Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Optimal Use Report

November 2012
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Second- and Third-Line Pharmacotherapy for Type 2 Diabetes — Update of CADTH 2010 Reviews — Project Protocol

November 2012

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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1 INTRODUCTION AND RATIONALE

In August 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) published an Optimal Therapy Report which assessed the clinical and cost-effectiveness of second-line therapies for patients with type 2 diabetes inadequately controlled on metformin. The results from the CADTH review indicated that there were no apparent differences in efficacy across drug classes, and that sulfonylureas were the most cost-effective treatment option. Based on these analyses, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee (CERC) recommended that most patients requiring a second treatment after metformin should be prescribed a sulfonylurea. CADTH followed this report with a Therapeutic Review which examined the evidence for third-line treatment options for adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea. The results demonstrated that insulins (basal, biphasic, bolus), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and thiazolidinediones (TZDs) all produced statistically significant reductions in hemoglobin A1C in combination with metformin and a sulphonylurea. Meglitinides and alpha-glucosidase inhibitors, however, did not. The addition of insulin neutral protamine Hagedorn (NPH) to metformin plus a sulfonylurea was associated with the most favourable cost-effectiveness estimates. CADTH's Therapeutic Review Panel (TRP) recommended that, for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea, insulin NPH should be added as the third-line agent. Long-acting insulin analogues at prices similar to insulin NPH were also considered an option for patients inadequately controlled on metformin and a sulfonylurea.

The original clinical reviews of second- and third-line pharmacotherapy for type 2 diabetes included GLP-1 analogues and DPP-4 inhibitors currently available in Canada;[1,2] however, the cost-effectiveness analyses[2,3] and subsequent recommendations[1,4] could not address the use of GLP-1 analogues, as there were no agents approved for use in Canada at the time of the reviews. Two GLP-1 analogues, exenatide (Byetta) and liraglutide (Victoza), are now approved for use in Canada. As well, sitagliptin and saxagliptin were the only DPP-4 inhibitors considered in the original economic analyses and recommendations, while agents in this class that were not yet approved by Health Canada (e.g., linagliptin) were excluded. Therefore, there is interest in updated optimal therapy recommendations for second- and third-line therapy in diabetes that incorporate the GLP-1 analogues and newer DPP-4 inhibitors.

Since the original CADTH reports were published, interest has emerged in the combined use of incretins and insulin, and some incretins have received regulatory approval for combined use with insulin in Canada and other jurisdictions.[5,6] Hence, the updated clinical reviews will also address a supplemental research topic regarding the combination use of incretin agents with insulin.

Table 1: Planned Reports Arising from the Update of Second- and Third-Line Diabetes Pharmacotherapy Projects	
CADTH Report	**Description**
Science Report	• Updated systematic review incorporating new RCT evidence for second- and third-line therapy in type 2 diabetes • Updated cost-effectiveness analyses for second- and third-line therapy, based on updated clinical results • Supplement containing summary and critical appraisal of the evidence for combination use of incretins and insulin in type 2 diabetes
Optimal Use Recommendations	Updated recommendations for second- and third-line therapy from CDEC based on Science report

CADTH = Canadian Agency for Drugs and Technologies in Health; CDEC = Canadian Drug Expert Committee; RCT = randomized controlled trial.

2 PROCESS FOR UPDATING SYSTEMATIC REVIEWS

2.1 Research Questions

The research questions to be addressed in the updated systematic reviews of second- and third-line diabetes pharmacotherapy are the same as in the original reviews:

1. What is the comparative efficacy and safety of second-line antidiabetes drugs in adults with type 2 diabetes inadequately controlled on metformin monotherapy?
2. What is the comparative efficacy and safety of third-line antidiabetes drugs in adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea?

