

*Canadian Agency for
Drugs and Technologies
in Health*

*Agence canadienne
des médicaments et des
technologies de la santé*

CADTH SUMMARY REPORT

June 2011

Second- and Third-Line Therapy for Patients
with Type 2 Diabetes

Supporting Informed Decisions

This summary is based on comprehensive Optimal Therapy Reports on the topic prepared by Canadian Agency for Drugs and Technologies in Health (CADTH). The conclusions were provided by experts. The authors have also considered input from other stakeholders.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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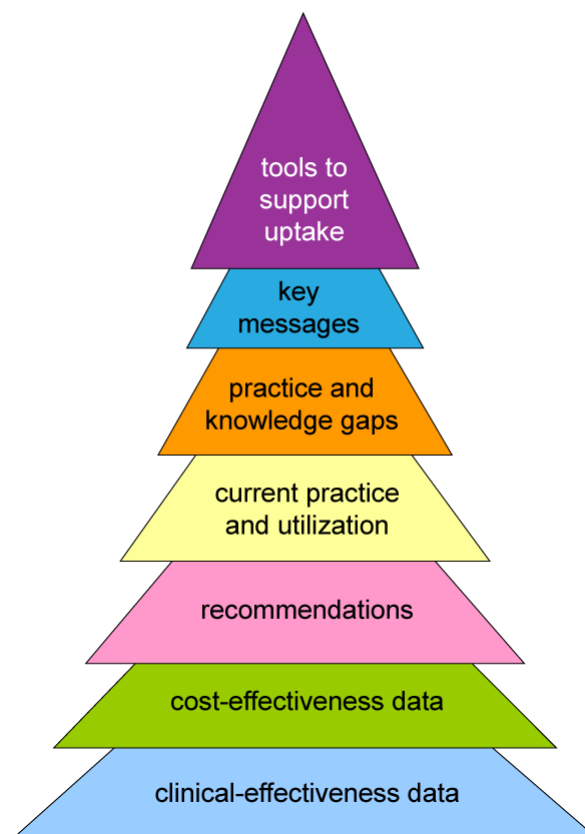
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SUMMARY REPORT:

Second- and Third-Line Therapy for Patients with Type 2 Diabetes

The Canadian Agency for Drugs and Technologies in Health (CADTH) has released a series of Optimal Therapy Reports on the prescribing and use of second-line therapy for patients with type 2 diabetes inadequately controlled on metformin, and a therapeutic review of third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea combination therapy. CADTH has also released intervention tools to support the uptake of this information.

This summary highlights the work done by CADTH, from the most concise information available, in user-friendly intervention tools, through to the evidence on which recommendations and tools were built. The following diagram presents each level of information; the corresponding sections in this summary include a link to the report or tool on the CADTH website.



More information and the full series of reports and tools may be found on the CADTH website <www.cadth.ca/t2dm>.

The following sections correspond to the diagram presented at the beginning of this summary. Each section represents a level of information from the most user friendly to the most detailed.

Tools to Support Uptake

Series of tools to support uptake

A range of intervention tools were developed based on the key messages targeted to optimize the use of second- and third-line therapies for patients with type 2 diabetes. Input from experts and potential users aided in the selection of tools based on the best available evidence. All these tools can be adapted to meet the unique needs of health care providers, policy-makers, or consumers.

Tool	Description
Optimal Therapy Newsletter	A succinct, four-page publication aimed at health care professionals, summarizing the main findings and recommendations on second- and third-line therapy for patients with type 2 diabetes.
Prescribing Aid	A two-page information sheet with a graphic depiction of key messages for health care professionals and chart comparing costs for different antidiabetes drugs.
Newsletter Articles	Short articles for publication in hospital newsletters and other regional publications, highlighting the project findings.
Guide to Starting and Adjusting Insulin	A fold-out pamphlet with information on selecting an initial regimen, starting dose, insulin type, and on adjusting dose.
Patient Q & A	Answers to questions that patients might have when initiating or changing their therapy.

In addition to these tools, CADTH is also supporting the uptake of information by hosting or assisting with presentations on this topic by experts throughout Canada, and by publishing articles in scientific journals, including in wiki format.

WHAT'S NEXT FOR MY PATIENTS WITH TYPE 2 DIABETES WHEN METFORMIN ALONE IS NOT ENOUGH ...?

In most adults with type 2 diabetes:

- A sulfonylurea should be added to metformin when metformin alone is not enough to adequately control hyperglycemia.
- Neutral protamine Hagedorn (NPH) insulin[†] should be added to metformin and a sulfonylurea when this combination therapy is not enough to adequately control hyperglycemia.

