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Optimal Use Recommendations for
Second- and Third-Line Therapy for
Patients With Type 2 Diabetes

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

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 to 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 this 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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ABBREVIATIONS

A1C	glycated hemoglobin
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CI	confidence interval
CrI	credible interval
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
ICUR	incremental cost-utility ratio
MD	mean difference
N	total number of patients
NPH	neutral protamine Hagedorn
QALY	quality-adjusted life-year
RCT	randomized controlled trial
TZD	thiazolidinediones

1 BACKGROUND

In August 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a systematic review and network meta-analysis assessing the comparative safety and efficacy of all available classes of antihyperglycemic therapies added to metformin in patients with type 2 diabetes who were experiencing inadequate glycemic control on metformin monotherapy.^{1,2} The results of this review indicated that there were no apparent differences in efficacy (as measured by glycated hemoglobin [hemoglobin A1C]) across the available drug classes, although there were differences in the risk of hypoglycemia and changes in body weight. A cost-utility analysis performed using the results of the systematic review found sulfonylureas to be the most cost-effective second-line treatment option.^{1,3} Based on these analyses, the Canadian Optimal Medication Prescribing and Utilization Service (or COMPUS) Expert Review Committee (or CERC) recommended that most patients requiring a second treatment after metformin should be prescribed a sulfonylurea.⁴

Following the review of second-line pharmacotherapy, CADTH published a systematic review and pharmacoeconomic analysis assessing the comparative efficacy, safety, and cost-effectiveness of all available antihyperglycemic drug classes for patients with type 2 diabetes with inadequate glycemic control on metformin and a sulfonylurea.^{5,6} Insulins, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and thiazolidinediones (TZDs) were all found to produce statistically significant reductions of a similar magnitude in hemoglobin A1C, in combination with metformin and a sulfonylurea, whereas meglitinides and alpha-glucosidase inhibitors did not. Similar to the analysis of second-line therapies, there were differences in hypoglycemic risk and changes in body weight across drug classes. The results of the systematic review were used to assess the cost-effectiveness of the various options for third-line therapy after metformin and a sulfonylurea.⁷ The findings suggested that the addition of insulin neutral protamine Hagedorn (NPH) to metformin and sulfonylurea combination therapy was the most cost-effective strategy. CADTH's Therapeutic Review Panel deliberated on the clinical and cost-effectiveness evidence, and recommended that, for most patients, insulin NPH should be added to metformin and a sulfonylurea when these treatments alone are insufficient to adequately control hyperglycemia.⁸

Although the original systematic reviews included clinical evidence for GLP-1 analogues,^{1,5} the cost-effectiveness analyses^{1,7} and subsequent recommendations^{4,8} could not address this class, as there were no drugs approved for use in Canada at the time. Two GLP-1 analogues, exenatide (Byetta) and liraglutide (Victoza), have since been approved. Therefore, there is interest in updated Optimal Use Recommendations for second-line and third-line therapy in type 2 diabetes that incorporate the GLP-1 analogues.

A supplemental issue related to the emerging practice of combining incretin drugs (i.e., GLP-1 analogues and DPP-4 inhibitors) with insulin was also addressed as part of the updated reviews, in light of recent Health Canada approvals for combined use of saxagliptin, sitagliptin, and exenatide with one or more basal or biphasic insulins.

Table 1: Drugs Available in Canada for the Treatment of Type 2 Diabetes

Drug Class	Generic Names
Biguanides	Metformin
Sulfonylureas	Gliclazide, glimepiride, glyburide, chlorpropamide, tolbutamide
Thiazolidinediones	Pioglitazone, rosiglitazone
Meglitinides	Nateglinide, 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.

2 POLICY AND RESEARCH QUESTIONS

2.1 Policy Questions

Evidence-informed recommendations were developed by the Canadian Drug Expert Committee (CDEC) to address the following policy questions:

1. What is the optimal second-line therapy for patients with type 2 diabetes experiencing inadequate glycemic control with metformin monotherapy?
2. What is the optimal third-line therapy for patients with type 2 diabetes experiencing inadequate glycemic control with metformin and a sulfonylurea?
3. If insulin continues to be the recommended third-line therapy for most patients, what alternative(s) are recommended for patients unable to use insulin?
4. What is the role, if any, for the combined use of insulins and incretin agents in patients with type 2 diabetes?

2.2 Research Questions

The following research questions were composed, given the previously listed policy questions:

2.2.1 Second-Line Pharmacotherapy

1. What is the comparative efficacy and safety of second-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?
2. What is the cost-effectiveness of second-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin monotherapy?

2.2.2 Third-Line Pharmacotherapy

1. What is the comparative efficacy and safety of third-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin and a sulfonylurea?
2. What is the cost-effectiveness of third-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin and a sulfonylurea?

