Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea: A systematic review and mixed treatment comparisons meta-analysis

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Abstract

Objective: Metformin and a sulfonylurea are often used in combination for the treatment of patients with type 2 diabetes. This systematic review and meta-analysis evaluates the comparative safety and efficacy of all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea combination therapy.

Methods: A literature search was conducted for randomized controlled trials (RCTs). Mixed-treatment comparison meta-analyses were used to calculate mean differences between drug classes for changes in HbA1c and body weight. When appropriate, pair-wise meta-analyses were used to estimate differences for other outcomes.

Results: 33 RCTs were included. The methodological quality of studies was generally poor. Insulin (basal, biphasic, or bolus), DPP-4 inhibitors, GLP-1 analogues, and TZDs all produced statistically significant reductions in HbA1c in combination with metformin and a sulfonylurea (range: -0.89 to -1.17); whereas, meglitinides and alpha-glucosidase inhibitors did not. Biphasic insulin, bolus insulin, and TZDs were associated with weight gain (range: 1.85 to 5.00 kg), DPP-4 inhibitors and α-glucosidase inhibitors were weight neutral, and GLP-1 analogues were associated with modest weight loss. Treatment regimens containing insulin were associated with increased hypoglycemia relative to comparators, but severe hypoglycemia was rare across all treatments.

Conclusion: Third-line agents for the treatment of type 2 diabetes are similar in terms of glycemic control, but differ in their propensity to cause weight gain and hypoglycemia. Longer term studies with larger sample sizes are required to determine if any of the drug classes are superior with regards to reducing diabetes-related complications.

INTRODUCTION

Clinical practice guidelines[1-8] recommend metformin as the first-line oral antihyperglycemic drug in most patients with type 2 diabetes mellitus when glycemic control cannot be achieved by dietary and lifestyle interventions. Since type 2 diabetes is a progressive disease, metformin alone often does not provide adequate glycemic control over the long term, hence there is frequently a need for additional therapy. Clinical recommendations from a number of bodies around the world promote the addition of a sulfonylurea for most patients inadequately controlled with metformin monotherapy.[2,5,6,8-11] Indeed, sulfonylureas are associated with similar hemoglobin A1c (HbA_{1c}) reductions as other drug classes, including the DPP-4 inhibitors and GLP-1 analogues, when used as second-line treatment after metformin failure.[12,13] Furthermore, recent Canadian utilization data reveal that over sixty percent of patients with type 2 diabetes requiring second-line therapy use a sulfonylurea.[14]

Over time, even dual therapy may not be sufficiently effective, and additional antidiabetes drugs may be required. Considerable uncertainty exists regarding optimal treatment for patients unable to meet glycemic targets with combination use of metformin and a sulfonylurea. A number of antihyperglycemic drugs are available to such patients, including meglitinides, α-glucosidase inhibitors, thiazolidinediones (TZDs), insulins, and more recently, DPP-4 inhibitors and GLP-1 analogues. Many guidelines[4,5,7,8] recommend that most patients initiate insulin when they are inadequately controlled with metformin and sulfonylurea combination therapy; however, others indicate that either insulin or a third oral agent from a different pharmacological class are viable options.[1,6] Unlike the relatively consistent use of sulfonylureas as second-line therapy, Canadian utilization data suggest substantial variability in the agents chosen as third-line therapy.[14]

Given the increasing prevalence of type 2 diabetes and the availability of newer, more expensive, therapeutic options, there is a need to better understand the relative merits and disadvantages of third-line treatments so that rational treatment decisions can be made by clinicians and patients. To address this knowledge gap, we conducted a systematic review and meta-analysis of the comparative efficacy and safety of all available antihyperglycemic drug classes for patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea.

METHODS

Literature search

This systematic review was conducted according to a protocol prepared in advance. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and The Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English language clinical articles published from 1980 to November 2009 (Appendix 1). Monthly OVID

AutoAlerts were reviewed from December 2009 to October 2010. Additional citations were obtained from grey literature, conference proceedings, and through stakeholder feedback.

Eligibility Criteria

The population of interest consisted of adults with type 2 diabetes requiring an antihyperglycemic agent due to inadequate control (i.e., HbA1c > 6.5%, FPG > 7 mmol/L, or 2-hour PPG > 10 mmol/L) on, or intolerance to, metformin and sulfonylurea combination therapy. We included agents from the following drug classes if they had approval from Health Canada, the Food and Drug Administration, or the European Medicines Agency as of December 2009: meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, insulins/insulin analogues, and alpha-glucosidase inhibitors. Outcomes of interest included HbA_{1c}, hypoglycemia, body weight, patient satisfaction with diabetes treatment, quality-of-life, long-term complications of diabetes, mortality, withdrawals due to adverse events, and severe adverse events. Active and non-active controlled RCTs published in English were included if they were at least four weeks in duration, and compared one or more relevant drugs in any of the following scenarios: 1) addition of a third agent while continuing metformin and sulfonylurea combination therapy (add-on therapy); 2) discontinuation of metformin or sulfonylurea upon initiation of third-line therapy (partial switch); and 3) discontinuation of both metformin and sulfonylurea upon initiation of third-line therapy (full switch). We included studies regardless of metformin and sulfonylurea doses used at baseline, or treatment history prior to metformin and sulfonylurea combination therapy. Study selection was conducted independently by two reviewers (BM, CY).