For full evidence-based project information, visit the CADTH website at www.cadth.ca/tzdm

*Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking NPH insulin may benefit from insulin analogues. However, severe hypoglycemia in type 2 diabetes is a relatively rare event.
[†]It is recognized that insulin may not be an option for all patients. When insulin is not adequate, the Canadian Expert Drug Advisory Committee recommends sitagliptin as a third-line therapy to be added to metformin and a sulfonylurea.

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Canadian Agency for Drugs and Technologies in Health

Guide to Starting and Adjusting Insulin for Type 2 Diabetes*

*Adapted from Guide to Starting and Adjusting Insulin for Type 2 Diabetes, ©2008 International Diabetes Center, Minneapolis, MN. All rights reserved.

Supporting Informed Decisions

Key Messages

In most adults with type 2 diabetes:

1. A sulfonylurea should be added to metformin when metformin alone is not enough to adequately control hyperglycemia.

Second-line therapy = metformin + sulfonylurea

2. Neutral protamine Hagedorn (NPH) insulin should be added to metformin and a sulfonylurea when this combination therapy is not enough to adequately control hyperglycemia.

Third-line therapy = metformin + sulfonylurea + NPH insulin*

**Although 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.*

CADTH works with Canadian jurisdictions, providing the information needed to make informed decisions. The reports and tools on second- and third-line therapy for type 2 diabetes may be used to support decisions related to the effective management of diabetes. CADTH facilitates the uptake of this information by providing materials adapted to meet user requirements.

Practice and Knowledge Gaps

In comparing the recommendations for second- and third-line therapy with both the results of the current practice and current utilization analyses, several gaps emerge.

Practice Gaps

- Metformin is discontinued, rather than continued, when second-line therapy is initiated in about a quarter of patients.
- Insulin is underutilized as a third-line therapy.
- Thiazolidinedione (TZD) utilization as a third-line intervention is prevalent although TZD is not indicated for this application in Canada.

Practice and knowledge gaps are identified through comparison of current practice and utilization information

with optimal therapy recommendations.

Knowledge Gaps

- Prescribers lack access to systematically reviewed findings on clinical effectiveness and cost-effectiveness of antidiabetes therapies.
- There is a perception that hypoglycemia and weight gain are common or significant problems associated with the use of sulfonylureas.
- Many patients lack awareness that diabetes is a progressive disease and that, even if they adhere to prescribed lifestyle changes and medications, they will likely need to add second- and third-line drugs to their therapy.
- Prescribers may feel a need for a specialist consult before prescribing the start of insulin.
- There is lack of awareness about the opportunity costs associated with therapeutic choices.

The identified gaps lend themselves well to the development and implementation of interventions and tools to potentially optimize the prescribing and use of second- and third-line therapies.

Current Practice and Utilization

[Current Practice Analysis of Health Care Providers and Patients: Second-line Therapy for Patients with Type 2 Diabetes Inadequately Controlled on Metformin](#)

[Current Utilization of Second- and Third-Line Therapies in Patients with Type 2 Diabetes](#)

The objective of the **Current Practice Analysis Report** was to explore the current views, beliefs, experiences, and practices of patients and health care professionals regarding the initiation and selection of second-line therapies for patients with diabetes inadequately controlled on metformin. Focus groups consisting of health care professionals and patients were used to gain this understanding.

The goal of the **Current Utilization Report** was to identify patterns of use of second- and third-line therapies in patients with type 2 diabetes inadequately controlled on metformin monotherapy or combination therapy with metformin and a sulfonylurea. This report also examined how the oral antidiabetes market has changed in Canada since the introduction of newer, more expensive oral drugs.

To determine patterns of utilization, a retrospective cross-sectional time-series analysis of oral antidiabetes drugs reimbursed by publicly and privately funded drug plans in Ontario during a 12-year period (1998 to 2009) was conducted.

Both of these Optimal Therapy Reports were used, together with the Optimal Therapy Recommendations, in the development of key messages and intervention tools.

Summary Interpretation of the Data

Current Practice

The Current Practice Analysis revealed that nearly all participating prescribers prefer to add a second-line drug to metformin rather than switching from metformin entirely, but that a consistently applied prescribing model is lacking. To select a second-line drug, health care professionals described a complex decision-making process in which they consider efficacy, affordability, short-term side effects, long-term adverse effects, and convenience of the therapy. There is considerable variability in the beliefs, perceptions, and considerations that underlie their choices. They also indicated that they rely on a wide variety of sources for information about second-line therapies, leading to diverse views and prescribing practices.

Current Utilization

During the past 12 years, utilization of and expenditure on oral antidiabetes drugs in the Ontario Public Drug Plan (OPDP) and private drug plans (PDPs) have increased significantly. A larger proportion of total expenditure in both public and PDPs has been on newer, more expensive drugs, despite lower utilization of them. Newer drug classes are more expensive than older drug classes – for each patient treated with a TZD or a dipeptidyl peptidase-4 (DPP-4) inhibitor, 8 to 12 patients could be treated with a sulfonylurea or metformin.