2.2 Literature Search Strategy

The literature searches used in the original CADTH reviews will be updated to identify English language documents published between January 1, 2009, and May 7, 2012. Published literature will be identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates via Ovid; Embase via Ovid; The Cochrane Library via Ovid; and PubMed. The search strategy comprises of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are diabetes, and second- and third-line antidiabetes drugs. Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and economic studies. See Appendix 1 for the detailed search strategies. Grey literature (literature that is not commercially published) will be identified by searching the Grey Matters checklist (www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, and professional associations. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

2.3 Eligibility Criteria

RCTs will be selected for inclusion in the updated systematic reviews of second- and third-line therapies if they meet the criteria outlined in Table 2. Other systematic reviews or health technology assessments of therapies for type 2 diabetes will also be retrieved for comparative studies if they employ a network meta-analysis (NMA) approach similar to the CADTH analyses.

Table 2: Eligibility Criteria for inclusion of RCTs in updated systematic reviews

Second-Line Pharmacotherapy	
Population	Inadequately controlled with metformin monotherapy*
Interventions/ Comparators	Metformin plus an agent from one of the following drug classes: sulfonylureas, GLP-1 analogues, DPP-4 inhibitor, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulins (basal, bolus, biphasic), placebo/no treatment
Third-Line Pharmacotherapy	
Population	Inadequately controlled with metformin and sulfonylurea combination therapy*
Interventions/ Comparators	GLP-1 analogues, DPP-4 inhibitors, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulins (basal, bolus, biphasic), placebo

α-glucosidase inhibitors = alpha-glucosidase inhibitors; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; RCT = randomized controlled trial.

*In the previous CADTH reviews, inadequate control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.[1,7]

2.4 Data Extraction, Critical Appraisal, and Statistical Analysis

Data extraction will be performed using data extraction forms designed a priori. The internal and external validity of RCTs will be assessed using the SIGN 50 checklist as a guide.[8] Both data extraction and validity assessment will be performed by one reviewer, and verified by a second reviewer. Any disagreements will be resolved by consensus when possible; otherwise, the judgment of a third reviewer will be considered final.

Compared with the original CADTH analyses, the update will assess a focused set of outcomes; i.e., those which were the primary considerations of CERC and TRP in developing the original recommendations. These include mortality, diabetes-related complications, hemoglobin A1C, body weight, hypoglycemia, and serious adverse effects. Evidence for diabetes-related complications will only be reviewed from RCTs that were designed and powered to compare the effect of two or more treatments on such an end point.

The original network meta-analyses for second- and third-line therapy will be updated with data from newly-identified trials that meet eligibility criteria for inclusion. The methodology employed will be the same as that used in the original CADTH analyses.[1,7,9] As the results of the original analyses were largely robust in subgroup and sensitivity analyses, such analyses will only be performed for the updated NMAs if the reference case results are sufficiently different from the results of the original analyses.

The deviance information criterion (DIC) statistic will be used to assess the goodness-of-fit for all models. Consistency between direct and indirect evidence will be assessed by comparing direct estimates obtained from pairwise meta-analysis with estimates from the MTC meta-analysis.

2.5 Supplemental Review of Incretin/Insulin Combinations

As a supplement to the updated systematic reviews of second- and third-line therapies, CADTH will summarize and critically appraise the evidence regarding the clinical effectiveness and harms of DPP-4 inhibitors or GLP-1 analogues when used in combination with insulin. The focus of the review will be on existing systematic reviews or health technology assessments of sufficient methodological quality (as appraised using AMSTAR) that have evaluated this issue. RCTs published after the literature cut-off date of the selected review(s) will also be assessed. Published literature will be identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates via Ovid; Embase via Ovid; The Cochrane Library via Ovid; and PubMed. The main search concepts will be diabetes, insulin, DPP-4 inhibitors, and GLP-1 analogues. Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and RCTs.

3 PROCESS FOR UPDATING THE PHARMACOECONOMIC REVIEW

The following research questions will be addressed in the updated pharmacoeconomic review of second- and third-line diabetes pharmacotherapy:

1. What is the cost-effectiveness of second-line antidiabetes drugs in adults with type 2 diabetes inadequately controlled on metformin monotherapy?
2. What is the cost-effectiveness of third-line antidiabetes drugs in adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea?

