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Type 2 Diabetes: Second- and Third-Line Therapies

CADTH Optimal Therapy Newsletter

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 adequately treat these patients as part of your busy practice?

The Canadian Agency for Drugs and Technologies in Health (CADTH) can help you answer that question. 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.

Pharmacotherapy

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

Metformin is typically used as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone.

But because type 2 diabetes is a progressive disease, glycemic levels are likely to worsen over time, with most patients eventually requiring the addition of more antidiabetes drugs or the addition of an insulin regimen. Choosing which drug to use for second- and third-line therapy in patients with type 2 diabetes can be challenging.

What's Next After Metformin?

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, there is considerable variability in the costs of diabetes treatments, and expenditures on antidiabetes drugs in Canada are on the rise.

To clear up this uncertainty and offer evidence-based guidance on sequential therapy in type 2 diabetes, in 2010 CADTH undertook a systematic review of the clinical evidence, and conducted a cost-effectiveness analysis of second- and third-line therapy drugs. The clinical and economic evaluations were used by CADTH's Expert Review Committee to generate optimal therapy recommendations. Since the time of this project, new antidiabetes drugs have been approved for use in Canada. In 2013, CADTH updated its reviews and recommendations.

Updated Findings in 2013 for Second-Line Therapies

Based on a systematic review and network meta-analysis of 69 RCTs, all drug classes added to metformin as second-line therapy demonstrated similar improvements in glycated hemoglobin (A1C) of –0.64% to –1.06%. Regarding changes to

Medication Classes Included in Second- and Third-Line Therapies Reviews

- Sulfonylureas[a]
- Meglitinides
- Alpha-glucosidase inhibitors
- TZDs
- DPP-4 inhibitors
- GLP-1 analogues
- Insulins:
  - Basal, Bolus, and Biphasic

[a]Reviewed for second-line use only.

body weight, treatment with sulfonylureas, meglitinides, thiazolidinediones (TZDs), basal insulin, and biphasic insulin resulted in significantly greater increases in body weight, ranging from 1.7 kg to 3.1 kg, with no significant differences between these drug classes. Dipeptidyl peptidase-4 (DPP-4) inhibitors and alpha glucosidase inhibitors were weight neutral, while glucagon-like peptide-1 (GLP-1) analogues were associated with a significant reduction in body weight (approximately –1.8 kg). The risk of hypoglycemia was elevated when treatment involved insulins, sulfonylureas, and meglitinides, but episodes of severe hypoglycemia were rare for all drug classes. There were insufficient data on the effect of treatments for the risk of long-term complications of diabetes or mortality.

In the economic analysis, sulfonylureas were the most cost-effective treatment option for second-line therapy, with an incremental cost-utility ratio (ICUR) of $8,445 per quality-adjusted life-year (QALY) gained compared with metformin alone.

Updated Findings in 2013 for Third-Line Therapies

Based on a systematic review and network meta-analysis of 41 RCTs, all drug classes added to metformin and a sulfonylurea as third-line therapy demonstrated similar improvements in A1C (ranging from –0.72% to –1.15%), except for alpha-glucosidase inhibitors and meglitinides, which did not significantly improve glycemic control. Regarding body weight, insulins and TZDs were associated with a significant increase in body weight, ranging from 1.9 kg to 5.0 kg. DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral, whereas, GLP-1 analogues were associated with statistically significant weight loss of 1.6 kg. Meglitinides appeared to be trending toward an increase in body weight, but there was

Sulfonylurea Added to Metformin — Quick Facts:

- A1C-lowering efficacy: ↓ by 0.8%.[a]
- Change in weight: ↑ by 2 kg.[a]
- Annual risk of hypoglycemia requiring third-party assistance: 1 in 175 patients[b]
- Added cost per day: $0.11 to $0.39.[c]

[a]On average.
[b]Estimated, based on data from Home et al. (2007).[1]
[c]Wholesale cost (excluding pharmacy markup or dispensing fee). Data obtained from the Ontario Drug Benefit Formulary and Quebec drug benefit programs.

Key Messages

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 NPH insulin when metformin and a sulfonylurea are not enough to adequately control hyperglycemia.[a]

OR

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

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

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

uncertainty in the estimate of effect. The risk of hypoglycemia was significantly increased with insulins, TZDs, DPP-4 inhibitors, and GLP-1 analogues. Treatments involving various combinations of insulin were typically associated with a greater risk of overall hypoglycemia, with biphasic and bolus insulins showing greater risk than basal insulin. However, events of severe and nocturnal hypoglycemia were relatively rare for all drug classes, limiting the ability to make meaningful comparisons between drug classes. There were insufficient data regarding the effect of treatments on the risk of long-term complications of diabetes or mortality.

In the economic analysis, the addition of insulin neutral protamine Hagedorn (NPH) — or another basal insulin available at an equivalent cost — to metformin and a sulfonylurea was the most cost-effective third-line therapy, with an ICUR of $68,442 per QALY gained over metformin and sulfonylurea alone. When insulins were excluded from the cost-effectiveness analysis to model the rare situations in which a patient is unable to use insulin, DPP-4 inhibitors were the next most cost-effective option for third-line therapy.

Recommendations

The Canadian Drug Expert Committee (CDEC), which is an advisory body to CADTH, considered the results of the reviews and generated evidence-based recommendations for optimal pharmacotherapy. CDEC recommended that a sulfonylurea be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone. CDEC also recommended that insulin NPH be added for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea. In circumstances where patients with type 2 diabetes are unable to use insulin as a third-line option, CDEC recommended that a DPP-4 inhibitor may be added to metformin and sulfonylurea therapy.

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

A1C lowering efficacy: ↓ by 1.2%.[a]
Change in weight: ↑ by 2 kg.[a]
Annual risk of hypoglycemia requiring third-party assistance: 1 in 85 patients.[b]
Added cost per day:[c] $1.14.[d]

[a]On average.
[b]Estimated, based on data from Holman et al. (2009)[2] and Singh et al. (2009).[3]
[c]Based on 40 units per day.
[d]Wholesale cost (excluding markup and dispensing fees). Data obtained from the Ontario

It was proposed that additional research should be undertaken (through well-designed, adequately powered studies) to address unanswered issues regarding long-term drug efficacy and safety, effects on patient quality of life, and patient characteristics (e.g., age) that may increase the risk of hypoglycemia.

References

1. Home PD, et al. Diabet Med. 2007;24(6): 626–34.
2. Holman RR, et al. N Engl J Med. 2009 Oct 29;361(18): 1736–47.
3. Singh SR, et al. CMAJ. 2009 Feb 17;180(4):385–97.