2.2.3 Combination Use of Insulin and Incretin Drugs

1. What is the clinical efficacy and safety of DPP-4 inhibitors used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen?
2. What is the clinical efficacy and safety of GLP-1 analogues used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen?

These research questions prompted CADTH to conduct systematic reviews of the published clinical trials to ascertain the relevant evidence and to undertake a pharmacoeconomic analysis. The research questions listed under 2.2.3 were addressed through a supplemental review. The results of these reviews and pharmacoeconomic analyses were utilized by CDEC to develop evidence-informed recommendations.

3 SUMMARY OF RECOMMENDATIONS

Recommendation 1:

The Canadian Drug Expert Committee (CDEC) recommends that a sulfonylurea be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone.

Recommendation 2:

The Canadian Drug Expert Committee (CDEC) recommends that insulin NPH be added for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea.

Recommendation 3:

In circumstances where patients with type 2 diabetes are unable to use insulin as a third-line option, the Canadian Drug Expert Committee (CDEC) recommends that a DPP-4 inhibitor may be added to metformin and sulfonylurea therapy.

4 RECOMMENDATIONS

Recommendation 1:

The Canadian Drug Expert Committee (CDEC) recommends that a sulfonylurea be added to metformin for most adults with type 2 diabetes inadequately controlled on metformin alone.

Reasons for Recommendation

1. All of the drug classes demonstrated similar improvements in hemoglobin A1C. Sulfonylureas were the most cost-effective treatment option, with an incremental cost-utility ratio (ICUR) of \$8,445 per quality-adjusted life-year (QALY) gained compared with metformin alone.
2. There are considerably more long-term safety data for sulfonylureas compared to drugs from the newer classes of antihyperglycemic agents.

Of Note

Although there were 69 randomized controlled trials (RCTs) included in the systematic review, the evidence was limited by the lack of adequate data for clinically important outcomes such as diabetes-related complications and severe hypoglycemia.

The Committee identified the values of safety, efficacy, and cost-effectiveness as being of particular importance in making this recommendation.

Recommendation 2:

The Canadian Drug Expert Committee (CDEC) recommends that insulin NPH be added for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea.

Reasons for Recommendation

1. Based on the results of a network meta-analysis of 24 RCTs in patients with type 2 diabetes mellitus and inadequate glycemic control on metformin and a sulfonylurea, statistically significant reductions in hemoglobin A1C of similar magnitude were found for all classes of antihyperglycemic drugs added to existing therapy, with the exception of alpha-glucosidase inhibitors and meglitinides. The addition of insulin NPH to metformin plus a sulfonylurea was associated with the most favourable cost-effectiveness estimate.
2. There are considerably more long-term safety data for the use of insulin NPH compared with drugs from the newer classes of antihyperglycemic agents.

Of Note

1. The evidence provided in the 40 RCTs that were included in the CADTH systematic review was limited by the lack of data for clinically important outcomes such as diabetes-related complications and severe hypoglycemia.
2. Long-acting insulin analogues at prices similar to insulin NPH would also be an option for patients inadequately controlled on metformin and a sulfonylurea.

3. Although there is more clinical experience with DPP-4 inhibitors and GLP-1 analogues since the original CADTH recommendations were published, the Committee concluded that there remains uncertainty regarding the long-term safety of these drug classes. The Committee noted that additional long-term follow-up data — including the results of ongoing trials designed to investigate the effects of DPP-4 inhibitors and GLP-1 analogues on cardiovascular end points — may help address this uncertainty in the future.

The Committee identified the values of safety, efficacy, and cost-effectiveness as being of particular importance in making this recommendation.

Recommendation 3:

In circumstances where patients are unable to use insulin as a third-line option, the Canadian Drug Expert Committee (CDEC) recommends that a DPP-4 inhibitor may be added to metformin and sulfonylurea therapy.

Reason for Recommendation

DPP-4 inhibitors were the most cost-effective option when insulins were excluded from the cost-effectiveness analysis.

Of Note

1. The Committee noted that there are few instances where patients with type 2 diabetes are unable to use insulin after adequate education and training. However, the Committee recognized that an alternative to insulin should be available to facilitate optimal glycemic control for such patients.
2. The Committee noted that although DPP-4 inhibitors were the most cost-effective option when insulin is not an option, the addition of agents from this drug class to metformin and a sulfonylurea was associated with a relatively high incremental cost per QALY gained relative to metformin and a sulfonylurea alone (\$113,254).

The Committee identified the values of efficacy and cost-effectiveness as of particular importance in making this recommendation.

