



Type 2 Diabetes — Treating Your Patients

Given the increasing prevalence of type 2 diabetes in Canada, chances are that a large portion of your practice consists of patients in this category. As a clinician, you know that if these patients are not adequately treated they are likely to have poor glycemic control, which in turn may result in serious diabetes-related complications such as blindness, end-stage renal disease, and lower limb amputation. But how do you decide how to treat these patients as part of your busy practice?

Helping you to answer that question is the Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH has identified the management of diabetes as a priority area for optimal practice initiatives – including the topics of insulin analogues, self-monitoring of blood glucose (SMBG), and second- and third-line therapy in type 2 diabetes. CADTH recognizes the importance of this information to physicians and other health care professionals like you and has carefully reviewed the evidence – both clinical and cost-effectiveness – to offer some practical guidance on the optimal management of diabetes.

Type 2 Diabetes – Management

The management of type 2 diabetes usually begins with lifestyle modifications and oral antidiabetes drugs.

Metformin is recommended as the **first-line** oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone. In fact, recent utilization data indicate that approximately 60% of patients with type 2 diabetes initiating pharmacotherapy in Canada are started on metformin.

As type 2 diabetes is a progressive disease, glycemic levels are likely to worsen over time, with most patients eventually requiring two or more oral

antidiabetes drugs or the addition of an insulin regimen. But, which drugs to choose for second- and third-line therapy in patients with type 2 diabetes has not always been clear.

Second-Line Therapy

A number of options are available for use as second-line therapy when metformin is inadequately effective. Current guidelines vary when recommending a second-line treatment, and usually little to no evidence is cited in relation to these recommendations. At the same time, the cost of oral antidiabetes drugs in Canada is on the rise with the average cost per oral antidiabetes drug prescription in publicly funded drug plans nearly doubling over the course of a decade (\$11.31 in 1998 to \$20.77 in 2007).¹ The increase in costs is likely due, at least in part, to the introduction of more costly antidiabetes drugs.

To clear up this uncertainty and offer evidence-based guidance on second-line therapy in type 2 diabetes, CADTH undertook a systematic review of the clinical evidence, which included 49 unique randomized controlled trials, and conducted a cost-effectiveness analysis of second-line therapy drugs (Table 1). The clinical and economic evaluations were used by CADTH's Expert Review Committee to generate optimal therapy recommendations.

All drugs achieved statistically significant reductions in A1C, ranging from 0.6% to 1.0%, and there were no statistically significant differences between drug classes. Events of severe hypoglycemia were very rare for all drugs; however, the insulins, sulfonylureas, and meglitinides were associated with a higher risk for overall hypoglycemia than the other drugs. Compared with metformin alone, sulfonylureas, meglitinides, thiazolidinediones (TZDs), and insulins were all associated with a modest increase in body weight (1.8 kg to 3 kg);

dipeptidyl peptidase-4 (DPP-4) inhibitors and alpha-glucosidase inhibitors were weight-neutral, while glucagon-like peptide-1 (GLP-1) analogues were associated with weight loss (about 1.8 kg). There was insufficient evidence regarding the effect of second-line antidiabetes drugs on the long-term complications of diabetes or mortality. In contrast to the other drugs, however, it should be noted that long-term safety data are available for sulfonylureas and human insulins as a result of their use in the landmark United Kingdom Prospective Diabetes Study.²

Sulfonylureas were found to be the most cost-effective second-line therapy in patients with diabetes inadequately controlled on metformin, primarily because of their lower cost compared with insulin and newer drugs. Cost-effectiveness results did not change significantly when various inputs and assumptions in the cost-effectiveness model were modified to test the robustness of the analysis.

Table 1: Medication Classes Included in Second- and Third-Line Review

Sulfonylureas*
Meglitinides
Alpha-glucosidase inhibitors
TZDs
DPP-4 inhibitors
GLP-1 analogues
Insulins: • Basal • Bolus • Biphasic

*Reviewed for second-line use only.

The Bottom Line

In most adults with type 2 diabetes, a sulfonylurea should be added to metformin when metformin alone is not enough to adequately control hyperglycemia.

**Second-Line Therapy =
metformin + a sulfonylurea**

Sulfonylurea Added to Metformin – Quick Facts:

A1C lowering efficacy: ↓ by 0.8%.*

Change in weight: ↑ by 2 kg.*

Annual risk of hypoglycemia requiring third-party assistance: 1 in 175 patients.[†]

Added cost per day: \$0.12 to \$0.49.^{‡,§}

*On average.

†Estimated based on data from Home et al. (2007).³

‡Based on half-maximal doses of glyburide, gliclazide modified-release (MR), and glimepiride.

§Wholesale costs (excluding mark up and dispensing fees), obtained from the Ontario Drug Benefit Program, except glimepiride, which was obtained from the Manitoba Drug Interchangeability Formulary.

Third-Line Therapy

As with second-line therapy, there is uncertainty regarding the most appropriate third-line therapy for patients with type 2 diabetes, when metformin together with a sulfonylurea is no longer adequate to control hyperglycemia. Although most guidelines recommend starting insulin as a third-line therapy, others recommend either insulin or a third oral antidiabetes drug.

As part of CADTH's Therapeutic Review pilot project, both a clinical and economic analysis were undertaken evaluating the comparative efficacy, harms, and cost-effectiveness of third-line drugs indicated for the treatment of type 2 diabetes. The results of the reviews were considered by CADTH's Expert Review Committee to generate evidence-based recommendations for third-line therapy for patients with type 2 diabetes not adequately controlled with metformin plus a sulfonylurea.

Evidence for all available classes of third-line antidiabetes therapies in adults with type 2 diabetes was identified within 33 unique randomized

controlled trials (Table 1). Compared with continued treatment with metformin and sulfonylurea combination therapy, the addition of a DPP-4 inhibitor, GLP-1 analogue, TZD, or bolus insulin produced statistically significant reductions in A1C of 0.9% to 1.2%, whereas the addition of a meglitinide or alpha-glucosidase inhibitor did not. Basal insulin, biphasic insulin, bolus insulin, and TZDs all resulted in an increase in body weight (2 kg to 5 kg); DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, while GLP-1 analogues were associated with weight loss (about 1.6 kg).

NPH Insulin Added to Metformin and a Sulfonylurea – Quick Facts:

A1C lowering efficacy: ↓ by 1.2%.*

Change in weight: ↑ by 2 kg.*

Annual risk of hypoglycemia requiring third-party assistance: 1 in 85 patients.[†]

Added cost per day: \$1.09.^{‡,§}

*On average.

†Estimated based on data from Holman et al. (2009)⁴ and Singh et al. (2009).⁵

‡Based on 40 units per day.

§Wholesale cost (excluding mark up and dispensing fees), obtained from the Ontario Drug Benefit Program.

The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators; however, severe hypoglycemic events were rare across all treatments. There was insufficient evidence to evaluate the comparative efficacy of third-line antidiabetes drugs in reducing clinically important long-term complications of diabetes. In contrast to the other drugs, however, it should be noted that long-term safety data are available for human insulins as a result of their use in the landmark United Kingdom Prospective Diabetes Study.²

The findings of the economic analysis suggested that the addition of neutral protamine Hagedorn (NPH) insulin to metformin and sulfonylurea combination therapy is the most cost-effective third-line therapy. This result was robust to most changes in model inputs and assumptions.

The Bottom Line

In most adults with type 2 diabetes, **NPH insulin** should be added to metformin and a sulfonylurea when this combination of therapy is not enough to adequately control hyperglycemia.

Third-Line Therapy = metformin + sulfonylurea + NPH insulin*

*Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking NPH insulin (an intermediate-acting insulin) may benefit from a long-acting insulin analogue. However, severe hypoglycemia in type 2 diabetes is a relatively rare occurrence.

References

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For more information, visit www.cadth.ca/t2dm-pdf

And don't forget CADTH's previous evidence-based recommendations on SMBG: www.cadth.ca/smbg-pdf

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