Based on an analysis of OPDP and PDPs in Ontario, the majority of patients are prescribed sulfonylureas after inadequate control with metformin alone. Most patients are prescribed a sulfonylurea to add to existing metformin. However, a significant proportion of patients are prescribed a second-line therapy that involves abandoning metformin.

Most patients in both public and private plans who need a third-line agent are prescribed a TZD in addition to their existing combination therapy of metformin and a sulfonylurea. TZD prescriptions are considerable despite not being indicated for this application in Canada. Many patients are also prescribed a switch to a TZD, which involves abandoning combination therapy with metformin and a sulfonylurea.

Recommendations

[*Optimal Therapy Recommendations for the Prescribing and Use of Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin*](#)

[*Optimal Therapy Recommendations for the Prescribing and Use of Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea*](#)

CADTH's expert review committees produced two recommendations on the use of second-line and third-line therapy for patients with type 2 diabetes.

Summary of recommendation for second-line therapy:

- A sulfonylurea should be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone.

Summary of recommendation for third-line therapy:

- Neutral protamine Hagedorn (NPH) insulin should be added as the preferred option for adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea.

For the second-line therapy project, CADTH used its optimal use process; for the third-line therapy project, CADTH used a pilot therapeutic review process.

CADTH applied the [Grading of Recommendations Assessment, Development and Evaluation \(GRADE\)](#) approach to summarize the available evidence and facilitate the generation of optimal therapy recommendations.

Research Gaps

Beyond providing scientific reports and recommendations, CADTH's work also reveals gaps or other areas where further research is required. These gaps can inform other researchers, research-funding agencies, and other decision-makers setting the Canadian health research agenda.

Category	Research Gap
Populations	<ul style="list-style-type: none">• Patients under 18 years or over 65 years• First Nations and other ethnic minorities• Patients at a higher risk of severe hypoglycemia or its consequences.
Interventions and comparators	<ul style="list-style-type: none">• Effects of insulins as second-line drugs• Comparisons between new drugs (e.g., DPP-4 inhibitors and glucagon-like peptide-1 analogues) and older drugs.
Outcomes	<ul style="list-style-type: none">• Long-term complications of diabetes• Mortality• Health-related quality of life• Patient satisfaction with diabetes care.

Researchers evaluating the effectiveness of second- and third-line therapies are encouraged to design studies that will address the gaps that CADTH has identified, in order to improve clinical practice and outcomes for patients.

Cost-Effectiveness Data

[Second-Line Therapy for Patients With Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis. Optimal Therapy Report – COMPUS 2010; 4\(2\)](#)

[CADTH Therapeutic Review Economic Evaluation: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and Sulfonylurea Combination Therapy](#)

Cost-effectiveness data for second-line therapy for patients with type 2 diabetes inadequately controlled with metformin and for third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea were derived from pharmaco-economic analyses conducted by CADTH using the United Kingdom Prospective Diabetes Study Outcomes Model. This model has been validated against published clinical and epidemiological studies to forecast long-term diabetes-related complications in patients with type 2 diabetes.

For the second-line therapy cost-effectiveness analysis, the same drug classes were analyzed as in the clinical-effectiveness analysis, except that glucagon-like peptide-1 (GLP-1) was excluded because Health Canada had not approved any agents within this class at the time of the analysis.

For the third-line therapy cost-effectiveness analysis, four different treatments were compared with placebo, all in combination with metformin and sulfonylureas: basal insulin, biphasic insulin, TZDs, and DPP-4 inhibitors. Alpha-glucosidase inhibitors and meglitinides, two additional classes indicated in Canada for the treatment of type 2 diabetes, were not included in the reference case because they are not widely used in Canadian clinical practice and do not yield significant improvements in glycemic control when added to metformin and sulfonylurea as third-line therapy. GLP-1 analogues were also excluded from the analysis because Health Canada had not approved any agents within this class at the time of the analysis.

It is important to note that there were limitations to the studies. The majority (62%) of the randomized controlled trials (RCTs) included in the review of second-line therapies were assessed to be of “poor” methodological quality. The analysis of third-line therapy options lacked clinical data from long-term, high-quality studies that evaluated the comparative efficacy of third-line drugs in terms of clinically relevant end points.

Summary Interpretation of the Data

Second-line therapy

When metformin alone becomes insufficient for treating patients with type 2 diabetes, adding a sulfonylurea is the most cost-effective second-line therapy. Sulfonylureas have a lower cost compared with insulin and newer drugs, and these cost-effectiveness results held true when the parameters in the analysis model were changed (as part of sensitivity analyses).