5 SUMMARY OF THE EVIDENCE

5.1 Review of Second-Line Pharmacotherapy

5.1.1 Literature Review

The Committee considered the results of a systematic review and network meta-analysis conducted to assess the comparative efficacy and safety of second-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemetic control on metformin monotherapy.⁹ Inadequate glycemetic control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour postprandial glucose > 10 mmol/L. The systematic review was performed as an update to a CADTH review conducted in 2010 and included a total of 69 unique RCTs. Evidence was available for the following eight drug classes: sulfonylureas (28 RCTs), DPP-4 inhibitors (24 RCTs), TZDs (20 RCTs), GLP-1 analogues (14 RCTs), basal insulin (six RCTs), alpha-glucosidase inhibitors (five RCTs), meglitinides (four RCTs), and biphasic insulin (four RCTs). A placebo treatment group was included in 35 RCTs.

5.1.2 Efficacy

There were no RCTs included in this review that were adequately powered to detect differences between treatments for long-term diabetes-related complications (e.g., microvascular and macrovascular events) or mortality. Hence, the relative efficacy of second-line drugs was assessed primarily based on hemoglobin A1C as a surrogate for diabetes-related complications.

Fifty-six RCTs (total number of patients [N] = 27,773) were included in a network meta-analysis comparing change from baseline in hemoglobin A1C across different drug classes. All classes of second-line drugs added to metformin significantly reduced hemoglobin A1C relative to metformin alone. The effect estimates ranged from -0.64% (95% credible interval [CrI], -0.92 to -0.38) for meglitinides to -1.04 (95% CrI, -1.30 to -0.78) for biphasic insulins. Sensitivity analyses and meta-regressions were conducted to investigate heterogeneity related to a range of patient characteristics (e.g., baseline hemoglobin A1C, duration of diabetes) and trial characteristics (e.g., duration of the RCT). All of the results from sensitivity analyses were consistent with the reference case. Due to the relatively short duration of the included trials, there was insufficient evidence to assess whether there were differences in drug classes with respect to the long-term durability of antihyperglycemic effects.

5.1.3 Harms

Harms associated with various second-line antidiabetes drugs were evaluated using the following end points: hypoglycemic events (overall and severe), changes in body weight, and adverse events. Network meta-analyses were conducted for change from baseline in body weight and overall hypoglycemia. Events of severe hypoglycemia and severe adverse events were too rare (e.g., the majority of trials reported zero events) in the included RCTs to perform meaningful comparisons across drug classes.

Thirty-five RCTs were included in a network meta-analysis for changes from baseline in body weight (N = 20,178). Treatment with sulfonylureas, meglitinides, TZDs, basal insulin, and biphasic insulin resulted in significantly greater increases in body weight than metformin monotherapy (range 1.7 kg to 3.1 kg), with no significant differences between these classes. DPP-4 inhibitors and alpha-glucosidase inhibitors did not significantly affect body weight. The only drug class associated with a significant reduction in body weight versus metformin monotherapy was GLP-1 analogues (-1.8 kg, 95% CrI, -3.0 to -0.5).

Forty-eight RCTs were included in the updated network meta-analysis for overall hypoglycemia (N = 24,284). Relative to metformin monotherapy, the risk of hypoglycemia was significantly elevated with insulins, sulfonylureas, and meglitinides (odds ratios were 4.1 to 7.0 for insulins, 7.5 for sulfonylureas, and 8.3 for meglitinides). TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 analogues were not associated with a significant increase in the risk of hypoglycemia.

5.1.4 Cost and Cost-Effectiveness

The Committee considered the results of a class-level cost-effectiveness analysis that compared alternative second-line therapies in adults with type 2 diabetes inadequately controlled with metformin monotherapy. The analysis compared nine treatment classes added to metformin as second-line therapy (alpha-glucosidase inhibitors, sulfonylureas, meglitinides, TZDs, basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, and placebo). The lowest cost alternative for each class of drugs was used in the primary economic analysis. The average daily costs of treatments were estimated with and without the additional cost of blood glucose test strips (Table 2).

Average test strip use, by type of pharmacotherapy, was obtained from an analysis of the Ontario Public Drug Programs.¹⁰ A cost of \$0.729 per test strip plus a pharmacy fee of \$7.00 per 100 test strips was applied. The United Kingdom Prospective Diabetes Study Outcomes Model¹¹ was used to forecast the cumulative incidence of diabetes-related complications during a 40-year time horizon, as well as associated costs. For each treatment strategy, inputs for predictive risk factors in the model — such as hemoglobin A1C, body mass index, and body weight — were informed by the results of the systematic review and network meta-analysis.¹² Overall hypoglycemia, severe hypoglycemia, and congestive heart failure (regarding TZDs) were also considered in the model.

In the reference-case analysis, the addition of a sulfonylurea to metformin monotherapy was associated with the most favourable cost-effectiveness estimate compared with metformin monotherapy, with an incremental cost per QALY gained of \$8,445 relative to metformin alone (Table 3). Other active treatments were more costly and associated with a range of QALYs gained compared with sulfonylureas, although absolute differences in QALYs across classes were small. Cost-effectiveness results were robust to variation in model inputs and assumptions. Cost-effectiveness acceptability curves showed that sulfonylureas had the highest probability of being the most cost-effective second-line treatment option for willingness-to-pay thresholds above ~\$22,000 per QALY gained.

A limitation of the economic analysis was the lack of adequate clinical data to inform key model inputs, especially the impact of insulin use and hypoglycemia on quality of life, and the incidence of hypoglycemia across various treatments.

Table 2: Average Daily Cost of Treatments With and Without the Cost of Blood Glucose Test Strips

Treatment	Assumed Doses	Daily Treatment Cost Without Test Strips ^a	Daily Treatment Cost With Test Strips ^b
AG inhibitors	Acarbose 300 mg daily	\$1.28	\$2.04
DPP-4 inhibitors	Linagliptin 5 mg daily	\$2.88	\$3.63
GLP-1 analogues	Exenatide 20 mcg daily	\$5.13	\$5.88
Sulfonylureas	Glyburide 10 mg daily	\$0.20	\$1.13
TZDs ^c	Pioglitazone 30 mg daily	\$1.33	\$2.08
Meglitinides	Repaglinide 4 mg daily	\$0.32	\$1.25
Basal human insulin	Insulin NPH 0.75 U per kg per day ^d	\$1.93	\$3.60
Long-acting insulin analogues	Insulin glargine 0.53 U per kg per day ^d	\$3.12	\$4.78
Biphasic human insulin	Insulin NPH 30/70 1.50 U per kg per day ^d	\$3.83	\$5.48

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

^a The cost of the lowest cost alternative was applied for each drug class, plus a 10% markup and \$7.00 pharmacy fee per 90-day supply. It was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.¹³

^b Patients using insulin were assumed to use 2.1 test strips per day, while those using sulfonylureas and meglitinides used 1.16 test strips per day. Remaining oral antidiabetes treatments used 0.94 test strips per day based on data from the Ontario Public Drug Programs.¹⁰

^c Based on the cost of 30 mg generic pioglitazone in Saskatchewan.

^d Insulin doses obtained from a patient sample in British Columbia (Dr. Marshall Dahl, unpublished data, 2008). This dataset reported insulin doses of 0.53 U/kg, 0.75 U/kg, and 1.5 U/kg for long-acting insulin analogues, insulin NPH, and biphasic human insulin, respectively. Total daily costs for insulins are based on an assumed body weight of 87 kg (derived from RCTs included in the systematic review).

Table 3: Total Lifetime Costs, QALYs, and Incremental Cost-Effectiveness Results from the Reference Case Economic Analysis

Treatment Added to Metformin	Cost	Effectiveness (QALY)	ICUR	
			Incremental vs. Metformin Monotherapy	Sequential
None/Placebo	\$47,949	8.6083	NA	NA
Sulfonylurea	\$48,397	8.6613	\$8,445	\$8,445
AG inhibitor	\$50,603	8.6662	\$45,783	\$452,630
GLP-1 analogue	\$60,254	8.6824	\$165,916	\$595,653
Treatments Ruled Out by Dominance or Extended Dominance				
Meglitinide	\$48,938	8.6520	\$22,589	Dominated by sulfonylurea
TZD	\$50,873	8.6600	\$56,548	Dominated by sulfonylurea and AG inhibitor
DPP-4 inhibitor	\$54,744	8.6602	\$130,710	Dominated by sulfonylurea and AG inhibitor
Basal insulin	\$56,077	8.6594	\$158,934	Dominated by sulfonylureas, AG inhibitor, TZD, and DPP-4 inhibitor
Biphasic insulin	\$60,891	8.6761	\$190,713	Dominated by GLP-1 analogue

AG = alpha-glucosidase; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year; TZD = thiazolidinedione; vs. = versus.

5.2 Review of Third-Line Pharmacotherapy

5.2.1 Literature Review

The Committee considered the results of a systematic review conducted to assess the comparative efficacy and safety of third-line antihyperglycemic drugs in adults with type 2 diabetes experiencing inadequate glycemic control on combination therapy with metformin and a sulfonylurea.¹² Inadequate glycemic control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L. The systematic review was performed as an update to a 2010 CADTH review of this topic, and included a total of 40 unique RCTs. Evidence was available for the following eight drug classes added to metformin and a sulfonylurea: DPP-4 inhibitors (three RCTs), GLP-1 analogues (seven RCTs), alpha-glucosidase inhibitors (five RCTs), meglitinides (one RCT), TZDs (10 RCTs), basal insulin (21 RCTs), biphasic insulin (13 RCTs), and bolus insulin (one RCT).