Validity Assessment and Data Abstraction

Risk of bias for the included RCTs was assessed using a ten-item questionnaire (SIGN-50)[15] and data were abstracted using a pre-designed form. Both were performed independently by two reviewers (BM, CY) with disagreements resolved by consensus.

Statistical Analysis

To compare the various classes of third-line antidiabetes agents, we elected to perform Bayesian mixed-treatment comparison (MTC) meta-analyses, where possible, for two reasons: 1) many of the available third-line antihyperglycemic agents have not been compared directly with one another, necessitating indirect comparisons between treatments; and 2) the number of individual pair-wise comparisons is unwieldy given the large number of treatment alternatives, hence summary effect estimates against a common comparator are likely to be of greater utility for clinical and policy decisions.[16] MTC meta-analyses were performed following careful assessment of study-level heterogeneity. Due to paucity of data and heterogeneity in outcome definition, MTC meta-analysis was only performed for HbA_{1c} and body weight. To ensure homogeneity, MTC analysis was restricted to studies in which a third agent was added on to metformin and sulfonylurea combination therapy. Reference case analyses were conducted at the drug class level using random effects models; analyses were also conducted using fixed effects models in sensitivity analyses. Conventional insulins were pooled with insulin analogues into groups based on time-action profile (i.e., basal, bolus, and biphasic insulins); a sensitivity analysis was used to assess the impact of separating insulin analogues from conventional insulins.

WinBUGS (MRC Biostatistics Unit, Cambridge, UK) was used for MTC meta-analyses according to the routine developed at the Universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/ mpes/). Metformin and sulfonylurea combination therapy was the reference category for all MTC analyses. Frequentist, pairwise, random effects meta-analyses were also performed for all outcomes using the statistical software package R (www.R-project.org/). Posterior densities for unknown parameters were estimated using Markov Chain Monte Carlo (MCMC) methods. Basic parameters were assigned non-informative or vague prior distributions. We assessed consistency between direct and indirect evidence by comparing direct estimates obtained from pairwise meta-analysis with estimates from the MTC meta-analysis. As well, we formally tested for inconsistency using a function (http://users.uoi.gr/hyepilab/assets/pdfs/help%20on%20MTcoherence.fun.pdf) that assesses each closed

loop of the network according to the method of Bucher.[17] Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic[18] were assessed to ensure model convergence. Two chains were fit in WinBUGS for each analysis, each employing ≥20,000 iterations, with a burn-in of ≥20,000 iterations. Model goodness of fit to observed data was measured by calculating the posterior mean residual deviance. The deviance information criterion was also calculated to provide a basis on which to compare competing models. These results are reported elsewhere.[19]

We conducted meta-regression to adjust for differences in baseline HbA_{1c}, duration of diabetes, duration of trial and baseline BMI (for body weight only) across trials. In other sensitivity analyses, we removed studies from the network that: employed a cross-over design; were less than 1 year in duration; failed to report dosage of sulfonylurea at baseline; or had a threshold HbA_{1c} of <7.0% in the inclusion criteria.

RESULTS

Study characteristics and validity assessment

Of 2856 citations identified in the literature search, 126 were reviewed as full-text articles, and 37[20-56] (representing 33 unique RCTs) were included in this review (figure 1). Most trials were 6-12 months long and the mean baseline HbA_{1c} ranged from 8.1% to 11.3%. The baseline duration of diabetes ranged from 3.5 to 12.7 years. The inclusion criteria for baseline HbA1c was typically 7.0-10.0%; however, some studies used thresholds as low as 6.5% or as high as 12.0%. There was a lack of consistent reporting regarding the duration and dosage of stable metformin and sulfonylurea therapy prior to the study. Nearly half of all studies failed to report mean doses at enrolment or baseline. Twenty-eight articles reported comparisons of interventions added-on to existing metformin and sulfonylurea combination therapy; [20,22,24,25,27-32,35-42,44-48,50-54] in the remaining studies, metformin, the sulfonylurea, or both were discontinued. Open-label trials[20-22,24,27,31,33-37,39-43,45,46,48-50,54,55,57] were more common than blinded trials[25,26,29,30,32,38,44,47,52] and the majority of studies (81%) were sponsored by the pharmaceutical industry.[20,21,24,26,29-37,39-41,43-45,47-50,52,54,55,57] About two-thirds of the studies identified were of poor methodological quality;[20,22,24,25,27,29-

[34,36,37,39-41,43,44,46,47,49,50,55] inadequate reporting of allocation concealment, failure to report an intention-to-treat analysis, and lack of blinding were common limitations.