Third-line therapy

Adding NPH insulin to metformin and sulfonylurea combination therapy is the most cost-effective third-line therapy. Only when the parameters in the analysis model were considerably changed did another option emerge. In certain scenarios, adding DPP-4 inhibitors (sitagliptin) instead of insulin may be the most cost-effective option. These scenarios include

the following: if insulin lowers the quality of life in patients to a high degree (high disutility of insulin), if insulin users experience a higher risk of hypoglycemia, and if costs of long-acting insulin analogues are applied to the basal insulin option rather than the cost of NPH insulin. It should also be noted that the quality of evidence informing the variations in model inputs is limited or of low quality; hence, results from sensitivity analyses should be interpreted with caution. Further research is needed to more precisely understand the relative cost-effectiveness of third-line agents.

Clinical-Effectiveness Data

[*Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis*](#)

[*CADTH Therapeutic Review Clinical Review: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea*](#)

To evaluate the clinical effectiveness of second-line therapy for patients with type 2 diabetes inadequately controlled with metformin, CADTH conducted a systematic review and mixed treatment comparison (MTC) meta-analysis of the following classes of drugs:

- sulfonylureas
- meglitinides
- alpha-glucosidase inhibitors
- TZDs
- DPP-4 inhibitors
- GLP-1 analogues
- insulins
- insulin analogues.

To evaluate the clinical effectiveness of third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea, CADTH conducted a systematic review and MTC meta-analysis of eight different classes of drugs:

- meglitinides
- alpha-glucosidase inhibitors
- TZDs
- DPP-4 inhibitors
- GLP-1 analogues
- basal insulins
- bolus insulins
- biphasic insulins.

For the analysis of second-line therapies, CADTH reviewed 49 unique RCTs.

For the analysis of third-line therapies, CADTH reviewed 33 unique RCTs.

Summary Interpretation of the Data

Second-line therapy

Compared with metformin therapy alone, all the reviewed drugs were able to significantly reduce A1C levels (by 0.6% to 1.0%) when added to treatment, and there were no statistically significant differences between drug classes.

In terms of weight gain, the clinical analysis revealed that, when used as second-line therapies, sulfonylureas, meglitinides, TZDs, and insulins were associated with a modest increase in body weight (1.8 kg to 3 kg); DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; and GLP-1 analogues were associated with weight loss (about 1.8 kg). Hypoglycemia risk increased with use of insulins, sulfonylureas, and meglitinides, but severe hypoglycemic events were rare for all drugs.

Third-line therapy

Compared with continued treatment with metformin and a sulfonylurea, DPP-4 inhibitors, GLP-1 analogues, TZDs, and the insulins produced statistically significant reductions in A1C (0.9% to 1.2%) when added to treatment, and there were no statistically significant differences between them. Meglitinides and alpha-glucosidase inhibitors did not reduce A1C. Biphasic insulin was also effective in reducing A1C by 1.9% when given with metformin alone (i.e., patients ceased taking sulfonylureas). The amount and quality of evidence was insufficient to draw conclusions regarding the relative efficacy of the add-on, partial-switch, and switch regimens in the initiation of insulin.

In terms of weight gain, the clinical analysis revealed that, when used as third-line therapies, basal insulin, biphasic insulin, bolus insulin, and TZDs resulted in statistically significant increases in body weight (2 kg to 5 kg); DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; and GLP-1 analogues were associated with weight loss (about 1.6 kg). Hypoglycemia risk increased with use of the various insulins, but severe hypoglycemic events were rare across all treatments.

Long-term complications of diabetes

In both the CADTH clinical-effectiveness analyses, there was insufficient evidence to evaluate the comparative efficacy of second- and third-line antidiabetes drugs in reducing clinically important long-term complications of diabetes. Longer-term studies with larger sample sizes are required.

Methods Highlight

CADTH used mixed treatment comparison (MTC) and pairwise meta-analysis where appropriate to determine the clinical effectiveness of second- and third-line therapies for patients with type 2 diabetes.

An MTC is a form of statistical analysis that overcomes the limitations of the traditional meta-analysis. A traditional meta-analysis combines direct evidence from multiple RCTs to obtain pooled estimates of efficacy. However, it can provide information on only one treatment comparison. In addition, an RCT may not have directly compared two treatments of choice. An MTC meta-analysis pools direct and indirect evidence, enabling researchers to estimate the efficacy of multiple treatments simultaneously and to learn the relative effects of each treatment compared with every other treatment in the set. It also enables researchers to estimate efficacy in the absence of trials between treatments.

For further information, please visit the CADTH website: www.cadth.ca/t2dm.



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