Pharmacologic Management of Type 2 Diabetes

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Lesson description

Chronic conditions such as diabetes mellitus impart a substantial health strain in Canada in terms of economic and clinical outcomes. As the prevalence and severity of diabetes increase with age, the aging of the population will likely increase the burden of diabetes to society.[1] The Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada emphasize the importance of optimal blood glucose, blood pressure, and lipid control for people with diabetes in an effort to prevent and manage the disease and its related complications. The challenge now is to achieve that optimal control. Ideally, this should involve the expertise of various allied health care professionals in a collaborative approach to guide the patient in self-management. This can often be overwhelming for the patient, requiring numerous visits to seek expertise regarding nutrition therapy, exercise guidelines, home blood glucose and blood pressure monitoring, and effective usage of oral agents and insulin. This continuing education lesson will equip pharmacists with knowledge regarding the proper use and timely addition of oral hypoglycemic agents so that they may provide innovative care and education to persons with diabetes.

Learning objectives

Upon successful completion of this continuing education lesson, you should be able to:

- discuss the prevalence and economic burden of diabetes
- understand the Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada pertaining specifically to the pharmacotherapy of type 2 diabetes
- discuss the importance of timely lowering of A1C to target levels
- distinguish between patients who should be started on lifestyle interventions and those who require immediate antihyperglycemic therapy
- understand the role, appropriate use, advantages, and disadvantages of the various classes of oral hypoglycemic agents
- be familiar with new agents in the pipelines of development

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1. Background

1.1 The diabetes epidemic

We are in the midst of a storm! The World Health Organization states that the number of people with diabetes is expected to increase alarmingly in the coming decades. In 1985, an estimated 30 million people worldwide had diabetes; in 2000, the figure had risen to over 150 million. By 2025, the figure is expected to rise to an alarming 380 million.[2] The impact of diabetes is also felt in Canada, where, in 2005, 1.8 million adult Canadians (5.5% of the population) had diabetes that had been diagnosed. That is an increase from 1998, when the physician-diagnosed prevalence of diabetes in Canada was 4.8%. Researchers project an increase of diagnosed diabetes in Canada to 2.4 million by the year 2016.[3] A recent study of the prevalence of diabetes in Ontario found that the incidence has increased substantially, and by 2005 had already exceeded the global rate that was predicted for 2030.[4] All over the world, traditional lifestyles and dietary patterns that have sustained people over generations are disappearing. The increasing incidence of diabetes can be attributable not only to the aging population but to an increase in obesity secondary to an abundant consumption of energy-dense foods and a more sedentary lifestyle.[5]

1.2 Definition of diabetes

According to the Canadian Diabetes Association Guidelines, "Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidneys, eyes, nerves, heart and blood vessels."[3]

1.3 Goals of therapy

Controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT)[6] in type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS)[7,8] and Kumamoto study[9] in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. These clinical trials support decreasing glycemia as an effective means of reducing long-term microvascular complications, including retinopathy, nephropathy, and neuropathy. The stated goal of therapy is to attain and maintain blood glucose (BG) levels close to the normal range (for those individuals in whom it is deemed safe).

Table 1. Glycemic targets[3]

	A1C (%)	FBG or preprandial BG (mmol/L)	2 hour postprandial BG (mmol/L)
Type 1 and Type 2 Diabetes	≤7.0	4.0–7.0	5.0–10.0 (5.0–8.0 if A1C target not being met)

Glycated hemoglobin (hemoglobin A1c, Hb_{A1c}, or A1C) is a laboratory test which measures the slow, irreversible binding of glucose to the hemoglobin molecule. It is directly proportional to the ambient glucose concentration, and hence is a standard measure of mean blood glucose during the preceding 120 days (lifespan of the hemoglobin molecule). The A1C test serves as an indicator of the risk of complications from diabetes and should be measured every 3 months to ensure that glycemic goals are being met.[10] The most recent A1C goal recommended by the Canadian Diabetes Association (CDA) is a value ≤7.0%. An A1C level of 4.0–6.0% is considered the non-diabetic range, but the 7.0% goal was selected as a realistic, achievable target that would produce a suitable estimated reduction in complications over time.

The glycemic targets recommended for most patients with type 1 and type 2 diabetes (non-pregnant, age >12) are listed in Table 1.

Clinical judgment is required to determine which people can reasonably and safely achieve these targets, as some patients may require more lenient goals. Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors (e.g., the patient's age, prognosis, level of glycemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia).[3]

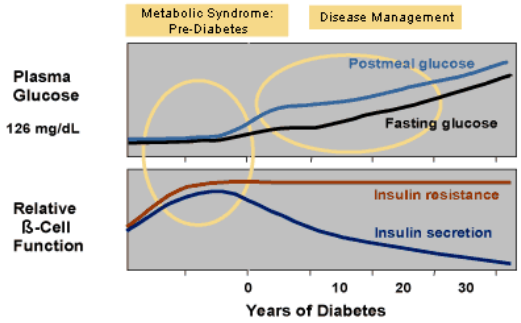
2. Pharmacologic management of type 2 diabetes

2.1 Introduction

To understand the basis for pharmacologic therapy in type 2 diabetes, it is important for pharmacists to understand the natural history of type 2 diabetes. Type 2 diabetes is a progressive disorder characterized by an initial phase of insulin resistance that requires a compensatory increase in

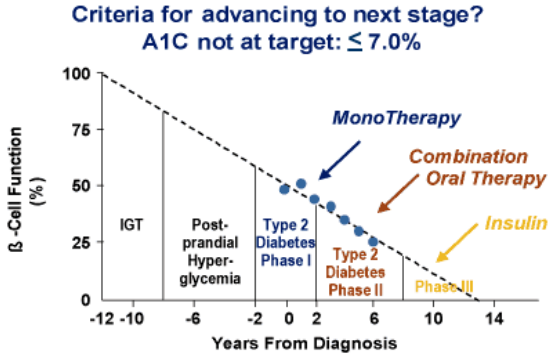
insulin secretion to maintain euglycemia. Insulin resistance, however, cannot by itself result in diabetes. Type 2 diabetes will develop when the insulin resistance is associated with abnormal beta-cell function, which is considered a key pathophysiologic abnormality. Progressive loss of beta cell function appears to begin years before the clinical diagnosis and, given the presence of insulin resistance, results in a state of "relative" insulin deficiency which results in hyperglycemia.[11] It is at this stage that impaired glucose tolerance and impaired fasting glucose may be present. With worsening pancreatic dysfunction and the inability to compensate fully for the degree of insulin resistance, clinically overt type 2 diabetes becomes present. (Figure 1) The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that progressive beta cell failure will continue in all treatment groups regardless of initial therapy. Typically, beta cell function has already been reduced to approximately 50% at the diagnosis of type 2 diabetes and will continue to decline over the life of the patient.[12] (See Figure 2.)

Figure 1. Natural history of type 2 diabetes[13]



(note 126 mg/dL = 7.0 mmol/L)
Reproduced from Cefalu W, New Options in Exogenous Insulin Therapy, www.diabetesroundtable.com/courses/update/options.asp.