Hemoglobin A1C

Thirty RCTs[20-22,24-27,29-41,43,45-52,54] (N = 7238) reported the change from baseline in HbA_{1c}. The MTC evidence network, which was restricted to trials of add-on therapy, was composed of 21 RCTs[20,24,25,27,29-32,35,37-41,45,47,48,50-52,54] representing eight drug classes in addition to placebo (see figure 2). With the exception of α-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in HbA_{1c} (range -0.89% to -1.17%) relative to metformin and sulfonylurea combination therapy alone (figure 3 and table 1). The addition of a basal or biphasic insulin produced the largest effects, with mean reductions of -1.17% (-1.57, -0.81) and -1.10% (-1.59, -0.67), respectively. However, there were no statistically significant differences between drug classes that resulted in significant HbA_{1c} reductions. The estimates of effect derived from the frequentist direct pair-wise comparisons aligned well with those obtained from the MTC with regards to both direction and magnitude. Differences between treatments in HbA_{1c} were similar across numerous sensitivity analyses, meta-regression analyses, and alternative modeling strategies (table 2).

Body weight

Twenty-three RCTs[20-22,24-26,29-35,38,41,45,46,48-52,54] (N = 6717) reported changes in body weight. As with HbA_{1c}, the MTC analysis was restricted to studies that involved addition to metformin and sulfonylurea combination therapy. The MTC evidence network was composed of 16 RCTs[20,24,25,29-32,35,38,41,45,48,50-52,54] representing eight drug classes in addition to placebo (figure 2). The estimates of effect derived from the frequentist direct pair-wise comparisons aligned well with those obtained from the MTC in both direction and magnitude.

When added to metformin and sulfonylurea combination therapy, treatment with basal insulin, biphasic insulin, rapid-acting insulin analogues, or TZDs was associated with a significantly greater increase in body weight than treatment with metformin and sulfonylurea combination therapy alone (range: 1.85-5.00 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; whereas, GLP-1 analogues were associated with statistically significant weight loss -1.59 kg (-3.01, -0.20). The large degree of uncertainty (i.e., very wide confidence interval) for the effect of meglitinides made it difficult to draw conclusions for this class; however, there was a trend towards weight gain [2.67 kg (-0.94, 6.32)]. These results were not significantly altered by sensitivity analyses, meta-regression analyses, or alternative modeling approaches.[19]

Hypoglycemia

We identified 21 RCTs[20,24-26,29,32-36,39,41,44-50,52,54] (n = 5899) that reported the number of patients experiencing severe hypoglycemia during the trial (i.e., an event requiring third-party assistance). Events of severe hypoglycemia were rare for all drug-classes including insulins; no events were reported in 35 out of 52 treatment arms. One RCT[54] reported a statistically significant increase in severe hypoglycemia with bolus insulin aspart vs. basal insulin detemir [OR (95% CI): 4.14 (1.36, 12.59)] and a trend towards more events with biphasic insulin apart vs. basal insulin detemir [OR (95% CI): 2.82 (0.89, 9.00)]. There were no significant differences in any of the other included RCTs.

There were 26 RCTs[20,21,24-27,30-36,39,41,43-50,52,54,57] (N = 7238) that reported overall hypoglycemia. Definitions of overall hypoglycemia were variable (threshold for blood glucose ranged from 3.1 to 3.9 mmol/l) and 15 RCTs failed to provide a definition.[22,27,29-31,33,36-38,40,47-50,52] Given the large differences in baseline overall hypoglycemia event rates in the control (i.e., metformin plus sulfonylurea combination therapy) arms across studies, MTC meta-analysis was not conducted for this outcome. The addition of basal insulin,[45] TZDs,[30,32] DPP-4 inhibitors,[52] or GLP-1 analogues[25,45] to metformin and sulfonylurea combination therapy was associated with a significantly higher risk of overall hypoglycemia than metformin and a

sulfonylurea alone (table 3). Active comparisons demonstrated that the addition of biphasic insulin[58] or bolus insulin[54] to metformin and sulfonlurea combination therapy was associated with a significantly higher risk of hypoglycemia than the addition of basal insulin. There was also a trend towards more hypoglycemia with bolus insulin aspart in comparison with biphasic insulin, although the difference was not statistically significant.[54] Pooled data from four RCTs,[20,27,41,48] demonstrated that add-on basal insulin was associated with significantly more hypoglycemia than add-on TZDs.