5.2.2 Efficacy

There were no RCTs included in this review that were adequately powered to detect differences between treatments for long-term diabetes-related complications (e.g., microvascular and macrovascular events) or mortality. Hence, the relative efficacy of third-line drugs was assessed primarily based on hemoglobin A1C as a surrogate for diabetes-related complications.

Twenty-four RCTs were included in the updated network meta-analysis for hemoglobin A1C (N = 8,517). With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in hemoglobin A1C (range -0.72% to -1.15%) relative to metformin and a sulfonylurea. The addition of a basal or biphasic insulin resulted in the largest effects, with mean differences (MDs) of -1.15% (95% CrI, -1.49% to -0.83%) and -1.12% (95% CrI, -1.52% to -0.75%), respectively. Sensitivity analyses and meta-regressions were conducted to investigate heterogeneity related to a range of patient characteristics (e.g., baseline hemoglobin A1C, duration of diabetes) and trial characteristics (e.g., duration of the RCT). All of the results from sensitivity analyses were consistent with the reference case. Due to the relatively short duration of the included trials, there was insufficient evidence to assess whether there were differences in drug classes regarding the long-term durability of antihyperglycemic effects.

5.2.3 Harms

Harms associated with various third-line antihyperglycemic drugs were evaluated using the following end points: hypoglycemic events (overall and severe), changes in body weight, and adverse events. A network meta-analysis was conducted for change from baseline in body weight; however, results for overall and severe hypoglycemia could not be pooled in this manner. Events of severe hypoglycemia and severe adverse events were too rare (e.g., the majority of trials reported zero events) in the included RCTs to perform meaningful comparisons across drug classes.

Eighteen RCTs were included in the updated network meta-analysis for body weight (N = 7,907). When added to metformin and a sulfonylurea, basal insulin, biphasic insulin, rapid-acting insulin analogue, and TZD were associated with significantly greater increases in body weight than occurred with metformin and sulfonylurea alone (range 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 (-1.6 kg, 95% CrI, -2.8 to -0.4). Meglitinides were associated with a non-significant trend toward increased body weight.

Basal insulin, TZDs, DPP-4 inhibitors, and GLP-1 analogues were associated with a significantly greater risk of overall hypoglycemia than placebo when given in combination with metformin and a sulfonylurea. The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators. Biphasic and bolus insulins were associated with a significantly greater risk of overall hypoglycemia than basal insulin. Events of severe hypoglycemia were relatively rare for all drug classes, limiting the ability to make meaningful comparisons between drug classes.

5.2.4 Cost and Cost-Effectiveness

The Committee considered the results of a class-level cost-effectiveness analysis that compared alternative third-line therapies in adults with type 2 diabetes inadequately controlled with metformin and a sulfonylurea. The analysis compared five classes added to metformin and a sulfonylurea as third-line therapy (basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, and placebo). The lowest cost alternative for each class of drugs was used in the primary economic analysis. TZDs were not included in the reference-case analysis, as they are not indicated for third-line treatment of type 2 diabetes in Canada, but they were included in a sensitivity analysis. The average daily costs of treatments were estimated with and without the additional cost of blood glucose test strips (Table 4). Average test strip use, by type of pharmacotherapy, was obtained from an analysis of the Ontario Public Drug Programs.¹⁰ A cost of \$0.729 per test strip, plus a pharmacy fee of \$7.00 per 100 test strips, were applied. The United Kingdom Prospective Diabetes Study Outcomes Model¹¹ was used to forecast the cumulative incidence of diabetes-related complications during a 40-year time horizon, as well as associated costs. For each treatment strategy, inputs for predictive risk factors in the model — such as hemoglobin A1C, body mass index, and body weight — were informed by the results of the systematic review and network meta-analysis.¹² Overall hypoglycemia, severe hypoglycemia, and congestive heart failure (regarding TZDs) were also considered in the model.