Figure 2. Stages of type 2 diabetes[13]



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2.2 Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada recommendations

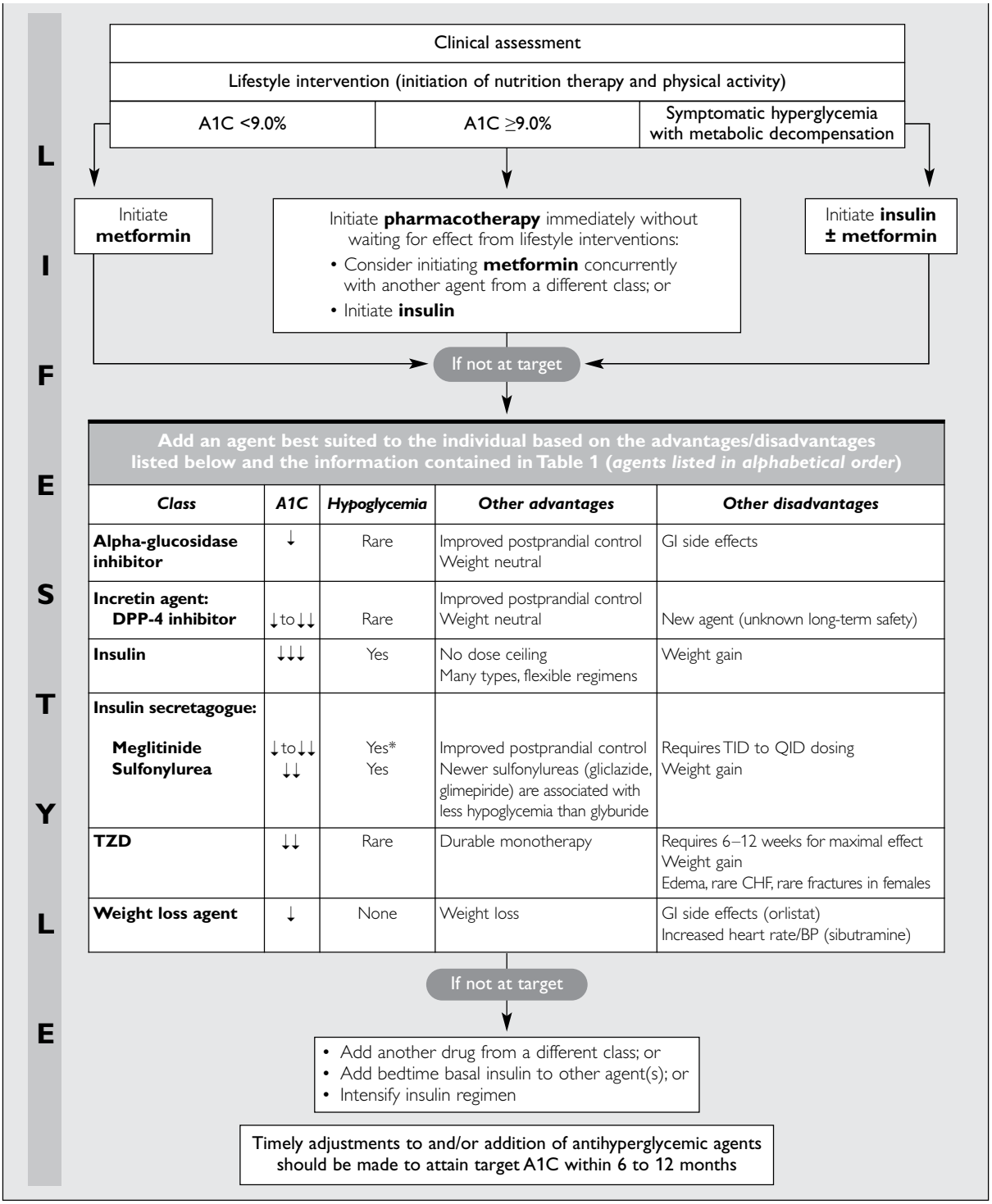
The Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada include a section dedicated to pharmacologic management of type 2 diabetes. The key messages of this chapter are:

1. If glycemic targets are not achieved within 2 to 3 months of lifestyle management (nutrition therapy and exercise recommendations), antihyperglycemic pharmacotherapy should be initiated.
2. Timely adjustments to and/or additions of antihyperglycemic agents should be made to attain target A1C within 6 to 12 months.
3. In patients with marked hyperglycemia (A1C ≥ 9.0%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to either initiating combination therapy with 2 agents or initiating insulin.[3]

For patients with severe hyperglycemia (i.e., A1C ≥ 9.0%), a combination of agents and/or insulin is usually required to reach the target A1C of ≤ 7.0%, and clinicians should not wait to assess the impact of lifestyle interventions before adding pharmacologic therapy. This is because nutrition therapy can reduce A1C by 1–2% and this alone is not sufficient to reduce severe hyperglycemia (>9.0%) to target.[3] At diagnosis, many patients will already have had the disease for some time and may present with microvascular and/or macrovascular complications. Because even short-term hyperglycemia can cause vascular damage, timely adjustments to and/or additions of oral hypoglycemic agents should be made to achieve target A1C levels within 6 to 12 months. (See Figure 3.) Furthermore, since type 2 diabetes is associated with progressive decline of pancreatic beta-cell function, a patient who was previously controlled will likely experience a loss of glycemic control despite continued adherence to current therapy. It is for this reason that treatment must be dynamic and there must be timely addition or adjustment of therapy. Achieving target values requires hard work and perseverance – a real team effort is required in which the person with diabetes undertakes an active role in self-management.[14]

Unfortunately, it is reported that current treatment practice fails to keep pace with disease

Figure 3. Management of hyperglycemia in type 2 diabetes[3]



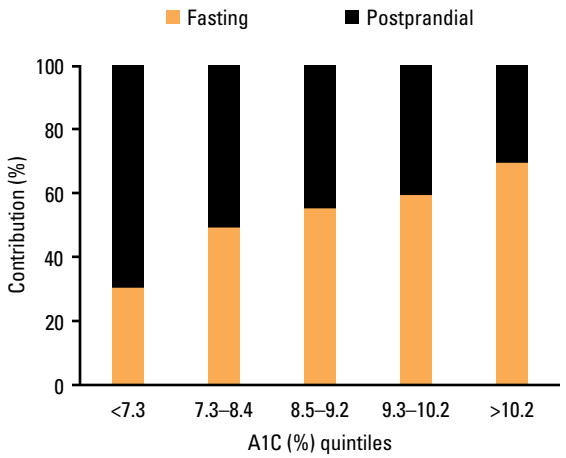
A1C = glycated hemoglobin
BP = blood pressure
CHF = congestive heart failure
DPP-4 = dipeptidyl peptidase-4
GI = gastrointestinal
TZD = thiazolidinedione
↓ = <1.0% decrease in A1C
↓↓ = 1.0–2.0% decrease in A1C
↓↓↓ = >2.0% decrease in A1C

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

*Less hypoglycemia in the context of missed meals

Reproduced from Can J Diabetes. 2008; 32 (suppl 1); S1-S201

Figure 4. Contribution of fasting and postprandial glycemia to A1C in type 2 diabetes[15]



progression, and near-normal glucose levels are rarely achieved. Often, clinical inertia occurs as providers fail to intensify management despite inadequate glycemic control.

2.3 Postprandial blood glucose testing

It is worth noting that, in general, as A1C levels decrease toward normal levels (<7.3%), postprandial BG control assumes greater importance for further A1C reduction.[15] This is an important fact to consider when a patient in your pharmacy inquires as to the best time to test his/her blood sugar. If their A1C is considerably elevated, preprandial testing should be suggested, but if their A1C is marginally elevated (<7.3%), postprandial testing may be of greater benefit for A1C reduction. (Figure 4)

3. Oral hypoglycemic agents and insulin

The pathophysiology that defines type 2 diabetes involves a variety of dysfunctions: insulin resistance, defective insulin secretion, and excessive hepatic glucose release. Correspondingly, oral antihyperglycemic medications can be divided into 5 groups by their mode of action:

- agents that reduce peripheral tissue insulin resistance (thiazolidinediones)
- agents that reduce glucose production by the liver (biguanides)
- agents that stimulate the pancreas to release more insulin (sulphonylureas and meglitinides)
- agents that slow the digestion of complex sugars and therefore decrease the rise in glucose (alpha-glucosidase inhibitors)
- agents that stimulate insulin secretion in a glucose-dependent fashion, inhibit glucagon secretion, and slow gastric emptying (incretin mimetics and DPP-4 inhibitors)

There is a vast selection of different medications available to achieve glycemic targets, and one consider a number of factors when selecting the treatment regimen for an individual with diabetes. These include the person's degree of hyperglycemia, the properties of the antihyperglycemic agents (effectiveness in lowering BG, durability of glycemic control, side effects, contraindications, risk of hypoglycemia), the presence of diabetes comorbidities, and the patient's ability to adhere to the regimen.[3] Unfortunately, the patient's ability to pay is also a determining factor in agent selection. Figure 3 outlines the advantages and disadvantages of each of the available classes of OHAs (oral hypoglycemic agents) with respect to efficacy, hypoglycemia, and tolerability. Each agent will be discussed in greater detail within the next section.