The cost-utility analysis will be conducted using a new version of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model previously used in the original CADTH reviews.[3,4] The newer UKPDS Outcomes Model will be updated to reflect the most current clinical evidence, drug prices, and management costs. The key feature of this update will be the incorporation of GLP-1 analogues.

4 PROCESS FOR UPDATING THE OPTIMAL THERAPY RECOMMENDATIONS

The evidence from the updated clinical and pharmacoeconomic reviews will be discussed by the Canadian Drug Expert Committee (CDEC), which will develop updated Optimal Therapy Recommendations for second- and third-line diabetes pharmacotherapy. CDEC is an advisory body to CADTH, composed of individuals with expertise in drug therapy, drug evaluation, and drug utilization; and including public members to bring a lay perspective.[10]

5 REFERENCES

1. Canadian Agency for Drugs and Technologies in Health. Clinical review: third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylureas [Internet]. Ottawa: The Agency; 2010 Aug. [cited 2010 Sep 30]. (CADTH therapeutic review). Available from: http://www.cadth.ca/media/pdf/Diabetes_TR_Clinical_Report_Final_e.pdf
2. Canadian Agency for Drugs and Technologies in Health. Second-line therapy for patients with type 2 diabetes inadequately controlled on metformin: a systematic review and cost-effectiveness analysis [DRAFT]. Ottawa: The Agency; 2010. (Optimal therapy report; vol. 4 no. 2).
3. Canadian Agency for Drugs and Technologies in Health. Economic evaluation: third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylureas [Internet]. Ottawa: The Agency; 2010 Aug. [cited 2012 Nov 5]. (CADTH therapeutic review). Available from: http://www.cadth.ca/media/pdf/Diabetes_TR_Economic_Evaluation_Final_e.pdf
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5. Januvia© (sitagliptin phosphate monohydrate): tablets 100 mg [product monograph]. Pointe-Claire - Dorval (QC): Merck Frosst Canada Ltd; 2010.
6. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.
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9. Canadian Agency for Drugs and Technologies in Health. Second-line Therapy for Patients with Diabetes Inadequately Controlled on Metformin: Addendum to Project Protocol - August 14, 2009 [Internet]. Ottawa: The Agency; 2009. [cited 2010 May 14]. Available from: http://www.cadth.ca/media/compus/pdf/C1110-Protocol-Addendum-as-posted.pdf
10. Canadian Agency for Drugs and Technologies in Health [Internet]. CADTH; 2012. Canadian Drug Expert Committee (CDEC); 2012 [cited 20120 Oct 1]. Available from: http://www.cadth.ca/en/products/cdr/committees/canadian-drug-expert-committee

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment EBM Reviews - NHS Economic Evaluation Database EMBASE Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases will be removed in Ovid.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; and economic literature.
Limits:	Publication years January 1, 2009 onwards English language Humans
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment EBM Reviews - NHS Economic Evaluation Database EMBASE Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases will be removed in Ovid.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

OVID MEDLINE & EMBASE STRATEGY	
#	**Strategy**
1	Hypoglycemic drugs/
2	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
3	Thiazolidinediones/
4	(glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab.
5	(122320-73-4 or 155141-29-0).rn.
6	Dipeptidyl-Peptidase IV Inhibitors/
7	(sitagliptin or Januvia or Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
8	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
10	275371-94-3.rn.
11	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
12	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
13	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.
14	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
15	(dpp adj IV adj inhibitor*).ti,ab.
16	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
17	DPP-4 inhibitors.ti,ab.
18	dipeptidyl peptidase-4 inhibitors.ti,ab.
19	exp Sulfonylurea Compounds/
20	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
21	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
22	alpha-Glucosidases/ai
23	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
24	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
25	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
26	Acarbose/
27	Lipase/ai
28	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
29	(96829-58-2 or 106650-56-0).rn.
30	(lipase adj inhibit*).ti,ab.
31	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
32	(135062-02-1 or 105816-04-4).rn.
33	Amyloid/