In the reference-case analysis, the addition of insulin NPH (representing the basal insulin class) to metformin plus a sulfonylurea was associated with the most favourable cost-effectiveness estimates among active treatments, with an incremental cost per QALY gained of \$68,442 relative to metformin plus a sulfonylurea alone (Table 5). Other active treatments were more costly and less effective in QALYs gained compared with insulin NPH, with the exception of GLP-1 agonists, which were associated with QALY gains of 8.2957 versus 8.2923 for insulin NPH. Differences between treatments in QALYs were small, hence cost-effectiveness results were driven primarily by lifetime costs. Cost-effectiveness results were sensitive to variation in model inputs and assumptions. In some circumstances, DPP-4 inhibitors became the most cost-effective therapeutic option in circumstances such as if insulin was considered undesirable by patients (i.e., high disutility was applied for insulin injections), if higher rates of hypoglycemia were assumed among patients using insulin than in the reference case analysis, or if a higher disutility was assigned to cases of mild to moderate hypoglycemia. Cost-effectiveness acceptability curves showed that the addition of insulin NPH had the highest probability of being the most cost-effective third-line treatment option for willingness-to-pay thresholds above ~\$69,000 per QALY gained.

To assess the cost-effectiveness of third-line therapies for patients unable to use insulin, a sensitivity analysis was performed in which insulins were removed as treatment options. In this scenario, the addition of a DPP-4 inhibitor to metformin and a sulfonylurea represented the most cost-effective option, with an ICUR of \$113,254 per QALY gained compared with the combination of metformin and a sulfonylurea. GLP-1 analogues were associated with an ICUR of \$171,000 compared with DPP-4 inhibitors in this analysis.

A limitation of the economic analysis was the lack of adequate clinical data to inform key model inputs, especially the impact of insulin use and hypoglycemia on quality of life and the incidence of hypoglycemia across various treatments.

Treatment	Assumed Doses	Daily Treatment Cost Without Test Strips ^a	Daily Treatment Cost With Test Strips ^b
DPP-4 inhibitors	Linagliptin 5 mg daily	\$2.88	\$3.81
GLP-1 agonists	Exenatide 20 mcg daily	\$5.13	\$6.05
Basal human insulin	Insulin NPH		
	0.75 U per kg per day ^c 0.42 U per kg per day ^d	\$1.93 ^c \$1.11 ^d	\$3.60 ^c \$2.78 ^d
Biphasic human insulin	Insulin NPH 30/70		
	1.50 U per kg per day ^c 0.76 U per kg per day ^d	\$3.83 ^c \$2.88 ^d	\$5.48 ^c \$4.53 ^d
Long-acting insulin analogues	Insulin glargine		
	0.53 U per kg per day ^c 0.35 U per kg per day ^d	\$3.12 ^c \$1.98 ^d	\$4.78 ^c \$3.64 ^d

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; U = unit.

^aThe cost of the lowest cost alternative was applied for each drug class, plus a 10% markup and \$7.00 pharmacy fee per 90-day supply. It was assumed that patients used the average defined daily dose from the World Health Organization for each treatment.¹³

^bPatients using insulin were assumed to use 2.1 test strips per day, while those using oral drugs in combination with sulfonylureas used 1.16 test strips per day, based on data from the Ontario Public Drug Programs.¹⁰

^cInsulin doses obtained from patient sample in British Columbia (Dr. Marshall Dahl, unpublished data, 2008). This dataset reported insulin doses of 0.53 U/kg, 0.75 U/kg, and 1.5 U/kg for long-acting insulin analogues, insulin NPH, and biphasic human insulin respectively. Total daily costs for insulins are based on an assumed body weight of 87 kg (derived from RCTs included in systematic review).

^dInsulin doses obtained from RCTs included in the original CADTH systematic review of second-line therapies, which reported insulin doses of 0.35 U/kg, 0.42 U/kg, and 0.76 U/kg for long-acting insulin analogues, insulin NPH, and biphasic human insulin respectively.

Treatment (Added onto Met + SU)	Cost	Effectiveness (QALY)	ICUR	
			Incremental vs. Met + SU	Sequential
Met + SU alone	\$46,746	8.2089	NA	NA
Basal insulin	\$52,453	8.2923	\$68,442	\$68,442
GLP-1 analogue	\$58,341	8.2957	\$133,662	\$1,752,233
Treatments Ruled Out by Dominance or Extended Dominance				
DPP-4 inhibitor	\$53,097	8.2650	\$113,254	Dominated by basal insulin
Biphasic insulin	\$57,117	8.2875	\$131,989	Dominated by basal insulin

GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; Met = metformin; NA = not applicable; QALY = quality-adjusted life-year; SU = sulfonylurea; vs. = versus.

