Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- If glycemic targets are not achieved within 2 to 3 months of lifestyle management, antihyperglycemic pharmacotherapy should be initiated.
- Timely adjustments to, and/or additions of, antihyperglycemic agents should be made to attain target glycated hemoglobin (A1C) within 3 to 6 months.
- In patients with marked hyperglycemia (A1C ≥8.5%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, 1 of which may be insulin.
- Unless contraindicated, metformin should be the initial agent of choice, with additional antihyperglycemic agents selected on the basis of clinically relevant issues, such as contraindication to drug, glucose lowering effectiveness, risk of hypoglycemia and effect on body weight.

Introduction

As people with type 2 diabetes form a heterogeneous group, treatment regimens and therapeutic targets should be individualized. As type 2 diabetes is characterized by insulin resistance and ongoing decline in beta cell function, glucose levels likely will worsen over time (1), and treatment must be dynamic as therapeutic requirements increase with longer duration of disease. The number of available antihyperglycemic agents is ever expanding, requiring the clinician to consider many of the following factors when choosing medications: degree of hyperglycemia, risk of hypoglycemia, medication effectiveness at reducing diabetes complications (microvascular and/or macrovascular), medication effects on body weight, medication side effects, concomitant medical conditions, ability to adhere to regimen and patient preferences. Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used as many agent classes can cause weight gain as a side effect.

Treatment Regimens

The diagnosis of type 2 diabetes is often delayed, and 20% to 50% of people with type 2 diabetes present with microvascular and/or macrovascular complications at the time of diagnosis (2,3). When lifestyle interventions fail to control blood glucose (BG) levels adequately, pharmacological treatment becomes necessary.

In the face of more severe hyperglycemia (i.e. glycated hemoglobin [A1C] ≥8.5%), combinations of agents are usually required. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the characteristics of the different medications. With timely adjustments to and/or additions of antihyperglycemic agents, the target A1C level should be attainable within 3 to 6 months.

In general, A1C will decrease by about 0.5% to 1.5% with monotherapy, depending on the agent used and the baseline A1C level, with the maximum effect of oral antihyperglycemic agent monotherapy seen at 3 to 6 months (4,5). By and large, the higher the baseline A1C, the greater the A1C reduction seen for each given agent. In general, as A1C levels decrease toward target levels (<7.3%), postprandial BG control assumes greater importance for further A1C reduction (6). Several classes of antihyperglycemic agents have greater efficacy at lowering postprandial BG levels (7–20), although adopting an approach of specifically targeting postprandial BG control has not been shown to be effective at reducing macrovascular diabetes complications (21).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (22–25). Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels (1). When combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents within the same class and/or from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides or dipeptidyl peptidase [DPP]-4 inhibitors and glucagon-like peptide [GLP]-1 agonists) is currently untested, may be less effective at improving glycemia and is not recommended at this time. Table 1 identifies the mechanism of action for all classes of antihyperglycemic agents to aid the reader in avoiding the selection of agents with overlapping mechanisms.

There is debate over which antihyperglycemic agent (including insulin) should be used initially and which agents should be added subsequently. There is also debate over which agents within a given...
# Table 1
Antihyperglycemic agents for use in type 2 diabetes

<table>
<thead>
<tr>
<th>Class and mechanism of action</th>
<th>Drug (brand name)</th>
<th>Expected decrease in A1C</th>
<th>Relative A1C lowering</th>
<th>Hypoglycemia</th>
<th>Other therapeutic considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitor: inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase</td>
<td>Acarbose (Glucobay) (7,81,82)</td>
<td>0.6%</td>
<td>↓</td>
<td>Negligible risk as monotherapy</td>
<td>• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥ 8.5%)&lt;br&gt;• Weight neutral as monotherapy&lt;br&gt;• GI side effects</td>
</tr>
<tr>
<td>Combined formulations</td>
<td>Avandamet (metformin + rosiglitazone) Janumet (metformin + sitagliptin) Jentadueto (metformin + linagliptin)</td>
<td>0.8%</td>
<td>↓↓</td>
<td>Negligible risk as monotherapy</td>
<td>• See metformin, TZDs, DPP-4 inhibitors and sulfonylureas</td>
</tr>
<tr>
<td></td>
<td>Avandaryl (glimepiride + rosiglitazone)</td>
<td>1.6%</td>
<td>↓↓↓</td>
<td>Moderate risk</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitor: amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP (45)</td>
<td>Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta)</td>
<td>0.7%</td>
<td>↓↓</td>
<td>Negligible risk as monotherapy</td>
<td>• Weight neutral&lt;br&gt;• Improved postprandial control&lt;br&gt;• Rare cases of pancreatitis</td>
</tr>
<tr>
<td>GLP-1 receptor agonist: activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1 (45–48)</td>
<td>Exenatide (Byetta) Liraglutide (Victoza)</td>
<td>1.0%</td>
<td>↓↓ to ↓↓↓</td>
<td>Negligible risk as monotherapy</td>
<td>• Improved postprandial control&lt;br&gt;• Significant weight loss&lt;br&gt;• Nausea and vomiting&lt;br&gt;• Administration parenteral&lt;br&gt;• Rare cases of pancreatitis&lt;br&gt;• Farafollicular cell hyperplasia&lt;br&gt;• Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2</td>
</tr>
<tr>
<td>Insulin: activates insulin receptors to regulate metabolism of carbohydrate, fat and protein (3,10,11,50,53,83–85)</td>
<td><strong>Bolus (prandial) insulins</strong> Rapid-acting analogues Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog) Short-acting Regular (Humulin-R, Novolin ge Toronto) <strong>Basal insulins</strong> Intermediate-acting NPH (Humulin-N, Novolin ge NPH) Long-acting basal analogues Detemir (Levemir) Glargine (Lantus) <strong>Premixed insulins</strong> Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)</td>
<td>0.9%—1.1%</td>
<td>↓↓↓</td>
<td>Significant risk (hypoglycemia risk highest with regular and NPH insulin)</td>
<td>• Potentially greatest A1C reduction and no maximal dose&lt;br&gt;• Numerous formulations and delivery systems (including subcutaneous-injectable)&lt;br&gt;• Allows for regimen flexibility&lt;br&gt;• When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used)&lt;br&gt;• Basal-bolus regimen recommended if above fails to attain glycemic targets&lt;br&gt;• Increased risk of weight gain relative to sulfonylureas and metformin</td>
</tr>
</tbody>
</table>
Insulin secretagogue: activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion

- **Sulfonylureas**
  - Gliclazide (Diamicron, Diamicron MR, generic) (86,87)
  - Glimepiride (Amaryl) (88–90)
  - Glyburide (Diabeta, Euglucon, generic) (3)

(Note: Chlorpropamide and tolbutamide are still available in Canada but rarely used)

- **Meglitinides**
  - Nateglinide (Starlix) (91)
  - Repaglinide (GlucoNorm) (92,93)

Minimal/moderate risk

Relatively rapid BG-lowering response

- All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective)

- Postprandial glycemia is especially reduced by meglitinides

- Hypoglycemia and weight gain are especially common with glyburide

- Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure)

- If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (94) and glimepiride is associated with less hypoglycemia than glyburide (90)

- Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal

- **Metformin:** enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase

  - Glucophage, Glumetza, generic (52,95)

  - Pioglitazone (Actos) Rosiglitazone (Avandia)

  - Orlistat (Xenical) (105–107,110)

Thiazolidinedione (TZD): enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors (28–30,33,35,97–104)

A1C, glycated hemoglobin; BG, blood glucose; BP, blood pressure; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; AMP, adenosine monophosphate.

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 detailed prescribing information.

* Listed in alphabetical order.

1 A1C percentage/relative reduction expected when agent from this class is added to metformin therapy (37,105,111) with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

2 Combining insulin with a TZD is not an approved indication in Canada.
Figure 1. Management of hyperglycemia in type 2 diabetes.
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.
A1C, glycated hemoglobin; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; TZD, thiazolidinedione.
class might be preferred in specific situations. Symptomatic patients with high BG and A1C levels require agents that lower BG levels substantially and quickly (e.g. insulin). However, the issue of how to reach glycemic targets may be less important than the need to achieve that target. Improved BG and A1C levels are associated with better outcomes, even if recommended glycemic targets cannot be reached (3). Each of the agents listed in Table 1 and Figure 1 has advantages and disadvantages to consider. Figure 2 illustrates the basis on which agent selection is influenced by renal function as dictated by product monograph precautions.

The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile, its long-term safety track record, its negligible risk of hypoglycemia and its lack of causing weight gain. The demonstrated cardiovascular benefit in overweight patients is also cited as a reason to select metformin as first-line treatment (26), but more recent evidence has been equivocal on this matter (27). While monotherapy with the thiazolidinedione (TZD) rosiglitazone produces more long-lasting glycemic control compared to metformin or glyburide therapy (28), the edema, weight gain, risk of congestive heart failure (CHF), increased risk of fractures (29,30) and inconsistent data regarding myocardial infarction (MI) risk (31–33) significantly limit the clinical utility of this drug class. Although meta-analyses of smaller, underpowered studies suggested possible risk of MI with rosiglitazone (31,32), this has not been demonstrated in a larger randomized clinical trial (33,34).

Conversely, the evidence for pioglitazone suggests a possible reduced risk of cardiovascular events, although heart failure and increased fractures are still concerning side effects (35,36).

Table 1 and Figure 1 provide information to aid decision making. In deciding upon which agent to add after metformin, there must be consideration of multiple factors. First of all, the agent’s effectiveness at BG lowering must be considered in terms of both the degree of baseline hyperglycemia needing correction and any heightened concerns regarding hypoglycemia (e.g. elderly patients or those with renal or hepatic dysfunction). The relative BG and A1C lowering of the various antihyperglycemic agent classes when added to metformin is shown in both Table 1 and Figure 1 and is based on network meta-analysis allowing the comparison between classes that have not yet had direct head-to-head comparison in a randomized clinical trial (37). Ideally, consideration would be made towards the selection of agents with evidence demonstrating ability to not only lower glucose levels, but also reduce the risk of diabetic microvascular and/or macrovascular complications. Unfortunately, the majority of evidence remains equivocal in this regard as most clinical trials compared varying levels of glycemic lowering as opposed to direct comparison between agents used to achieve such glycemic control (38–40). More recent studies looking at the benefits seen with select agents are of such short duration that their results are still preliminary with respect to proving clinical event reduction (41–44) and confirmation awaits the results of more definitive long-term studies.