The guidelines state that in general, oral hypoglycemic agent monotherapy will lead to a decrease in A1C of between 0.5% and 1.5%, depending on the agent used and the baseline A1C. Typically, the higher the baseline A1C, the greater the A1C reduction one can expect from the addition of each oral agent.[16] If glycemic targets are not achieved with a single OHA, it can be combined with another agent from one or more other classes. In fact, the initial use of combinations of less than maximum dosages of different OHAs produces more rapid and greater glycemic control than the maximum dosage of any one agent. These benefits occur without a substantial increase in side effects.[17] When considering combination therapy (with or without insulin), the guidelines state that the agents selected should be from classes of agents that have different mechanisms of action.[3]

There is debate over which agent should be used initially and which agent should be added sequentially to achieve target A1C level. It seems as if the issue of how to reach glycemic targets may be less important than the need to achieve that target. It is well established that metformin should be recommended as the initial agent in most patients based on its effectiveness in lowering BG, its relatively mild side effect profile, and its demonstrated benefit in overweight patients. According to the guidelines, monotherapy with an insulin sensitizer (thiazolidinedione) produces more long-lasting glycemic control compared to metformin or sulfonylurea therapy, but the edema, weight gain, small risk of congestive heart failure (CHF),

increased risk of fractures in women, and inconsistent data regarding cardiovascular outcomes offset the potential for this class to be recommended as first-line therapy.[3]

3.1 Alpha-glucosidase inhibitors (acarbose [Prandase, Glucobay])

Alpha-glucosidase inhibitors reversibly block a number of alpha-glucosidase enzymes (e.g., maltase), consequently delaying the absorption of sugars from the gut. By doing so, they reduce both postprandial glucose and insulin levels. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A1C levels by a modest 0.5–0.8%.[18,19] There are no major safety considerations with acarbose, but there are significant tolerability issues. These effects are due to the agent's direct effects in the intestines, where they competitively inhibit the enzymes responsible for the conversion of complex sugars into simple sugars, thereby shunting some of the partially digested carbohydrate into the large bowel, where it is fermented to gases and short chain fatty acids. Bloating, abdominal discomfort, diarrhea, and flatulence occur in approximately 20% of patients who take this agent.[20] Hypoglycemia is not a major concern with this agent when used in monotherapy. It is also considered to be weight neutral or associated with very modest weight loss.[21]

In order to be effective, these agents must be taken with the first bite of food. The best way to minimize the adverse effects of acarbose is to initiate it at minimal dosages and gradually increase the amount as tolerance improves in a week or so. For example, a patient can be instructed to start with half of the smallest tablet with one meal per day, then at each meal, and then increase the dosage until blood glucose is at target. An effective way to engage patients in self-management is to instruct them to test both pre- and postprandial blood sugar. Start with one meal per day. By aiming for an appropriate rise in blood glucose following a meal (2.0–4.0 mmol/L), patients can quickly determine if acarbose is helping and what the correct dosage should be. Although adverse effects tend to decrease over time, the person with pre-existing digestive problems needs to take special care. Because the digestion of sugar, fruit, and juice is delayed by acarbose, the person who adds a secretagogue or insulin to the regimen must treat hypoglycemia with glucose (dextrose) tablets or, if glucose is unavailable, milk or honey.[3]

Dosage and titration

Acarbose should be initiated at a dose of 50 mg once daily, with the first bite of a meal. Increase to 50 mg BID and then TID (titrate over 1–2 weeks if needed), based on 2-hour postprandial glucose levels and tolerance. Once a maintenance dosage of 50 mg TID is achieved, some patients may benefit from further increasing the dosage to 100 mg TID after 4–8 weeks of therapy. Maximum dosage recommended is 100 mg TID.[22]

When educating patients regarding the mechanism of action of acarbose, a simple analogy can be made as follows: "Acarbose can be compared to a turnstile in an arena. Just as the turnstile allows only one person to enter at a time, acarbose allows a limited amount of carbohydrate to be digested at a time."[10]

3.2 Biguanides (metformin)

Metformin is the only biguanide available worldwide. It is available both as a single-entity medication (Glucophage, Glumetza) and as a combination pill (Avandamet [rosiglitazone/metformin] and Janumet [sitagliptin/metformin]) in Canada. It is well tolerated with no major safety issues. Its primary effect is to decrease hepatic glucose output and lower fasting blood glucose. Typically, metformin monotherapy will lower A1C levels by approximately 1.5%; hence, it has been recommended as the preferred first-line oral agent by the authors of the 2008 CDA guidelines.[3] Metformin monotherapy is not usually accompanied by hypoglycemia. One of the major benefits of metformin is weight stability or modest weight loss, in contrast with many of the other blood-glucose-lowering medications.

Metformin is generally safe; however, the use of metformin has been associated with the development of lactic acidosis, a rare but serious condition with a case fatality rate of up to 50%. Therefore, the list of contraindications and precautionary conditions for the use of metformin is extensive and primarily includes CHF, renal or hepatic insufficiency, co-existing acidosis, and the use of iodinated contrast. Studies have revealed that contraindications to the use of metformin are ignored in a significant number of patients. This could reflect physicians' general lack of awareness of the prescribing guidelines or perhaps due to the fact that many physicians believe that the benefits associated with the use of metformin far outweigh the minor risks in the presence of underlying CHF or renal or hepatic insufficiency.[23]

Guidelines regarding the dose of metformin according to eGFR (estimated glomerular filtration rate) are as follows:

Action should be taken as outlined below if the eGFR is abnormal on 2 consecutive results at least 6 weeks apart:

- eGFR > 50: no need to alter metformin
- eGFR 30–50: reduce metformin dose to 500 mg BID
- eGFR <30: stop metformin[24]

While clinical trial and real-life experience have shown this agent to be quite safe, there are considerable tolerability issues for some patients. Approximately 10–15% of patients taking metformin will experience abdominal discomfort, anorexia, bloating, and/or diarrhea.[25] To minimize GI upset, it can be effective to advise the patient to start with a low dose (250 mg, or ½ of a 500 mg tab) and instruct them to take it once daily at the largest meal and increase the dose by 250 mg (½ tab) every 4–7 days as tolerated, until the desired dosage as prescribed by the physician is attained. If gastrointestinal side effects appear as doses advance, decrease to previous lower dose and try to advance the dose at a later time.

Vitamin B_{12} deficiency is reported as a consequence of metformin therapy. Patients should be advised to have their vitamin B_{12} level monitored, as this is not routinely done by many family physicians.[26]

Dosage and titration

Initiate at 250–500 mg with a meal and titrate as tolerated or needed to a maximum of 2.5 grams/day. There appears to be minimal clinical benefit in increasing the dose beyond 2000 mg per day.[27] Adherence may be improved if patients are advised to take metformin twice daily (2 at breakfast and 2 at supper) instead of 1 tablet 4 times daily.