5.3 Review of Combination Use of Incretin Drugs and Insulin

5.3.1 Literature Review

The Committee considered the results of a literature review conducted to summarize and critically appraise the evidence regarding the clinical effectiveness and harms of combination use of DPP-4 inhibitors or GLP-1 analogues with insulin. There were two systematic reviews and six RCTs that investigated the use of incretin drugs in patients who were inadequately treated with an insulin-containing treatment regimen. Neither systematic review performed a meta-analysis; therefore, the Committee considered the results of the individual clinical trials. The six RCTs included five placebo-controlled trials investigating the use of four DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, and vildagliptin) and one GLP-1 analogue (exenatide). There was one RCT that compared sitagliptin (100 mg once daily) with an increased dosage of insulin. Patients allocated to the increased insulin dosage group were instructed to increase their daily dosage of insulin as follows: at least 10% at randomization; at least 10% at the 12-week follow-up, if their hemoglobin A1C was not within the target level (i.e., $\leq 7.0\%$); and an additional 2 U every week, based on the results of self-monitoring of blood glucose.

5.3.2 Efficacy

In the trials comparing the addition of an incretin drug to insulin versus the addition of placebo, changes from baseline in hemoglobin A1C in the DPP-4 inhibitor groups ranged from -0.5% to -0.7% . All of the DPP-4 inhibitors demonstrated statistically significant improvements in hemoglobin A1C relative to placebo (range -0.3% to -0.6%). Exenatide also demonstrated a significant improvement compared with placebo (-0.7%).

Compared with augmentation of insulin doses, the addition of sitagliptin (100 mg once daily) to stable insulin doses was associated with statistically significant improvements in hemoglobin A1C [MD (95% confidence interval [CI]), -0.42% (-0.91 to -0.11)]. The mean dosage of insulin at baseline was numerically greater in the sitagliptin group (39.6 ± 19.1) compared with the intensified insulin group (35.4 ± 16.3). After 24 weeks, the mean insulin dosage in the intensified insulin group had increased by 10.1 U per day and had decreased in the sitagliptin group by 2.5 U per day ($P < 0.05$).

5.3.3 Harms

In the placebo-controlled trials, the addition of a DPP-4 inhibitor did not result in significant changes in body weight relative to placebo, while the addition of exenatide resulted in statistically significant weight loss (-2.7 kg). Trials involving saxagliptin, vildagliptin, alogliptin, and exenatide demonstrated no significant increase in risk of overall hypoglycemia relative to placebo; however, a single trial involving sitagliptin showed a significantly increased risk of hypoglycemia compared with placebo [odds ratio (95% CI), 2.16 (1.30 to 3.59)]. Events of severe hypoglycemia were rare in the placebo-controlled trials. Compared with an increased insulin dosage, the addition of sitagliptin (100 mg once daily) was associated with a statistically significant improvement in body weight [MD (95% CI), -1.7 kg (-2.5 to -0.5)] and lower rates of overall and severe hypoglycemia (both $P < 0.01$).

6 DISCUSSION POINTS

6.1 Second-Line and Third-Line Pharmacotherapy

6.1.1 Efficacy

- In the absence of adequate data regarding the comparative effects of antihyperglycemic drugs on the risk of macrovascular and microvascular diabetes-related complications, the Committee was required to use changes in hemoglobin A1C as a surrogate measure for assessing relative efficacy across drug classes.
- The Committee noted that the correlation between improvement in hemoglobin A1C and the prevention of cardiovascular complications remains unclear.
- The Committee noted the importance of educating and motivating patients with type 2 diabetes to improve lifestyle and dietary habits when glycemic control wanes on metformin and sulfonylurea therapy, regardless of the second- or third-line antihyperglycemic regimen chosen.

6.1.2 Safety

- With the exception of overall hypoglycemia and changes in body weight, the Committee could not assess comparative safety across drug classes due to the lack of adequate data. Ongoing clinical trials designed to assess the effects of DPP-4 inhibitors and GLP-1 analogues may help address this uncertainty in the future. Despite the fact that there are considerably more long-term safety data and years of clinical experience with sulfonylureas as compared with drugs in the newer classes of antihyperglycemic agents, there remains uncertainty regarding the comparative risk of cardiovascular events and mortality with sulfonylureas relative to other drug classes.
- Changes in body weight associated with various classes of antihyperglycemic therapy were generally modest; however, the Committee recognized that these changes may be important from the perspective of individual patients. The Committee also noted a lack of sufficient evidence regarding the persistence of changes in body weight and the relationship between weight gain/loss due to antihyperglycemic therapies and either long-term clinically important outcomes or quality of life.
- Change in body weight was included in the harms section of the CADTH reviews of second-line and third-line pharmacotherapy; however, the Committee noted that weight loss, if clinically relevant, could be considered a benefit.
- The Committee noted that events of severe hypoglycemia were infrequent in the included trials, and that the incidence of severe hypoglycemia may be higher in clinical practice. More evidence is required to accurately determine the risk of severe hypoglycemia across drug classes, the impact of these events on the health and quality of life of patients, and the patient characteristics (e.g., age) that may be associated with an increased risk of these events.