OVID MEDLINE & EMBASE STRATEGY	
#	**Strategy**
34	(Pramlintide or symlin).ti,ab.
35	(amylin adj analog*).ti,ab.
36	151126-32-8.rn.
37	exp insulin/
38	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
39	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
40	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
41	(nph insulin or humulin or novolin).ti,ab.
42	11061-68-0.rn.
43	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
44	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
45	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
46	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
47	or/1-46
48	exp Diabetes Mellitus, Type 2/
49	Diabetes mellitus/
50	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
51	(Mody or niddm or t2dm).ti,ab.
52	or/48-51
53	Metformin/
54	Metformin.ti,ab.
55	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
56	(657-24-9 or 1115-70-4).rn.
57	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
58	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
59	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
60	or/53-59
61	47 and 52 and 60
62	61 use pmez
63	Antidiabetic agent/
64	Oral Antidiabetic agent/
65	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
66	exp *glitazone derivative/

OVID MEDLINE & EMBASE STRATEGY	
#	**Strategy**
67	(glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab.
68	(122320-73-4 or 155141-29-0).rn.
69	exp *Dipeptidyl Peptidase IV Inhibitor/
70	(sitagliptin or Januvia or Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
71	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
72	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
73	275371-94-3.rn.
74	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
75	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
76	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab.
77	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
78	(dpp adj IV adj inhibitor*).ti,ab.
79	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
80	DPP-4 inhibitors.ti,ab.
81	dipeptidyl peptidase-4 inhibitors.ti,ab.
82	exp *sulfonylurea derivative/
83	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
84	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
85	exp *"Alpha Glucosidase Inhibitor"/
86	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
87	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
88	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
89	Lipase inhibitor/
90	*Tetrahydrolipstatin/
91	*Sibutramine/
92	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
93	(96829-58-2 or 106650-56-0).rn.
94	(lipase adj inhibit*).ti,ab.
95	*Meglitinide/
96	*Repaglinide/
97	*Nateglinide/
98	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
99	(135062-02-1 or 105816-04-4).rn.
100	*Pramlintide/

OVID MEDLINE & EMBASE STRATEGY	
#	**Strategy**
101	(Pramlintide or symlin).ti,ab.
102	(amylin adj analog*).ti,ab.
103	151126-32-8.rn.
104	*biphasic insulin/ or *human insulin/ or *insulin/ or *insulin aspart/ or *insulin detemir/ or *insulin glargine/ or *insulin glulisine/ or *insulin lispro/ or *isophane insulin/ or *long acting insulin/ or *monocomponent insulin/ or *neutral insulin/ or *recombinant human insulin/ or *synthetic insulin/
105	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
106	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
107	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
108	(nph insulin or humulin or novolin).ti,ab.
109	11061-68-0.rn.
110	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
111	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
112	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
113	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
114	*exendin 4/
115	*albiglutide/ or *liraglutide/ or *lixisenatide/ or *taspoglutide/
116	or/63-115
117	*Diabetes Mellitus/
118	*Maturity Onset Diabetes Mellitus/
119	*Non Insulin Dependent Diabetes Mellitus/
120	*Lipoatrophic Diabetes Mellitus/
121	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
122	(Mody or niddm or t2dm).ti,ab.
123	or/117-122
124	Metformin/
125	Metformin.ti,ab.
126	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
127	(657-24-9 or 1115-70-4).rn.
128	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
129	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
130	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or imethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
131	or/124-130
132	116 and 123 and 131

OVID MEDLINE & EMBASE STRATEGY	
#	**Strategy**
133	132 use emef
134	62 or 133
135	limit 134 to english
136	limit 135 to yr="2009 -Current"
137	exp animals/
138	exp animal experimentation/
139	exp models animal/
140	exp animal experiment/
141	nonhuman/
142	exp vertebrate/
143	animal.po.
144	or/137-143
145	exp humans/
146	exp human experiment/
147	human.po.
148	or/145-147
149	144 not 148
150	136 not 149
151	remove duplicates from 150
152	meta-analysis.pt.
153	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
154	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
155	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
156	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
157	(data synthes* or data extraction* or data abstraction*).ti,ab.
158	(handsearch* or hand search*).ti,ab.
159	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
160	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
161	(meta regression* or metaregression* or mega regression*).ti,ab.
162	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
163	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
164	(cochrane or (health adj2 technology assessment) or evidence report).jw.
165	(meta-analysis or systematic review).md.
166	or/152-165
167	Randomized Controlled Trial.pt.
168	Randomized Controlled Trials as Topic/
169	"Randomized Controlled Trial (topic)"/
170	Randomized Controlled Trial/
171	Randomization/
172	Random Allocation/