When educating patients with regards to the mechanism of action of metformin, a simple analogy is as follows: "In type 2 diabetes, the liver 'leaks' excess glucose, much like a faulty tap leaks water. Metformin can be compared to a wrench that 'turns off' the 'leaky liver.'"[28]

3.3 Incretin agents

Incretin hormones such as GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) are endogenous hormones that are released from the intestine in response to food. They help regulate blood glucose via effects on the GI tract, endocrine glands, and the central nervous system. Actions of incretin hormones include glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, reduction of appetite, and delay of food absorption.[29] Unfortunately, our bodies destroy GLP-1 within a few minutes. The enzyme that destroys GLP-1 is called dipeptidyl-peptidase 4 (DPP-4), and intense research is underway to determine ways to disable the enzyme so that GLP-1 can do its job for longer periods of time.

With the aim of enhancing and prolonging the actions of the endogenous incretin hormones, various incretin therapies have been investigated for the treatment of type 2 diabetes. Agents studied can be broadly grouped into 2 major subcategories and they work through 2 distinct but related mechanisms. The GLP-1 receptor agonists (e.g., liraglutide, exenatide) mimic the actions of endogenous GLP-1. Exenatide is a GLP-1 mimetic, while liraglutide is a GLP-1 analogue. DPP-4 inhibitors (e.g., saxagliptin, sitagliptin, vildagliptin) work through the inhibition of the enzyme DPP-4, responsible for breakdown of native GLP-1. These agents are an important addition to the diabetes treatment paradigm because they target physiologic defects not addressed by other medications and are not associated with hypoglycemia or weight gain. Incretin mimetics such as exenatide (Byetta) and liraglutide (Victoza) are under development and will be discussed in greater detail in Section 3.8.[30]

3.3.1 Dipeptidyl peptidase four (DPP-4) inhibitors

Sitagliptin (Januvia) belongs to a new class of oral anti-hyperglycemic known as a DPP-4 inhibitor or incretin enhancer, used for the treatment of type 2 diabetes. The primary advantage of this approach to prolonging the effects of GLP-1 is that DPP-4 inhibitors can be given orally. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower fasting and postprandial glucose and hence lower hemoglobin A1C.[31]

A Cochrane Review in 2008 of 11 studies (12–52 weeks), including over 6000 patients, found sitaglipitin reduced A1C levels by an average of 0.7%, with similar efficacy to monotherapy or add-on therapy.[32] Sitagliptin is considered to be weight neutral; no clinically significant increase in weight has been observed. Hypoglycemia is uncommon with sitagliptin, as its effects are evident only in the presence of glucose.

Sitagliptin is approved for use in Canada as add-on therapy to metformin. Clinical studies have shown improvement in beta-cell function, suggesting a potential for preservation of beta-cells.[33,34]

Dosage and titration

Sitagliptin is dosed at 100 mg daily. It may be taken with or without food.

In October 2009, a combination product containing sitagliptin and metformin (Janumet) received its Notice of Compliance and is now available. It is recommended that the dosage of Janumet be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2,000 mg metformin. Janumet should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal side effects due to metformin.[35] Janumet is available in two strengths: 50 mg/500 mg and 50 mg/1000 mg (sitagliptin/metformin).

In November 2009, Health Canada approved another DPP-4 inhibitor, saxagliptin (Onglyza). Onglyza is indicated for patients with type 2 diabetes to improve glycemic control in combination with metformin or a sulfonylurea when metformin or the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control. It is available as a once-daily tablet (5 mg). Safety analyses reveal that the most common adverse events reported with saxagliptin include nasopharyngitis, bronchitis, and urinary tract infection.[36] Other drugs in this class are currently under development and include vildagliptin (Galvus), linagliptin, and alogliptin.[37]

3.4 Insulin

Insulin allows glucose to enter the cells and inhibits the conversion of glycogen, fat, and protein into glucose. Endogenous insulin is secreted in two ways: a small continuous basal flow to balance the release of glycogen from the liver during fasting, and bolus amounts in response to rising blood glucose after food intake. The purpose of insulin therapy is either to replace the person's endogenous insulin completely (type 1 diabetes) or to supplement it in order to maintain blood glucose within appropriate targets (type 2 diabetes).

There is no question that insulin initiation is time consuming and requires extensive initial and ongoing education for the patient. It requires new information and a new skill set, as well as the ability to problem-solve and self-manage. Information provided includes how to care for and use insulin; prevention, recognition, and treatment of hypoglycemia; sick-day management; self-monitoring of blood glucose; and adjustments for food intake (carbohydrate counting) and variable physical activity.[3]

In patients with marked hyperglycemia (A1C ≥9.0%), initiation of insulin is an effective recommendation. It may also be used if oral hypoglycemic agents (OHAs) are contraindicated or ineffective as well as for temporary use during pregnancy, illness, a medical procedure, or surgery. The guidelines state that when insulin is added to OHAs, a single injection of NPH, glargine, or detemir may be used. This approach may result in better glycemic control with a smaller dose of insulin and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone.[3] Historically, physicians did not routinely recommend insulin for type 2 diabetes until complications appeared. Unfortunately, patients were often threatened with being "put on the needle" if they did not do as they were told. As a result, insulin was often viewed as a form of punishment or a "last resort." Today, many physicians prefer to initiate insulin earlier rather than later to minimize exposure to hyperglycemia and its ensuing complications. In fact, lessons learned from UKPDS indicate that newly diagnosed patients with type 2 diabetes already have lost approximately 50% of their beta-cell function and despite treatment with diet, metformin, or sulfonylureas, this loss will continue at an approximate rate of 4–5% per year.[38]

It is important to promote insulin in a positive way and to discuss insulin as a treatment option. Patients need to know that they may eventually require insulin therapy to complement their progressively diminishing endogenous supply. Insulin therapy can easily be equated to vitamin supplements in the sense that it "corrects a deficiency."

When a patient is presented with the benefits of insulin, witnesses the ease of injections with new insulin pens, and understands that it is a natural progression of type 2 diabetes rather than instilling blame, he or she may well be in favour of starting this therapy when the time comes.

When educating patients with regard to the actions of insulin, a simple analogy that can be made is as follows: "Insulin works like a key to open the locks on the cell doors (receptors) to allow sugar (glucose) to enter the cell where it can be used to create energy."

Education surrounding the vast variety of insulins and regimes available to health care providers is extensive and deserving of a separate continuing education module, hence they will not be discussed in greater detail within the scope of this lesson.

3.5 Insulin secretagogues

3.5.1 Sulfonylureas

Sulfonylureas were the first oral agents introduced for the treatment of type 2 diabetes and have been used for approximately 50 years.[39] Agents in this class include gliclazide (Diamicron), glimepiride (Amaryl), and glyburide (Diabeta, Euglucon). In addition to single-entity medication, a combination

pill containing both rosiglitazone and glimepiride (Avandaryl) is available. Sulfonylureas are considered to be second-line therapy according to the 2008 CDA Guidelines. They lower blood glucose by enhancing insulin secretion, regardless of blood glucose level. Due to this mechanism of action, they are associated with the most significant risk of hypoglycemia among the OHAs. Within the class, there are also differences in the likelihood of hypoglycemia, with glyburide having the highest risk, glimepiride a more moderate risk, and gliclazide a minimal-to-moderate risk.[3] The higher risk for hypoglycemia with glyburide might be due to its time-activity profile.[40] This refers to the fact that glyburide has a longer duration of binding to the sulfonylurea receptor in the pancreas than other drugs in its class. The result is a higher degree of fasting hyperinsulinemia than with other sulfonylureas. Glimepiride and gliclazide are thought to be more glucose-sensitive in their stimulation of insulin secretion.[41] Sulfonylureas are also known to lead to weight gain. This is particularly true of glyburide, although both glimepiride and gliclazide are known to cause weight gain as well. In terms of efficacy, they are similar to metformin, lowering A1C levels by approximately 1.5%. Although the onset of the glucose-lowering effect of sulfonylurea monotherapy is relatively rapid compared with, for example, the thiazolidinediones (TZDs), maintenance of glycemic targets over time is not as good as monotherapy with a TZD or metformin.[42] Consider using other classes for those at high risk for hypoglycemia (e.g., the elderly), but if a sulfonylurea must be used for such individuals, gliclazide and glimepiride are best.

Dosage and titration

Glyburide (Diabeta): Initial dose should be 2.5 mg or 5.0 mg once daily and titrated to a maximum of 10 mg BID, given prior to breakfast and supper.

Gliclazide (Diamicron): Initial dose for Diamicron should be 80 mg daily and titrated biweekly to a maximum of 160 mg BID. Initial dose for Diamicron MR 30 should be 30–60 mg once daily at breakfast and titrated to a maximum of 120 mg once daily.

Glimepiride (Amaryl): Initial dose should be 1 mg with breakfast or the first main meal of the day. The usual maintenance dose is 1–4 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 1 mg at 1- to 2-week intervals based on the patient's blood glucose response. The maximum recommended dose is 8 mg once daily.[43]

3.5.2 Meglitinides

Like the sulfonylureas, the meglitinides (repaglinide [GlucoNorm], nateglinide [Starlix]) stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor.[44] Unlike sulfonylureas, repaglinide and nateglinide stimulate first-phase insulin release in a glucose-sensitive manner. They effectively deliver an early transient "burst" of insulin at the initiation of a meal. This early insulin release may more rapidly suppress hepatic glucose production and reduce the stimulus for additional insulin required subsequently to dispose of a larger glucose load. In addition, the pattern of insulin stimulation, essentially a more rapid onset and shorter duration, will reduce the risk for postabsorptive hypoglycemia and limit exposure to hyperinsulinemia.[41]

Meglitinides have a shorter circulating half-life than the sulfonylureas and, as a result, must be administered more frequently. Of the two meglitinides currently available in Canada, repaglinide (GlucoNorm) is almost as effective as metformin or the sulfonylureas, decreasing A1C levels by approximately 1.5%. Nateglinide (Starlix) is somewhat less effective in lowering A1C than repaglinide and yields a reduction in A1C in the region of 1%. The risk of weight gain is similar to that for the sulfonylureas, but nateglinide and repaglinide are associated with less hypoglycemia in the context of missed meals.[3]

Dosage and titration

Nateglinide (Starlix): Recommended dosage is 180 mg BID to 180 mg TID, taken 1 to 30 minutes before meals.

Repaglinide (Gluconorm): Recommended dosage is 0.5 mg to 4 mg, 1 to 30 minutes before each meal to a maximum of 16 mg per day. Dosage is usually titrated to achieve target postprandial blood glucose of <10.0 mmol.

When educating patients regarding the mechanism of action of sulfonylureas or meglitinides, a simple analogy can be made as follows: "These medications stimulate the pancreas to produce more insulin, similar to wringing out a damp washcloth until drops of water are produced." Another simple analogy can be made by explaining that these medications work like "personal trainers" to help whip the "pooped out" pancreas into releasing more insulin.

3.6 Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs or glitazones) are peroxisome-proliferator-activated receptor gamma modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers").[45] Two single-

entity agents are available in Canada, pioglitazone (Actos) and rosiglitazone (Avandia), as well as a combination pill containing rosiglitazone and metformin (Avandamet) and rosiglitazone and glimepiride (Avandaryl). TZDs appear to lower A1C by approximately 1.5%, which is similar to metformin and sulfonylureas. There is data to suggest that they have a more durable effect on glycemic control, particularly when compared to sulfonylureas.[42] There is negligible risk of hypoglycemia with TZDs in monotherapy.[3] TZDs are recommended as a second- or third-line agent for patients not at goal on monotherapy or as combination therapy to produce a more rapid and sustained glycemic effect. Unfortunately, these agents have been associated with significant safety concerns. These include edema, weight gain, risk of congestive heart failure (rare), increased risk of fractures in women (rare), and possible increased overall cardiovascular risk. The most common adverse effects with TZDs are weight gain and fluid retention, with peripheral edema and a two-fold increased risk for congestive heart failure.[46]

Although blood glucose levels may decrease in 4–8 weeks, a response may not be evident for 8–12 weeks when TZDs reach their maximum effect. The combination of insulin and an insulin sensitizer has not been approved in Canada, although it is often used together in other countries.[47] Many practitioners find dual therapy helpful, particularly in cases of severe insulin resistance; however, they must monitor the patient carefully. If a TZD is added to insulin therapy (an unapproved indication), the person generally needs to decrease the insulin dosage by 10–20% after one week, and may be able to reduce it further if FBG is <7.0 mmol/L.[10]

TZDs have beneficial clinical effects beyond lowering blood glucose, including a positive influence on some cardiovascular parameters, such as HDL, TC/HDL profiles, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic status.[48]

The big question that has concerned physicians and their patients of late is the relationship between TZDs, specifically rosiglitazone, and the risk of cardiovascular disease and death. This controversy started in May of 2007, when a meta-analysis was reported in the New England Journal by Dr. Steven Nissen, a clinical cardiologist from the Cleveland Clinic.[49] This article identified potential concerns about rosiglitazone and its risk for myocardial infarction in cardiovascular disease. Subsequently, it has been shown that the Nissen meta-analysis was flawed, due to a variety of reasons. Four large randomized controlled clinical trials (RECORD, ADVANCE, VADT, ACCORD), meta-analyses, and epidemiological cohort studies have *not* shown any signals or statistically significant outcomes for TZDs and myocardial infarctions or cardiovascular death.[50] Controversy regarding the cardiovascular safety of TZDs still exist, as highlighted in a recent Medical Post Article in September of this year.[51]

Dosage and titration

Pioglitazone (Actos): Initial recommended dosage is 15–30 mg once daily without regard to meals. Dose may be titrated by 15 mg every 12 weeks to a maximum of 45 mg once daily.[52]

Rosiglitazole (Avandia): Recommended dosage is 4 mg once daily or divided doses BID. If response is inadequate after 8–12 weeks, the dose may be increased to 8 mg daily (or divided BID). The dose of Avandia in combination with a sulfonylurea should not exceed 4 mg daily.[53]

When educating patients regarding the mechanism of action of TZDs on the insulin receptors in the muscle, liver, and fat cells, it can simply be explained as follows: "In type 2 diabetes, the locks on the cell doors that allow glucose to enter become 'rusty.' TZDs can be compared to WD-40, which 'lubricates' the rusty locks (receptors) on the cell doors, and allows the insulin (key) to open the door and move glucose into the cell."

3.7 Antiobesity agents

Obesity is the result of energy intake exceeding energy expenditure. Obesity can contribute to insulin resistance; hence, a reduction in body weight can increase the body's sensitivity to insulin production or administration. A 5–10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations.[54]

Currently available prescription drugs for managing obesity reduce weight by decreasing dietary fat absorption (orlistat) or inducing satiety (sibutramine).

3.7.1 Orlistat (Xenical)

Xenical acts locally to inhibit GI lipases, blocking the absorption of approximately 30% of dietary fat. It is indicated for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet. Xenical is also indicated to reduce the risk of weight regain after prior weight loss. It is indicated for obese patients with an initial body mass index (BMI) of >30 kg/m^2, or >27 kg/m^2 in the presence of other risk factors, such as type 2 diabetes, hypertension, and dyslipidemia.[55]

BMI (body mass index) is defined as the individual's body weight (in kilograms) divided by the square of his or her height (in metres). BMI is a

useful tool to estimate a healthy body weight based on a person's height. People are classified as being underweight, overweight, or obese.

When taking Xenical, patients should be advised to take a multivitamin supplement containing fat-soluble vitamins to ensure adequate nutrition. This is because Xenical has been shown to reduce the absorption of some fat-soluble vitamins, including beta-carotene, and because the levels of some fat-soluble vitamins and beta-carotene may be low in obese patients compared to non-obese patients.[71] The supplement should be taken once a day at least 2 hours before or after administration of Xenical, for example at bedtime. Unfortunately, many patients taking Xenical experience increased flatulence with discharge or uncontrolled oily leakage when eating fatty food.

Dosage and titration

The recommended dose of Xenical is one 120 mg capsule 3 times a day, once with each main meal containing fat (during or up to 1 hour after the meal). The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over 3 main meals. If a meal is occasionally missed or contains no fat, the dose of Xenical can be omitted. Doses above 120 mg 3 times a day have not been shown to provide additional benefit.

3.7.2 Sibutramine (Meridia)

Sibutramine acts as a reuptake inhibitor of both norepinephrine and serotonin to regulate satiety.[56] It is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet. Sibutramine is recommended for obese patients with an initial body mass index ≥30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).

Dosage and titration

The recommended starting dose of sibutramine is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after 4 weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration. Doses above 15 mg daily are not recommended.[57] Sibutramine is contraindicated in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or cerebrovascular disease (stroke or transient ischemic attack [TIA]). It is also contraindicated in patients with inadequately controlled (BP>145/90 mmHg) or unstable hypertension.[58]

Cases of life-threatening serotonin syndrome have occurred during combined use of sibutramine and SSRIs, SNRIs, and triptans. If concomitant use of sibutramine and SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and SNRIs (desvenlafaxine, duloxetine, venlafaxine) is clinically warranted, then careful monitoring of the patient is advised.[58]

3.8 New agents in the pipelines

3.8.1 Glucagon-like peptide-1 agonists (exenatide [Byetta], exenatide LAR, liraglutide)

Glucagon-like peptide-1 (GLP-1), a naturally occurring peptide produced by the l-cells of the small intestine, has multiple effects to control hyperglycemia. These include the following effects on the following organs:

- intestine: slowing gastric emptying and promoting satiety
- liver: inhibiting glucagon secretion and hepatic glucose production
- pancreas: augmentation of glucose-induced insulin secretion, increased insulin biosynthesis, and promotion of beta-cell differentiation
- adipose and muscle tissue: improving glucose uptake[59]

Unfortunately, naturally occurring GLP-1 has an extremely short half-life, as it is inactivated within minutes by DPP-4. One way to get around the problem of DPP-4 is to administer a form of GLP-1 that is resistant to destruction. Such forms of GLP-1 have already been found in an unexpected source: the poisonous saliva of the Gila monster lizard. The Gila monster eats four times a year, and at these times, a GLP-1, exendin-4, is released to "turn the pancreas on."[60] GLP-1 (called exendin-4) from these reptiles has a few distinct differences from the form found in humans, one consequence of which is immunity to DPP-4.

Synthetic exendin-4 (exenatide [Byetta]), a GLP-1 mimetic, was approved for use in the US in 2005 and although there is less published data on this new compound than the other blood-glucose-lowering medications, exenatide appears to lower A1C levels by 0.5–1.0%.[61] Exenatide also suppresses glucagon secretion and slows gastric motility. It is not associated with hypoglycemia but can cause gastrointestinal disturbances such as nausea, vomiting, or diarrhea. These side effects tend to abate over time. One of the unique benefits of exenatide is that it is associated with significant

and sustained weight loss.[62] There have been news reports of nondiabetic individuals using exenatide off-label to lose weight. This has caused concerns regarding the safe use of exenatide, since the drug has not been studied for weight loss.[63] The initial dose of exenatide is 5 µg twice daily, within 60 minutes before the morning and evening meal. It should not be administered after a meal. After one month of therapy, if adequate glycemic control has not been achieved, the dose can be increased to 10 µg twice daily. Doses should be administered subcutaneously, in the thigh, abdomen, or upper arm.[64]

Although exenatide has been approved for clinical use, it requires twice-daily injections to be effective. Consequently, GLP-1 receptor agonist development has evolved with the generation of longer-acting GLP-1 mimetic agents that require less frequent dosing, ranging from daily to weekly to biweekly administration. Agents currently under investigation include exenatide LAR (Byetta LAR), albiglutide (Syncria), and liraglutide (Victoza).[65,66,67,68]

3.8.2 Pramlintide (Symlin)

Pramlintide (Symlin) is a synthetic analog of the human neuroendocrine hormone amylin. Symlin was approved for use in the United States in March 2005 and is indicated for type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy. It is also indicated in type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin. It works by modulating gastric emptying, preventing an increase in serum glucagon following a meal, and increasing the feeling of satiety, resulting in decreased caloric intake and potentially weight loss.[69]

Symlin is administered subcutaneously prior to each main meal. When initiating therapy with Symlin, initial insulin dose reduction is required in all patients (approximately 50%) to reduce the risk of insulin-induced hypoglycemia. The initial dosage in type 1 diabetes is 15 µg and titrated to a maintenance dose of 30–60 µg. In type 2 diabetes, this initial dose is 60 µg and titrated to a maintenance dose of up to 120 µg as tolerated.[70] Mild nausea is the primary side effect of Symlin.

References

1. Ohinmaa A, Jacobs P, Simpson SH, Johnson JA. The projection of prevalence and cost of diabetes in Canada: 2000 to 2016. Can J Diabetes 2004;28(2):116–123
2. Diabetes Prevalence. www.idf.org. Accessed September 14, 2009
3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2009 Clinical Practice Guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32(Suppl 1):S1–S201
4. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007;369(9563):750–756
5. Type 2 Diabetes Case: Examining the Evidence. www.mdbriefcase.com/process/view.asp?case_id=628&section=in. Accessed September 14, 2009
6. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. NEJM 1993;329:978–986
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS 33). Lancet1998;352:837–853
8. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34). Lancet1998352:854–865
9. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with NIDDM: a randomized prospective 6-year study. Diabetes Res Clin Pract 28;1995:103–117
10. O'Grady D. To Teach, To Learn, To Live, 2nd Edition. Healthy Self, 2006
11. Cefalu WT. Pharmacotherapy for the Treatment of Patients with Type 2 Diabetes Mellitus: Rationale and Specific Agents. Clin Pharmacol Ther 2007;(81):636–649
12. Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. www.ncbi.nlm.nih.gov/pubmed/17353295. Accessed September 14, 2009
13. Cefalu W. New Options in Exogenous Insulin Therapy. http://www.diabetesroundtable.com/courses/update/options.asp. Accessed September 14, 2009.
14. Dunbar P, McSherry JA. Insulin Therapy: Repositioning a misunderstood science. Canadian Diabetes 1998;11(3):1–8

15. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003;26:881–885.
16. Bloomgarden ZT, Dodis R, Viscoli CM, et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 2006;29:2137–2139.
17. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab 2002;4:201–208
18. Van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev 2005;2:CD003639
19. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM Trial. JAMA 2003;290:486–494
20. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet 2002;359(9323):2072–2077.
21. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care 1999;22(6):960–964
22. Glucobay Product Monograph. www.bayer.ca/files/GLUCOBAY-PM-ENG-10JUN2008-120538.pdf. Accessed September 14, 2009.
23. Khandwala H. The Prevalence of Contraindications to the use of Metformin. Can J Diabetes 2004;28(4):380–384
24. The Tayside Diabetes Handbook: Screening and Management of Kidney Complication. www.diabetes-healthnet.ac.uk/HandBook/ScreeningOfKidney2.aspx. Accessed September 14, 2009.
25. Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ 2005;172(2):213–226
26. Hermann LS, Nilsson B, Wettre S. Vitamin B12 Status of Patients Treated With Metformin: A Cross-Sectional Cohort Study. Br J Diabetes Vasc Dis 2004;4(6):401–406.
27. Garber AJ. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med 1997;103(6):491–497
28. Swenson K, Brackenridge B. Diabetes Myths, Misconceptions and Big Fat Lies. www.diabetestraining.com. Accessed September 14, 2009
29. Perfetti R, Brown T, Velikina R et al. Control of Glucose Homeostasis by Incretin Hormones. Diabetes Tech Therapeut 1999:1(3):297–305
30. Halimi S, Debaty I, Villaret L et al. New therapies for type 2 diabetes: What place for incretin-based agents and rimonabant compared to the previous ones? Rev Med Interne 2008;29(11):881–890
31. Januvia product monograph. www.merckfrosst.ca/assets/en/pdf/products/JANUVIA_1125-a_3_08-E.pdf. Accessed September 14, 2009
32. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007;298:194–206
33. New Drug: Januvia (Sitagliptin). Pharmacist's Letter. February 2008.
34. Sitagliptin for Type 2 diabetes. The Medical Letter 2007;49(251):1–3
35. Janumet: Efficacy:Starting Therapy. www.januvia.com/sitagliptin/januvia/hcp/janumet/index.jsp. Accessed September 14, 2009.
36. Onglyza product monograph. www.bmscanada.ca/upload/File/pdf/products/ONGLYZA%20PM%20English%20Approved%202009-09-14.pdf. Accessed September 14, 2009.
37. FDA Approves next the DPP-4 Inhibitor Onglyza. Diabetes in Control.com. 2009;480 (August 1). www.diabetesincontrol.com/index.php?option=com_content&view=article&id=8185&catid=1&Itemid=8. Accessed September 14, 2009
38. Triplitt C, Chiquette E. Exenatide: From the Gila Monster to the Pharmacy. J Am Pharmaceut Assoc 2006;46(1):44–55
39. Pharmacist's Letter 2009 (April);25:250423
40. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 Diabetes. Diabetic Medicine 2008;25:245–254
41. Cefalu WT, Waldman S, Ryder S. Pharmacotherapy for the treatment of patients with type 2 diabetes mellitus: rationale and specific agents. Clin Pharmacol Therapeut 2007;81(5):636–649
42. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. NEJM 2006;355:2427–2443
43. Amaryl Product Monograph. www.sanofi-aventis.ca/products/en/amaryl.pdf. Accessed September 14, 2009
44. Malaisse WJ. Pharmacology of the meglitinide analogs: new treatment options for type 2 diabetes mellitus. Treat Endocrinol 2003;2(6):401–414
45. Yki-Jarvinen H. Drug therapy: thiazolidinediones. NEJM 2004;351:1106
46. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleoanalysis. Diabetes Care 2007;30:2248–2254
47. Conway R. Concomitant Use of TZDs and Insulin. www.diabetesclinic.ca/en/avandia/avandia_insulin.htm. Accessed September 14, 2009
48. Diabetes Vignettes Series. Putting the Evidence into Practice. www.mdbriefcase.com/process/view.asp?section=c2&subsection=iq#qa_top. Accessed

September 14, 2009
49. Nissen S, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. NEJM 2007;356(24:2457–2471
50. MD Briefcase. www.mdbriefcase.com/process/view.asp?section=kp&case_id=673. Accessed September 14, 2009
51. McAllister J. Ontario study reheats rosiglitazone controversy. Medical Post 2009; 45(18)
52. Actos product monograph. www.lilly.ca. Accessed September 14, 2009
53. Avandia product monograph. www.gsk.ca/english/docs-pdf/Avandia_PM_20090312_EN.pdf. Accessed September 14, 2009
54. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. The evidence report. Washington, DC: U.S. Department of Health and Human Services, 1998; NIH publication no. 98-4083
55. Xenical product information. www.xenical.com. Accessed September 14, 2009
56. McNeely W, Goa KL. Sibutramine: A review of its contribution to the management of obesity. Drugs 1998;56:1093–1124.
57. Meridia. www.rxlist.com/meridia-drug.htm. Accessed September 14, 2009
58. Meridia product monograph. www.abbott.ca. Accessed September 14, 2009
59. Brubaker PL, Drucker D. Endocrinology 2004;145:2653–2659
60. Bahal O'Mara N. New Drug; Exenatide (Byetta). Canadian Pharmacist's Letter 2005;12(June)
61. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083–1091
62. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092–1100
63. Berenson A. Diabetics see hope (and weight loss) in new drug. New York Times, March 2, 2006. www.nytimes.com/2006/03/02/business/worldbusiness/02iht-drug.html. Accessed September 14, 2009
64. Byetta (exenatide) prescribing information. Amylin Pharmaceuticals, Inc. www.byetta.com. Accessed September 14, 2009
65. Baggio LL, Drucker DJ. Glucagon-like Peptide-1 Analogs Other Than Exenatide. ADA 68th Scientific Sessions. Medscape. Accessed September 14, 2009
66. DeNoon D. Victoza for Diabetes: Better than Byetta? www.diabetes.webmd.com/news/20090608/victoza-for-diabetes-better-than-byetta. Accessed September 14, 2009
67. GlaxoSmithKline starts Phase III trial of Syncria (albiglutide) type 2 diabetes medication. February 18 2009. www.news-medical.net/news/2009/02/18/45982.aspx. Accessed September 14, 2009
68. Maida A, Drucker D. Exenatide. July 31, 2008. Medscape
69. Symlin Prescribing Information. www.symlin.com/hcp/default.aspx. Accessed September 14, 2009
70. Symlin. www.rxlist.com/symlin-drug.htm. Accessed September 14, 2009
71. Xenical Product Information. www.xenical.com/hcp/3_productinfo.asp . Accessed February 24, 2010.

Questions

1. True or false: For a patient who presents with an A1C of 11.1%, achieving an A1C of 7.5% should be considered a therapeutic success, with no further action required.
   a. true
   b. false

2. The natural progression of type 2 diabetes can best be described as which of the following?
   a. an initial phase of insulin resistance that requires a compensatory increase in insulin secretion to maintain normal blood glucose levels
   b. an initial phase of decreased insulin secretion which results in insulin resistance
   c. an initial phase of increased insulin secretion which results in insulin resistance

3. Which oral agent is recommended as the initial agent of choice for both overweight and non-overweight patients with type 2 diabetes?
   a. thiazoladinedione
   b. alpha-glucosidase inhibitor
   c. sulfonylurea
   d. metformin
   e. DPP-4 inhibitor

Questions 4–6 pertain to the following scenario:
Mr. Silva presents in your pharmacy with a prescription for a blood glucose meter. He tells you that he has just been diagnosed with diabetes and his doctor told him that he needs to start testing his sugar at home. He tells you that his doctor said that he has 2–3 months to try dieting and exercise before he needs any medication. He hands you a prescription for the meter and, surprisingly, a copy of his recent labwork. You notice that his A1C is 9.4%.

4. Is the information provided by his physician in accordance with the 2008 CPGs?
   a. Yes, this is the recommended time allotted for assessment of lifestyle modifications for all patients with type 2 diabetes.
   b. No, he should start medication immediately.

5. If antiphyerglycemic agents were to be started in Mr. Silva, the most appropriate choice of therapy (in addition to lifestyle management) would be:
   a. glyburide
   b. metformin
   c. metformin and gliclazide
   d. pioglitazone and sitagliptin

6. For best patient care, Mr. Silva's physician should adhere to timely adjustments and/or additions of antihyperglycemic agents to attain target A1C within how many months?
   a. 18
   b. 2–3
   c. 6–12
   d. 8

7. Which type of oral antihyperglycemic agent therapy is associated with the highest risk of hypoglycemia?
   a. DPP-4 inhibitor
   b. thiazolidinedione
   c. sulfonylurea
   d. metformin

8. As A1C levels decrease towards the target level, the importance of postprandial glucose for A1C reduction:
   a. increases
   b. decreases
   c. stays the same

9. For a person with type 2 diabetes uncontrolled with oral antihyperglycemic therapy, which approach is likely to be associated with a lower incidence of weight gain and hypoglycemia?
   a. Stop all oral agents and switch to basal insulin.
   b. Add basal insulin to the oral hypoglycemic agents.
   c. The two strategies would have an equal risk of hypoglycemia and weight gain.

10. Mrs. DaCosta comes into your pharmacy and asks you to recommend a medication to help stop her diarrhea. She states that she just started taking metformin last week and takes faithfully with food, 1 tablet 3 times daily, at each meal. What would be the most appropriate recommendation for Mrs. DaCosta?

a. Try Imodium, since there are no drug interactions noted with metformin. Take 2 tablets after the first loose stool, then 1 tablet after each loose stool, maximum 8 tablets per day. Drink plenty of water to prevent dehydration.
b. Reassure Mrs. DaCosta that gas, bloating, and diarrhea is a normal side effect of metformin and it should subside in a week or two, without treatment.
c. Explain to Mrs. DaCosta that gas, bloating, and diarrhea is a normal side effect of metformin and can sometimes be avoided if the dose is started at 250 mg daily and slowly titrated every 4–7 days as tolerated. Offer to contact her physician to see if he/she will agree to a slow titration schedule.
d. It is obvious that Mrs. DaCosta cannot tolerate metformin. Offer to contact her physician to switch to another agent such as gliclazide.

Questions 11 and 12 pertain to the following scenario:

You are meeting today with your 62-year-old patient, Mr. Jenkins, to perform a medication review. He brings in all of his prescription bottles and you note that he is taking the following medications:

- *Avandamet 2/1000 mg, one tablet twice daily*
- *Crestor 10 mg, one tablet daily*
- *Altace 5 mg, one capsule daily*
- *ASA 81 mg, one tablet daily*

He also presents you with a new prescription for Lantus insulin 10 units at bedtime. He states that he is testing his blood glucose regularly and presents his logbook. You review his logbook with him and note that his fasting blood sugar is routinely in the 8.5–9.5 mmol range but by suppertime it has reduced to the 7.0–7.5 mmol range. He says, "I can't believe my doctor is sticking me with insulin now! I feel fine and I thought my sugars were OK. Isn't it good if your sugars are under 10?" You reassure Mr. Jenkins that insulin therapy is the safest and most effective medication to lower A1C. You dispense the prescription for Lantus insulin and review injection technique, site rotation, and storage and disposal of the solostar pen. You remind him to use a new needle tip for each injection.

11. Upon review and analysis of Mr. Jenkins's current pharmacotherapy, you recommend the following:

a. He is to continue taking all other oral medications as previously prescribed. The use of both Avandamet and insulin is quite safe and effective.
b. The Avandamet needs to be stopped when the insulin is started because it is not indicated for concurrent use in Canada.
c. You need to contact his physician to discuss the use of Avandamet. Avandia is not indicated for use with insulin in Canada; therefore, you need to inquire with the prescribing physician whether he wants to switch Avandamet to metformin alone, or proceed with Avandamet as an unapproved indication and inform the patient of the associated risks.

12. With regards to Mr. Jenkins's self monitoring of blood glucose, you would have which of the following comments/recommendations for him?

a. Review appropriate targets for pre- and postprandial blood sugars. You would concur with him that for a man his age, his blood sugars are under control if most of them are <10.0, and he may not actually need insulin right now but you would consult with his physician to be sure.
b. Review appropriate targets for pre- and postprandial blood sugars. You would inform him that if most blood sugars are <10.0 two hours after eating, then his blood sugars are deemed to be in good control. However, if his blood sugars are up to 10.0 before eating, this is considered out of range and he should strive to achieve a lower target of 4.0–7.0 mmol/L .
c. Review appropriate targets for pre- and postprandial blood sugars. You would inform him that it is satisfactory if his post-meal blood sugars are up to 10.0 but not his pre-meal blood sugars (these should be 4.0–7.0). However, if his A1C is not at target after achieving standard pre and post targets, he should aim for tighter post-meal blood sugars in the 5.0–8.0 range (if achieved without hypoglycemia).

13. DPP-4 inhibitors are responsible for which of the following actions?
   a. increasing the plasma concentrations of the active forms of GLP-1 and GIP
   b. decreasing the plasma concentrations of the active forms of GLP-1 and GIP
   c. increasing insulin release and increase glucagon levels in a glucose-dependent manner
   d. increasing insulin release and decrease glucagon levels in a glucose-independent manner

14. Mr. Rosenblum comes into your pharmacy and asks to speak to you in private. He tells you that he just had an appointment with his physician and was told that his three-month average blood sugar (A1C) is 10.4%, so he needs to intensify his therapy. Mr. Rosenblum states that he feels fine and doesn't understand why he needs more medication. You have developed a rapport with him over the last several years, so he feels comfortable telling you that he thinks his doctor is a "pill pusher" and would like your honest opinion. His current therapy is as follows: metformin 500 mg, 2 tablets twice daily, and Diamicron MR 30, 3 tablets at breakfast. What would be the most appropriate response?
   a. "I would agree that you need to intensify your therapy. I would recommend adding Januvia, which is the newest and most effective oral medication."
   b. "I would agree that you need to intensify your therapy. I would recommend adding Avandia, but we can give it in the format of a combined pill with metformin (Avandamet) so you don't have to be taking more pills per day."
   c. "I would agree that you need to intensify your therapy. I would recommend adding bedtime insulin."
   d. "I would not agree with intensifying your therapy. All you need to do is increase the dose of Diamicron to 4 pills per day."

15. Postprandial hyperglycemia is best managed by which of the following agents?
   a. metformin
   b. sitagliptin
   c. basal insulin
   d. pioglitazone

16. Which of the following agents are weight neutral or associated with minimal weight gain?
   a. glyburide and pioglitazone
   b. sitagliptin and metformin
   c. rosiglitazone and glimepiride
   d. repaglanide and acarbose

17. Mrs. Rigato comes into your pharmacy to discuss her diabetes therapy. She is currently taking metformin 500 mg, one at breakfast and one at supper. She tells you that her A1C is 7.3% but her doctor would like it to be under 7.0%. She shows you her logbook as follows:

Date	Before bkfst	After bkfst	Before lunch	After lunch	Before supper	After supper	Bed-time
Mon	5.5				6.8	11.2	
Tues			6.1	10.2			
Wed	6.8						7.3
Thur	4.9	9.8			6.3	12.9	
Fri	6.7	10.8			7.1	10.9	

What would be the most appropriate medication recommendation?
   a. add pioglitazone
   b. add basal insulin
   c. add repaglinide
   d. increase the dose of metformin

18. Which of the following agents have to potential to reduce A1C by the greatest amount?
   a. sitagliptin
   b. acarbose
   c. metformin
   d. pioglitazone

19. Which of the following statements is true?
   a. Sulfonylureas stimulate insulin secretion in a glucose-dependent manner.
   b. Meglitinide stimulates insulin secretion in a glucose-dependent manner.
   c. DPP-4 inhibitors stimulate insulin secretion in a glucose-dependent manner.
   d. DPP-4 inhibitors stimulate insulin secretion in a glucose-independent manner.

20. Nutrition therapy has the ability to reduce A1C by:
   a. 0.1–0.5%
   b. 0.5–1.0%
   c. 1.0–2.0%
   d. 2.0–3.0%