6.1.3 Cost and Cost-Effectiveness

- The Committee noted that the reference-case analyses did not assign a disutility for weight gain, although the results were similar in a sensitivity analysis that included a decrement based on National Institute for Health and Clinical Excellence (NICE) obesity guidelines.
- The Committee noted the considerable uncertainty regarding the disutility associated with insulin use, weight gain, and hypoglycemia, as well as event rates for severe hypoglycemia. In the absence of sound data for these inputs, conservative estimates were used for the reference-case analysis, and these assumptions were tested in sensitivity analyses.

- The reference-case analyses assumed that patients remained on the same second- or third-line therapy during their lifetime. While this approach was necessary given the uncertainties regarding durability of treatment effects and choice of treatments during a lifetime horizon, the Committee acknowledged that treatments are unlikely to remain static in clinical practice given the progressive nature of the disease. Furthermore, the results of sensitivity analyses in which it was assumed that insulin would be initiated when hemoglobin A1C reached 9% were not substantially different from the reference case.
- Costs related to education and support for patients initiating insulin were not included in the model because of the lack of adequate data. However, the Committee considered that these one-time costs were likely modest compared with lifetime treatment costs; hence, a substantial impact on the cost-effectiveness results was improbable.

6.1.4 Other Discussion Points

- The Committee discussed the challenges of defining “patients who are unable to use insulin.” Although there is an absence of standardized criteria, the Committee concluded that there are few instances in clinical practice where patients are unable to use insulin with adequate education and training. The Committee noted that upon initiation of basal insulin as third-line therapy, clinicians should assess the need for, and safety of, continued treatment with metformin and the sulfonylurea based on individual patient factors. There was insufficient evidence available to address whether one or both drugs should be withdrawn once insulin is started.

6.2 Combination Use of Incretin Drugs and Insulin

- The Committee concluded that there was insufficient evidence to assess the comparative clinical effectiveness of adding an incretin drug versus the intensification of insulin for patients who are inadequately controlled on their existing insulin regimen. The only trial that directly compared the addition of an incretin drug versus intensification of insulin was conducted exclusively in Korea, had a small sample size, and used an open-label design. Therefore, the Committee was unable to make any recommendations on the combined use of insulin and incretin drugs.
- The Committee noted that incretin-insulin combinations would likely be associated with higher treatment costs than optimized insulin regimens. In the absence of adequate clinical evidence, the cost-effectiveness of such combinations is uncertain.
- Due to the short duration of the included studies, the persistence beyond six months of antihyperglycemic effects observed with the addition of an incretin drug to existing insulin could not be assessed.
- The Committee noted that, despite the addition of an incretin drug, patients may eventually require intensification of insulin to maintain long-term glycemic control. The clinical benefits of continued incretin therapy in the setting of insulin intensification are uncertain, and such regimens could be associated with significant costs.

7 RESEARCH GAPS

To facilitate comparisons of antihyperglycemic drugs, the Committee proposed that the following issues be addressed through well-designed, adequately powered studies:

7.1 Second-Line and Third-Line Pharmacotherapy

7.1.1 Efficacy

- Direct or indirect comparisons assessing the relative efficacy of different antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications.
- Due to the relatively short duration of the included trials, it was impossible to accurately determine whether there were differences in the durability of antihyperglycemic effects across the various drug classes.

7.1.2 Harms

- The long-term safety profile of newer classes of antihyperglycemic drugs (e.g., DPP-4 inhibitors and GLP-1 analogues).
- The incidence of severe hypoglycemia within each drug class when combined with metformin and a sulfonyleurea.
- The impact of changes in body weight (both weight loss and weight gain) and hypoglycemia on the quality of life of patients with type 2 diabetes. While a number of studies have reported disutilities for hypoglycemia, uncertainty remains in this area due to methodological limitations and considerable variability in the reported estimates.
- Patient characteristics (e.g., age) that may increase the risk of hypoglycemia.

7.2 Combination Use of Incretin Drugs and Insulin

- Additional direct comparisons between the addition of an incretin drug to an existing insulin regimen and intensification of insulin treatment for patients inadequately controlled on their existing insulin regimen.
- A cost-effectiveness analysis based on robust clinical data comparing the addition of an incretin drug with an existing insulin regimen and intensification of insulin treatment for patients inadequately controlled on their existing insulin regimen.

Members of the Canadian Drug Expert Committee:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. James Silvius, and Dr. Adil Virani

Regrets:

Two CDEC members were unable to attend the meeting.

Conflicts of Interest:

None

Other participants:

An external Clinical Expert attended the meeting and participated in the discussion but did not vote on the recommendations.

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