Multiple other agent-specific advantages and disadvantages should be weighed as treatment is individualized to best suit the patient’s needs and preferences. In particular, attention should be paid to the agent’s effects on body weight as this is a clinically relevant issue for many people with type 2 diabetes, and some agents cause significant weight gain while others can help to promote significant weight loss. GLP-1 receptor agonists are particularly effective at promoting concomitant glycemic control and weight reduction (45–48), but long-term efficacy and safety data are currently lacking for this class.

A combination of oral antihyperglycemic agents and insulin often effectively controls glucose levels. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting (NPH) (49) or a long-acting insulin analogue (insulin glargine or insulin detemir) (50) may be added. This approach may result in better glycemic control with a smaller dose of insulin (51), and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone (52). The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (53). While combining insulin with a TZD is not an approved indication in Canada, the addition of such agents to insulin in carefully selected patients improves glycemic control and reduces insulin requirements (54). Such combinations can result in increased weight, fluid retention and, in few patients, CHF. DPP-4 inhibitors and GLP-1 receptor agonists have been shown to be effective at further lowering glucose levels when combined with insulin therapy (55–58).

Insulin can be used at diagnosis in individuals with marked hyperglycemia and can also be used temporarily during illness, pregnancy, stress or for a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (59,60). The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial studied the use of basal insulin titrated to a fasting glucose of ≤5.3 mmol/L in people at high cardiovascular risk with prediabetes or early type 2 diabetes over 6 years. There was a neutral effect on cardiovascular outcomes and cancer, a reduction in new-onset diabetes and a slight increase in hypoglycemia and weight. Indeed, use of insulin earlier in the course of type 2 diabetes can be an effective strategy over oral antihyperglycemic agents (60,61). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid excessive hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1 to 4 per day) and the timing of injections may vary, depending on each individual’s situation (62). The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day (63). Insulin regimens based on basal or bolus insulin appear to be equally effective (21,64) and superior with respect to glycemic lowering compared to biphasic insulin-based regimens (63).

As type 2 diabetes progresses, insulin requirements will likely increase, additional doses of basal insulin (intermediate-acting or

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**Figure 2. Antihyperglycemic medications and renal function.** Based on product monograph precautions. CKD, chronic kidney disease; GFR, glomerular filtration rate; TZD, thiazolidinedione. Designed by and used with the permission of Jean-François Yale MD CSPQ FRCPc.
long-acting analogues) may need to be added and bolus insulin (short-acting or rapid-acting analogues) may also be required. Generally, once bolus insulin is introduced into a treatment regimen, either as a separate meal time bolus or as part of a pre-mixed containing regimen, insulin secretagogues, such as sulfonylureas and meglitinides, are usually discontinued. Concomitant metformin therapy, unless contraindicated, should be continued with regimens containing bolus insulin, including intensive basal-bolus regimen, to allow for improved glycemic control with less risk of weight gain and hypoglycemia (65).

Although not commonly practiced, the use of intensive insulin therapy (basal-bolus regimen or continuous subcutaneous insulin infusion pump), for a transient period of approximately 2 to 3 weeks at the time of diagnosis or early in the disease course, has been shown to induce diabetes remission, subsequently allowing adequate glycemic control with lifestyle management alone (66). This normoglycemic state is often transient, however, and such interventions have been tested only in patients early in the course of disease where the degree of residual beta cell function is relatively preserved (67).

Epidemiological evidence suggesting a possible link between insulin glargine and cancer has not been substantiated in review of clinical trial data for either glargine or detemir (68,69).

### Hypoglycemia

Medication-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in up to approximately 20% of patients taking insulin secretagogues (70). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group, particularly for patients using insulin therapy (3). Although the risk of hypoglycemia was less than that seen in the patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT), each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode, and 40% had a hypoglycemic episode of any severity (3). Protocols designed to achieve normoglycemia targets (A1C ≤6.5%) further increase the risk of severe hypoglycemia without providing any substantial reduction in the incidence of diabetes complications (71,72).

Lower rates of hypoglycemia have been observed in some studies of patients with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (19,73,74). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine) reduces the risk of nocturnal hypoglycemia compared to treatment with NPH insulin (19,50,75–79).

### Other Relevant Guidelines

| Targets for Glycemic Control, p. S31 |
| Pharmacotherapy in Type 1 Diabetes, p. S56 |
| Hypoglycemia, p. S69 |
| Weight Management in Diabetes, p. S82 |
| Type 2 Diabetes in Children and Adolescents, p. S163 |
| Diabetes and Pregnancy, p. S168 |
| Diabetes in the Elderly, p. S184 |

### Relevant Appendix

Appendix 3: Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

### References