OVID MEDLINE & EMBASE STRATEGY

#	Strategy
173	Double-Blind Method/
174	Double Blind Procedure/
175	Double-Blind Studies/
176	Single-Blind Method/
177	Single Blind Procedure/
178	Single-Blind Studies/
179	Placebos/
180	Placebo/
181	(random* or sham or placebo*).ti,ab,hw.
182	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
183	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
184	or/167-183
185	151 and 166
186	185 not conference abstract.pt.
187	151 and 184
188	187 not conference abstract.pt.
189	(economic adj2 model*).mp.
190	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
191	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
192	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
193	(cost or costs or economic*).ti. and (costs or cost-effectiveness or markov).ab.
194	or/189-193
195	151 and 194
196	195 not conference abstract.pt.

OVID COCHRANE STRATEGY

#	Searches
1	Hypoglycemic drugs/
2	((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab.
3	Thiazolidinediones/
4	(glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab.
5	(122320-73-4 or 155141-29-0).rn.
6	Dipeptidyl-Peptidase IV Inhibitors/
7	(sitagliptin or Januvia or Janumet or vildagliptin or Galvus or gliptin or incretin agent* or exenatide or Byetta or Bydureon or Exendin-4 or liraglutide or Victoza).ti,ab.
8	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9	(taspoglutide or R-1583 or R1583 or BIM51077 or BIM-51077 or lixisenatide or AVE0010 or AVE-0010 or albiglutide).ti,ab,rn.
10	275371-94-3.rn.
11	(saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.

OVID COCHRANE STRATEGY	
#	**Searches**
12	(361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn.
13	(linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn.
14	(668270-12-0 or 850649-62-6 or 852329-66-9).rn.
15	(dpp adj IV adj inhibitor*).ti,ab.
16	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
17	DPP-4 inhibitors.ti,ab.
18	dipeptidyl peptidase-4 inhibitors.ti,ab.
19	exp Sulfonylurea Compounds/
20	(sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab.
21	(64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn.
22	alpha-Glucosidases/ai
23	(acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
24	(56180-94-0 or 72432-03-2 or 83480-29-9).rn.
25	((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
26	Acarbose/
27	Lipase/ai
28	(Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
29	(96829-58-2 or 106650-56-0).rn.
30	(lipase adj inhibit*).ti,ab.
31	(repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
32	(135062-02-1 or 105816-04-4).rn.
33	Amyloid/
34	(Pramlintide or symlin).ti,ab.
35	(amylin adj analog*).ti,ab.
36	151126-32-8.rn.
37	exp insulin/
38	(long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
39	(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
40	(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
41	(nph insulin or humulin or novolin).ti,ab.
42	11061-68-0.rn.
43	(short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab.
44	(Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.
45	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
46	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.

OVID COCHRANE STRATEGY	
#	**Searches**
47	or/1-46
48	exp Diabetes Mellitus, Type 2/
49	Diabetes mellitus/
50	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab.
51	(Mody or niddm or t2dm).ti,ab.
52	or/48-51
53	Metformin/
54	Metformin.ti,ab.
55	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
56	(657-24-9 or 1115-70-4).rn.
57	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.
58	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
59	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.
60	or/53-59
61	47 and 52 and 60
62	remove duplicates from 61

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used

Grey Literature

Keywords:	Will include terms for diabetes, and second- and third-line antidiabetes drugs
Limits:	Publication years 2009 to 2012

The following sections of the CADTH grey literature checklist, *Grey Matters: A Practical Tool For Evidence-Based Medicine* (www.cadth.ca/resources/grey-matters) will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals.