

Type 2 Diabetes: What's Next After Metformin?

Type 2 diabetes is a metabolic disease that is increasing in prevalence in Canada. Poor glycemic control can lead to complications such as blindness, end-stage renal disease, and lower limb amputation.¹

When lifestyle modifications are not enough to achieve glycemic control, metformin is typically used as the first-line oral antidiabetes drug. But diabetes is a progressive disease, so most patients will eventually need multiple drugs that work through different mechanisms. With so many available treatments, choosing second- and third-line therapy can be challenging.

2013 CADTH Review

In 2013, CADTH conducted a systematic review and network meta-analysis of the clinical evidence, as well as a cost-effectiveness analysis, of second- and third-line therapies for type 2 diabetes.^{2,3} An expert committee made recommendations on the optimal use of these drugs.⁴

Drugs Included

Drug Class	Generic Names
Biguanides	Metformin
Sulfonylureas	Gliclazide, glimepiride, glyburide, chlorpropamide, tolbutamide
Thiazolidinediones	Pioglitazone, rosiglitazone
Meglitinides	Nateglinide, ^a repaglinide
DPP-4 inhibitors	Sitagliptin, saxagliptin, linagliptin
GLP-1 analogues	Exenatide, liraglutide
AG inhibitors	Acarbose
Basal insulins	Insulin NPH, insulin detemir, insulin glargine
Biphasic insulins	Premixed regular NPH, biphasic insulin aspart, biphasic insulin lispro
Bolus insulin	Human insulin, insulin aspart, insulin lispro, insulin glulisine

AG = alpha-glucosidase; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn.

^a No longer available in Canada.

Key Findings From the 2013 Review

For most of your adult patients with type 2 diabetes, when proper diet and exercise are not enough to control hyperglycemia:

- Start oral therapy with metformin.
- Add a sulfonylurea to metformin when metformin alone is not enough to adequately control hyperglycemia.
- Add neutral protamine Hagedorn (NPH) insulin when metformin and a sulfonylurea are not enough to adequately control hyperglycemia.*

OR

- Add a dipeptidyl peptidase-4 (DPP-4) inhibitor to metformin and a sulfonylurea in the rare instances when insulin is not an option.

Optimize the dose of the drug at each stage of therapy before moving to the next. Proper diet and exercise should be encouraged at every stage.

*Patients experiencing significant hypoglycemia during efforts to reach target glycated hemoglobin (A1C) with NPH insulin may benefit from a switch to a long-acting insulin analogue (i.e., insulin glargine or insulin detemir).

Quick Facts

Combinations of Second- and Third-Line Therapies	A1C-Lowering Efficacy	Change in Weight	Annual Risk of Hypoglycemia Requiring Third-Party Assistance	Added Cost per Day
Sulfonylurea added to metformin	↓ by 0.8% ^a	↑ by 2 kg ^a	1 in 175 patients ^b	\$0.11 to \$0.39 ^c
Insulin NPH added to metformin and a sulfonylurea	↓ by 1.2% ^a	↑ by 2 kg ^a	1 in 85 patients ^d	\$1.14 ^{c,e}

A1C = glycated hemoglobin; NPH = neutral protamine Hagedorn.

^a On average.

^b Estimated, based on data from Home PD, et al. *Diabet Med.* 2007;24(6): 626–34.⁵

^c Wholesale cost (excluding pharmacy markup or dispensing fee). Data obtained from the Ontario Drug Benefit Formulary⁶ and Quebec drug benefit programs.⁷

^d Estimated, based on data from Holman RR, et al. *N Engl J Med.* 2009 Oct 29;361(18): 1736–47;⁸ and Singh SR, et al. *CMAJ.* 2009 Feb 17;180(4):385–97.⁹

^e Based on 40 units per day.

Insulin as Third-Line Therapy

Starting insulin therapy can be time-intensive for health care providers and intimidating for patients. For helpful tips, consult CADTH's Guide to Starting and Adjusting Insulin for Type 2 Diabetes.¹⁰ cadth.ca/smbg/tools/guide-starting-and-adjusting-insulin-type-2-diabetes

Newer Antidiabetes Drugs

Five new drugs have become available in Canada since the 2013 review.

CADTH Recommendations on Newer Antidiabetes Drugs

Drug	Generic Names	CDEC's Recommendation to Public Drug Plans
Alogliptin (Nesina)¹¹	DPP-4 inhibitor approved by Health Canada in November 2013.	Do not list. Comparative clinical benefit relative to other oral antidiabetes drugs is uncertain.
Dulaglutide (Trulicity)¹²	GLP-1 analogue approved by Health Canada in November 2015	List with criteria: Drug plan cost not to exceed the least costly pharmacotherapy reimbursed in combination with metformin and a sulfonylurea.
Canagliflozin (Invokana)¹³	New class of drugs known as sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin was approved in May 2014, and dapagliflozin in December 2014. The US Food and Drug Administration has issued a warning about SGLT2 inhibitors and the increased risk of ketoacidosis. ^a	List with criteria: Add canagliflozin when metformin and a sulfonylurea are not enough to adequately control hyperglycemia and insulin is not an option. This drug would have a similar place in therapy as the DPP-4 inhibitors included in the 2013 review.
Dapagliflozin (Forxiga)¹⁴	This triggered a safety review by Health Canada, which concluded that SGLT2 inhibitors may increase the risk of experiencing diabetic ketoacidosis and recommended an update to product information to better explain the symptoms of ketoacidosis. ^b	List with criteria: Add dapagliflozin in any of four scenarios: <ol style="list-style-type: none"> 1. Metformin is not enough to adequately control hyperglycemia, AND sulfonylurea or insulin are not options 2. Sulfonylurea is not enough to adequately control hyperglycemia, AND metformin or insulin are not options 3. Metformin and insulin are not enough to adequately control hyperglycemia 4. Insulin is not enough to adequately control hyperglycemia, and metformin is not an option. Do not list for use in combination with metformin and a sulfonylurea.
Empagliflozin (Jardiance)¹⁵		List with criteria: Add empagliflozin when metformin and a sulfonylurea are not enough to adequately control hyperglycemia and insulin is not an option. This drug would have a similar place in therapy as the DPP-4 inhibitors included in the 2013 review.

CDEC = Canadian Drug Expert Committee; DPP-4 = dipeptidyl peptidase-4.

^a FDA Drug Safety Communication, May 15, 2015.¹⁶

^b Health Canada Summary Safety Review, May 16, 2016.¹⁷

In light of these new drugs becoming available on the Canadian market, CADTH is undertaking a new review of second- and third-line therapies for type 2 diabetes. The project will be completed in 2017, and reports will be posted as they become available on the CADTH website at cadth.ca/newdrugsT2DM.

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