



## Condition

Type 2 diabetes is a chronic disease that results when the pancreas does not produce enough insulin, or the body does not properly use the insulin that it makes.

## Technology

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.<sup>1</sup>

Medication classes for second- and third-line therapy include:

- Sulfonylureas (reviewed for second-line use only)
- Thiazolidinediones (TZDs)
- Meglitinides
- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase-4 (DPP-4)
- Glucagon-like peptide-1 (GLP-1) analogues (reviewed for second-line use only)
- Insulins:
  - Basal
  - Bolus
  - Biphasic.

## Issues

The treatment of patients with type 2 diabetes usually begins with lifestyle modifications and treatment with 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.

Given that type 2 diabetes is a progressive disease, glycemic control is likely to worsen over time, with most patients eventually requiring two or more oral antidiabetes drugs or the addition of insulin. 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. The average cost per oral antidiabetes drug prescription in publicly funded drug plans has nearly doubled over the course of a decade (\$11.31 in 1998 to \$20.77 in 2007).<sup>2</sup> This increase is likely due, at least in part, to the introduction of more costly antidiabetes drugs.

## 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**

There is also uncertainty about the most appropriate third-line therapy for patients with type 2 diabetes when metformin together with a second-line agent 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.

To optimize both health outcomes and the cost-effective use of these drugs, there is a need for clear recommendations based on clinical and cost-effectiveness evidence to guide both second- and third-line therapy for patients with type 2 diabetes.

## Methods

### Second-Line Therapy:

Research efforts to develop optimal second-line therapy recommendations for patients with type 2 diabetes not adequately controlled on metformin alone focused on:

- Clinical evaluation (systematic reviews and meta-analysis)
- Pharmaco-economic analysis
- Current utilization and current practice analyses
- Identification of practice and knowledge gaps
- Identification of barriers to optimal use.

The expert review committee of the Canadian Agency for Drugs and Technologies in Health (CADTH) used the clinical and economic evaluations to develop recommendations.

### Third-Line Therapy:

As part of its new Therapeutic Review pilot project, CADTH undertook both a clinical and an economic review (cost-utility analysis) to evaluate the comparative

efficacy, harms, and cost-effectiveness of third-line agents indicated for the treatment of type 2 diabetes. CADTH's expert review committee used the clinical and economic reviews to develop evidence-based recommendations (as well as knowledge gaps) for third-line therapy for patients with type 2 diabetes not adequately controlled with metformin plus a second-line agent.

## Results

- Evidence-based recommendations for second- and third-line therapy were produced.
- Key messages based on the recommendations were developed.
- Intervention tools were developed and are available to encourage the optimal prescribing and use of second- and third-line therapies for type 2 diabetes.

## References

1. Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes [Internet]. 2008 [cited 2010 Jan 27];32(Suppl 1):i-S201. Available from: <http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf>
2. Utilization of oral antiglycemics in Canada. [unpublished dataset]. Ottawa (ON): Brogan, Inc.; 2008.

For complete Optimal Therapy Reports and Intervention Tools: [www.cadth.ca/t2dm](http://www.cadth.ca/t2dm).

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