptine mesylate-quick release is being marketed under the brand name Cycloset® since its May 2009 approval for type 2 diabetes.¹³ Bromocriptine is an ergot derivative and dopamine-2 receptor agonist and the mechanism by which it reduces blood glucose is unknown. A leading theory relates to the relationship between dopamine and its effects on control over energy expenditure as well as initiation and cessation of food intake.²⁰⁻²¹ Reduced dopamine neurotransmission can lead to insulin resistance, especially in obese populations that may have decreased receptors. The dopamine agonist is thought to potentially decrease insulin resistance and hepatic glucose production through an increase in dopaminergic neurotransmission which can “reset” the hypothalamus and improve insulin sensitivity when given early in the morning. This is meant to mimic our natural circadian dopaminergic peak at this time of day.²⁰⁻²¹

Efficacy

A small, 16-week study in 22 obese subjects showed a statistically significant reduction in A1c (from 8.7 to 8.1% or -0.6%) and changes in fasting plasma glucose.²² The Cycloset Trial was designed to meet the new FDA guidelines which require that all diabetes agents be evaluated for cardiovascular risk and safety.⁶ A

randomized, double-blind, placebo-controlled 52-week study in 3070 subjects with type 2 diabetes demonstrated non-inferiority to placebo in terms of cardiovascular safety.²³

Concerns

Bromocriptine has known tolerability issues including dizziness, headache, hypotension, nausea and constipation, about which patients will need to be counseled.¹³ Nausea is the side effect with the highest reported rate (32.2% vs 7.6% placebo).²⁰ It is also important to educate patients to take the bromocriptine with food within 2 hours of waking in the morning for best efficacy. Dosing is initiated at 0.8 mg daily and titrated by 0.8 mg weekly to a minimum effective dose of 1.6 mg and a maximum of 4.8 mg per day. Bromocriptine is a cytochrome P450 3A4 inhibitor and caution must be used with drugs that are metabolized by this system, such as macrolide antibiotics and protease inhibitors.

Place in Therapy

At this time, bromocriptine is not a recommended therapy in any of the guidelines or algorithms. It may be considered as an alternative therapy in multiple-therapy resistant patients with a need for an A1c reduction of < 0.6%.

ORLISTAT

Orlistat is another alternative agent that has been studied in randomized controlled trials for both delaying onset of type 2 diabetes and improving glycemic control in obese, glucose-intolerant and type 2 diabetes patients.²⁴ Orlistat is a lipase inhibitor for obesity management that does not have an indication as a diabetes treatment. A recent retrospective analysis of pooled data from seven multicenter, double-blind, placebo controlled studies in obese type 2 diabetes patients showed improvement in glycemic control in the orlistat-treated patients to be greater than what would be predicted from weight loss alone.²⁵ The mechanisms suggested include reduced digestion of dietary fat, reduction of visceral adipose tissue, increased glucagon-like peptide-1 (GLP-1) secretion and improvement in insulin sensitivity.¹⁹ More studies are needed to confirm the mechanism and quantify the effect on A1c.

Recently-approved Type 2 Diabetes Therapies: Incretin System Agents

The “incretin” system has been the target for development of diabetes agents marketed in the past few years. The currently available drugs that work via the incretin system include the injectable GLP-1 receptor agonists and the oral dipeptidyl peptidase-4 (DPP-4) inhibitors.

A quick review of the incretin mechanism: Eating provokes the release of multiple gastrointestinal hormones, including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which have various effects on the body and work in concert with the stomach, liver, pancreas and brain to help the body transport and metabolize the incoming glucose load to improve blood glucose. (See sidebar on opposite page for more information.)

The incretin effect is estimated to be responsible for 50-70% of the total glucose-mediated insulin secretion.²⁷ Research has shown that patients with type 2 diabetes have deficient GLP-1 secretion and increased GIP secretion with beta cell resistance to GIP.^{27,28}

GLP-1 TWICE DAILY AGONIST: EXENATIDE

The first incretin-type agent, released in June 2005, was the GLP-1 receptor agonist exenatide (Byetta®), derived from the venom of the gila monster.^{29,30} Exenatide does reduce blood glucose with advantages including a potential weight loss and a low risk of hypoglycemia. The disadvantages include a high incidence of nausea, the need for twice daily subcutaneous injections and high cost. Also, exenatide is currently under FDA investigation for post-marketing reports of pancreatitis and altered kidney function (acute renal failure and renal insufficiency).^{31,32}

GLP-1 ONCE DAILY ANALOGUE: LIRAGLUTIDE

The new once daily injectable GLP-1 analogue, liraglutide (Victoza®), was approved by the FDA in January 2010 for the treatment of type 2 diabetes in adults with a dosage of 0.6 mg to 1.8 mg per day via a pre-filled, multi-dose pen.³³ Approval was based on the five double-blind, randomized, controlled clinical trials named Liraglutide Effect and Action in Diabetes (LEAD), which directly compared liraglutide to glimepiride, rosiglitazone, placebo and glargine insulin.³⁴ A sixth LEAD trial has since been released that compares liraglutide to exenatide.³⁵ Overall, in comparison to exenatide, liraglutide shows a slightly greater reduction in A1c (1.12% vs 0.79% exenatide), less severe and persistent nausea, with a similar degree of weight loss (-3.24 kg vs exenatide -2.87 kg) and consistent low rate of hypoglycemia.^{35,36} Liraglutide also shares the drawbacks of exenatide, including high cost and subcutaneous dosing. Pancreatitis is also of concern due to a small incidence in clinical

trials and monitoring is ongoing.³⁴ Unique to liraglutide is the black box warning for potential thyroid c-cell tumor development, which remains under review via the Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA for continued study.³⁷ Liraglutide is NOT recommended as first-line therapy but is a potential second-line agent in patients who could benefit from GLP-1 therapy.

DPP-4 INHIBITORS

The second generation of incretin therapies to reach the market was the oral DPP-4 inhibitors, approved for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. DPP-4 is the enzyme that degrades endogenous GLP-1 hormones, which have a very short half life of a few minutes.³⁸ Inhibition of DPP-4 enzyme results in a two to four-fold increase in endogenous GLP-1 concentrations.³⁹ The first agent released in October 2006 was sitagliptin (Januvia®). The second agent, approved in 2009, is saxagliptin (Onglyza®). Efficacy of these agents in combination in efficacy to the injectable GLP-1 agonists (A1c decrease approximately 1%). They have the advantage of no nausea and the reduced risk of hypoglycemia but are weight neutral. The DPP-4 inhibitors are costly and lack the long-term safety data of older generic agents or data related to their effect on micro- and macrovascular complications. Post-marketing reports have identified several cases of acute pancreatitis with sitagliptin, which is under FDA review, similar to exenatide.⁴⁰ Saxagliptin is metabolized via the cytochrome P450 3A4 system, requiring a decrease in dose when used in combination with strong 3A4 inhibitors.

INCRETIN COMPARISON: GLP-1 VERSUS DPP-4

A recent 26-week, parallel-group, open label trial evaluated liraglutide versus sitagliptin as add-on therapy to metformin.⁴¹ Liraglutide had a significantly better lowering of mean A1c (-1.5% for 1.8 mg/day, -1.24% for 1.2 mg/day) versus the DPP-4 inhibitor sitagliptin (-0.9%). As expected, however, nausea was more common with the GLP-1 agents (21-27%) versus the DPP-4 agents (5%). See Table 2 for a comparison of the available incretin agents.

PLACE IN THERAPY

The ADA/EASD algorithm notes that long-term safety of both of these classes is not currently supported by clinical data.⁸⁻¹⁰

The GLP-1 agonists are a secondary option for patients with type 2 diabetes who may have failed initial therapy and could benefit from the potential weight loss and low rate of hypoglycemia. DPP-4 inhibitors are not a part of this algorithm because there were not any approved agents at the time the algorithm was published. The AACE/ACE algorithm for glycemic control does recommend the use of DPP-4 inhibitors as a potential first-line therapy for A1c between 6.5 to 9%.¹¹ GLP-1 drugs are potential first-line therapy for A1c between 7.6% and 9%. The current practical application of this class is for the insured patient with type 2 diabetes as an add-on in combination with well-validated therapies such as metformin. The class may also be considered for patients who have failed or are intolerant to conventional treatments. The durability and long-term safety of DPP-4 inhibition, as well as clinical positioning in relation to GLP-1 mimetics, is yet to be established.

Diabetes Drugs in the Pipeline

FUTURE INCRETINS

GLP-1 Once-weekly Agents

The once-weekly formulation of exenatide (Bydureon®) is currently under FDA review, with the next information from review expected in fall of 2010. A New Drug Application, submitted to the FDA in 2009, was denied in March 2010 pending a labeling revision for a Risk Evaluation and Mitigation Strategy and a clarification of manufacturing processes. Phase 3 study results suggest once-weekly exenatide offers superior efficacy and similar safety to twice-daily exenatide.⁴² The four double-blind, randomized clinical trials for this drug were called DURATION-1 through DURATION-4 which reveal safety, tolerability and efficacy similar to or slightly better than comparator oral therapies of metformin, sitagliptin plus sulfonylurea and pioglitazone.⁴³⁻⁴⁶ Another once-weekly analogue that has shown efficacy for reducing A1c as add-on therapy to metformin and pioglitazone in phase 3 trials, is taspoglutide.⁴⁷

More in the Pipeline

This is a growing field for future diabetes therapies, with several drugs in clinical trials.⁴⁸ There are 26 phase 3 and 4 studies ongoing for GLP analogues, including more weekly analogues, albiglutide and taspoglutide. There are 43 phase 3 and 4 studies in DPP-4 entities. Vildagliptin (Galvus®) is available in Europe, but has not been approved in the US since the FDA requested additional clinical data

regarding skin lesions and kidney impairment in animal studies. Alogliptin has been submitted in Japan and linagliptin has recently completed four phase 3 trials. Linagliptin is anticipated to be submitted to the FDA soon.

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

Mechanism of Action

SGLT2 inhibitors prevent glucose reabsorption in the kidney and promote glucose excretion into the urine.⁴⁹⁻⁵¹ The kidneys filter and reabsorb up to 180 grams of glucose daily. The SGLT co-transporters are membrane proteins that transport glucose, amino acids, vitamins, ions and osmolytes across the membrane of the proximal renal tubules and intestinal epithelium. The SGLT2 co-transporter is exclusive to the kidney and is responsible for 90% of glucose reabsorption.⁴⁹ Inhibition of

THE ACTIONS OF INCRETIN HORMONES INCLUDE:²⁶

- Pancreas:
 - Enhance glucose-dependent insulin secretion by beta-cells
 - Suppress inappropriate post-meal glucagon secretion
 - Promote beta-cell proliferation
- Liver: suppress glucagon action and reduce glucose output
- Stomach: slow gastric emptying rate and glucose absorption
- Brain: improve and promote satiety

this transporter promotes glucose excretion in the urine, which reduces serum blood glucose levels. This glucosuria causes a caloric loss of 200-300 calories per day, which could be an advantageous mechanism for weight loss.

There are several agents in different phases of clinical trials that show dose-dependent increased glucose urinary excretion and seem to be well tolerated. At this time the entity with the most published clinical data is dapagliflozin.^{49,51}

Efficacy

In relatively small, short-term trials, once daily administration of dapagliflozin shows a dose-dependent glucosuria in healthy volunteers and patients with type 2 diabetes. Two randomized, double-blind, placebo-controlled

trials evaluated dapagliflozin as an add-on to metformin or insulin with oral antidiabetic drugs in type 2 diabetes participants.^{52,53} The decrease in A1c over the dosing range of 2.5 to 20 mg is -0.6 to -0.8%. Approximately 24% of subjects also had a greater than 5% weight loss at 24 weeks, although average weight loss is approximately 2.5 kg. A separate trial evaluated the efficacy and safety in treatment-naïve

subjects of dapagliflozin at doses of 2.5, 5, and 10 mg.⁵⁴ The decreases in A1c at week 24 were -0.58%, -0.77% and -0.89% for the respective doses versus -0.23% for placebo.

Concerns

A concern with many new agents is the lack of long-term safety data. However, a rare autosomal recessive disorder due to a mutation in SGLT2 gene that causes glucosuria

in affected individuals provides a model for questions regarding kidney function or morbidity. These affected patients have persistent glucosuria, with normal fasting blood glucose and no major clinical sequelae.⁵⁵ In clinical trials, the adverse events reported were more common in patients on metformin and were gastrointestinal.⁴⁹ The rate of hypoglycemia was close to placebo when given with metformin (2.2-3.7% vs 2.9% placebo),⁵² but was significant when added to insulin (25 -29.2% vs 13% placebo).⁵³

The increase in urinary glucose does bring up concerns about infections, polyuria and potential electrolyte imbalances. Although there is a demonstrated diuretic effect, clinical trials to date have not shown significant changes in kidney function or major electrolyte imbalances.^{50,54} This diuretic effect has an observed decrease in blood pressure (2.6-6.4 mmHg) and increases uric acid and magnesium concentrations, although the clinical significance is unknown.⁵⁰ Urinary tract infections and genital infections secondary to increased glucosuria have both been evaluated. Urinary tract infection rate in one trial was similar to placebo (4.4-8.1% vs 8% placebo).⁵² Genital infections did occur more frequently than placebo, but were still lower than typical occurrences for diabetes patients (8 -13.1% vs 5.1% placebo). These risks will need further study to assess clinical impact.

Potential Advantages and Place in Therapy

The mechanism of SGLT2 inhibitors is uniquely insulin-independent. The action is not affected by the severity of beta-cell dysfunction or insulin sensitivity, offering another prospective tool to reduce blood glucose. As an add-on agent to oral therapy, it has a low risk of hypoglycemia and a potential for incurring weight loss or reducing the weight gain associated with insulin therapy and a small positive effect on blood pressure. Further trials in large numbers of patients will hopefully provide answers regarding the significance of safety concerns and this drug's place in therapy for prevention or treatment of type 2 diabetes and/or obesity.

11-BETA-HYDROXYSTEROID DEHYDROGENASE (11-BETA-HSD) TYPE 1 INHIBITORS

Five drugs in this class are currently being investigated in Phase 1 and 2 studies; results of one study have been published.

Mechanism of Action

11-beta-HSD type 1 is an enzyme that catalyzes conversion of intracellular cortisone

TABLE 2: OVERVIEW OF APPROVED INCRETIN-BASED THERAPIES

	Exenatide	Liraglutide	DPP-4 Inhibitors (sitagliptin and saxagliptin)
Dosage forms	Disposable, pre-filled pens for each dose: 5 mcg/1.2 mL pen and 10 mcg/2.4 mL pen	Same pen delivers: 0.6 mg, 1.2 mg or 1.8 mg doses Pen size: 6 mg/mL, 3 mL total	Oral tablets
Dosage	<i>Initiate:</i> 5 mcg subcut BID within 60 min before AM & PM meal <i>After 1 month:</i> may increase to 10 mcg BID	<i>Initiate:</i> 0.6 mg subcut once daily <i>After 1 week:</i> increase to 1.2 mg daily Max dose: 1.8 mg daily	Sitagliptin: 100 mg daily Saxagliptin: 5 mg daily
ACTIONS			
Glucose-dependent insulin increase	Yes	Yes	Yes
Glucose-dependent glucagon decrease	Yes	Yes	Yes
Low hypoglycemia risk (if not with sulfonylureas)	Yes	Yes	Yes
Slows gastric emptying	Yes	Yes	No
POTENTIAL ADVANTAGES			
Average decrease in A1c as monotherapy	-0.9% (10 mcg BID)	-1.1% (1.8 mg/day)	-0.4% to -0.9%
Effect on fasting glucose	Modest	Good	Modest
Effect on postprandial glucose	Good	Modest	Modest
Effect on CVD risk factors	Modest improvement	Modest improvement	No consistent change
Effect on weight (non-significant diff. in GLPs)	-2.87 kg (avg wt loss)	-3.24 kg (avg wt loss)	Weight neutral
ADVERSE EFFECTS <i>All comparable to placebo</i>			
Overall GI	42.7%	45.5%	
Nausea	28%	25.5%	
Vomiting	23%	14%	
Diarrhea	12.1%	12.3%	
Hypoglycemia (minor)	34%	26%	
Price: (monthly) from http://www.drugstore.com	5 mcg BID: \$250 10 mcg BID: \$275	1.2 mg/day: \$250 1.8 mg/day: \$400	Sitagliptin: \$215 Saxagliptin: \$205
References:			
1. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6).			
2. Package inserts for all drugs			

to cortisol in hepatic, lung, ovary, vascular, adipose and brain tissues.⁵⁶ In obese individuals, the activity of this enzyme is increased.⁵⁷ Thus, by inhibiting the activity of this enzyme, endogenous glucocorticoid activity may be decreased, especially in the liver and adipose tissue, eventually resulting in a lowering of plasma glucose.

Efficacy

The only published trial to date is a double-blind, randomized, parallel, 74-center study in two hundred twenty-eight overweight and obese subjects (body mass indexes 25 to 45 kg/m²) with suboptimal glycemic control on metformin.⁵⁷ Subjects were assigned to 11-beta-HSD type 1 inhibitor INCB13739 at one of five different oral doses to be taken once daily for 12 weeks. Glycemia indices improved in a dose-related manner; mean A1c decreased by -0.56%, fasting plasma glucose by -24 mg/dL, and insulin resistance by -24% (results from the highest dose group).

Concerns

No hypoglycemia occurred and no differences in adverse effects overall were noted for INCB13739 as compared to placebo.⁵⁷

Potential Place in Therapy

INCB13739 offers a new, unique mechanism of action with modest changes in A1c and fasting plasma glucose. Its opportunity for once-daily oral administration is attractive and it may be particularly useful in obese patients since such patients have increased activity of 11-beta-HSD type 1.

ANTI-OBESITY COMBINATION DRUG: CONTRAVE®

Contrave® is a combination drug for treatment of obesity and contains 32 mg sustained-release naltrexone with 360 mg sustained release bupropion. Although a new drug application for the treatment of obesity was submitted by the sponsor in March 2010,⁵⁸ the drug also affects parameters of glycemia.

Efficacy

In a 56-week, phase 3 double-blind, placebo-controlled trial (COR-Diabetes), 265 subjects with diabetes taking oral diabetes agents or no drug therapy received Contrave® and 159 subjects received placebo.⁵⁹ Mean weight loss in the Contrave® group was 5% as compared to 1.8% in the placebo group. Mean A1c improvement was -0.6% in Contrave® subjects, though subjects with baseline A1c more than 8% experienced a mean decrease in A1c of -1.1% and those with baseline A1c more than 9% experienced a mean A1c decrease of -1.2%.

TABLE 3: PIPELINE CHART?

Drug Name	Class	Status
colesevelam (Welchol®)	Bile acid sequestrant	New indication for DM type 2
bromocriptine mesylate-quick release (Cycloset®)	Dopamine-2 receptor agonist	New indication for DM type 2
exenatide once weekly (Bydureon®)	GLP-1 agonist	FDA review pending labeling revision for a REMS and clarification of manufacturing processes
raspoglutide	GLP-1 analogue	In phase 3 trials
albiglutide	GLP-1 agonist	In phase 3 trials
alogliptin	DPP-4 inhibitor	Submitted in Japan
linagliptin	DPP-4 inhibitor	In phase 3 trials
dapagliflozin	SGLT2 inhibitor	Published phase 3 trial data
INCB13739	11-beta-HSD type 1 inhibitor	In phase 2 trials
Naltrexone/bupropion mix (Contrave®)	Opioid antagonist/norepinephrine and dopamine uptake inhibitor	New drug application for obesity indication submitted to FDA March 2010

Concerns

Subjects in the COR-Diabetes study experienced nausea (42.3%), constipation (17.7%) and vomiting (18.3%) as compared to respective placebo adverse event frequencies of 7.1%, 7.1% and 3.6%.⁵⁹ Hypoglycemia did not occur and drug therapy was not associated with depression or suicidal ideation.

Potential Place in Therapy

Although an indication for treatment of diabetes is not currently sought, this drug potentially could treat obesity and hyperglycemia; it may even be beneficial to help limit or stop tobacco use. The high frequency of side effects is not surprising and most study participants were able to continue therapy. Patients with higher A1c at baseline had greater A1c declines, a promising benefit for patients with uncontrolled diabetes. Lack of hypoglycemia and no noted mental health effects are attractive features of this combination agent. There are several other anti-obesity agents and combinations in the pipeline that may also have therapeutic benefit in diabetic patients.

CONCLUSION

The growing prevalence and burden of type 2 diabetes mellitus in Wisconsin and the United States presents ongoing pharmacotherapeutic challenges regarding appropriate selection of antihyperglycemic agents given unique patient characteristics, economic issues and drug efficacy/safety data. Old drugs with new indications such as colesevelam and bromocriptine as well as recently-approved agents in the incretin class have broadened

diabetes drug therapy options in the past five years. On the horizon are investigational incretin entities in addition to SGLT2 inhibitors, 11-beta-HSD type 1 inhibitors and even an anti-obesity combination drug which will likely present exciting future options for battling this epidemic disease. (see Table 3) The pharmacist's role in diabetes drug therapy selection, use and monitoring is becoming more complex with each new agent approved and used to treat hyperglycemia associated with type 2 diabetes mellitus. ●

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