Long-term complications of diabetes

The majority of RCTs included in this review did not report data for long-term complications or mortality, and those that did were inadequately powered to detect significant differences between treatments.

Patient Satisfaction with Diabetes Treatment

Four RCTs[20,28,46,57] reporting results for the the Diabetes Treatment Satisfaction Questionnaire (DTSQ) found no statistically significant differences between treatments.

Adverse events

Withdrawals due to adverse events (WDAE) were reported in 23 RCTs.[20-22,24,26,27,29,30,32-34,38,39,41,42,44,45,47,48,50,52,54,55] Three RCTs[24,44,50] involving exenatide reported a statistically significant increase in WDAEs relative to placebo, insulin glargine, and biphasic insulin aspart, with nausea and vomiting cited as the primary reasons for withdrawal. The other two RCTs[25,35] of exenatide did not report WDAE. One three arm trial[45] also showed an increase in WDAE for patients treated with liraglutide (4.7%), in comparison with those receiving insulin glargine (2.1%) or placebo (0.9%). This study also cited nausea as the primary adverse event in the liraglutide treatment arm. There were no statistically significant differences between any other treatment groups with respect to WDAEs.

Thirteen RCTs[20,25,26,30,32,34,35,41,45,47,52,54,59] reported total severe, serious, or major adverse events; however, only five studies[24,41,42,54,55] provided definition for these outcomes. Due to the low incidence of such events, the ability to perform statistical comparisons across drug classes was limited..

DISCUSSION

Metformin and a sulfonylurea are commonly prescribed in combination to achieve glycemic control in patients with type 2 diabetes. The decision regarding subsequent treatment is complicated by several factors, including the availability of numerous drug classes, evidence on safety or long-term effects that is sometimes conflicting,[60,61] patient and clinician preferences and attitudes, clinical factors, and cost differences. Negative patient and clinician attitudes towards the initiation of insulin and a preference for oral therapies are also important determinants in the choice of third-line therapy,[62-64] as are the propensity of agents to cause weight gain or hypoglycemia.[62] Rational decision-making regarding third-line therapy for type 2 diabetes based on individual values and preferences requires a comprehensive asssessment of the relative advantages and disadvantages between the available alternatives. Ours is the first systematic review to simultaneously assess the relative safety and efficacy of all currently available treatment options for patients with type 2 diabetes who are inadequately controlled with metformin and a sulfonylurea.

There were no RCTs adequately powered to detect differences in clinically important long-term complications of diabetes or mortality, a finding consistent with previous systematic reviews.[13,65,66] Nevertheless, studies outside the third-line setting are instructive in this regard. Previous studies of TZDs have demonstrated higher risks of fracture and heart failure compared with other agentswere consistent with past studies,[65,67,68] and there is conflicting evidence regarding the effects of TZDs on the risk of ischemic heart disease.[61] The safety profile of the newest drug classes (i.e., DPP-4 inhibitors, GLP-1 analogues) requires further study in long-term observational studies and RCTs although there is evidence, albeit inconsistent, that they may be associated with pancreatitis.[69,70] Advantages of older drug classes

such as conventional insulins are the availability of trial data regarding long range safety,[71,72] as well as extensive clinical experience in their use.

Due to the paucity of data on long-term complications of diabetes, we had to rely on HbA1c to assess relative efficacy across drug classes. MTC meta-analyses demonstrated that adding DPP-4 inhibitors, TZDs, GLP-1 analogues, and all strategies involving the addition of insulin to ongoing therapy with metformin and a sulfonylurea significantly reduced HbA_{1c} relative to placebo (range: 0.89% to 1.17%).. There were no significant differences between these treatments. Meglitinides and alpha-glucosidase inhibitors did not provide statistically significant reductions in HbA_{1c} over metformin and a sulfonylurea alone. The association between HbA_{1c} lowering and risk of developing macrovascular complications in patients with type 2 diabetes has been the focus of recent high-profile RCTs,[73,74] meta-analyses,[75,76] and observational studies.[77] Despite the ongoing controversy, our results show that there are no important differences between insulins, DPP-4 inhibitors, GLP-analogues, and TZDs in terms of antihyperglycemic efficacy as measured by HbA_{1c}.

Non-insulin third-line agents providing sustained glycemic control may delay the onset of insulin initiation, which may be desirable for some patients and could result in cost savings due to the expense of insulin therapy. Unfortunately, there were insufficient data to assess differences between treatments in the durability of the glycemic response. There is speculation that DPP-4 inhibitors, GLP-1 analogues, and TZDs may be associated with prolonged glycemic control due to a slowed decline of beta-cell function. However, a recent systematic-review of DPP-4 inhibitors reported that no definite conclusions could be made regarding their effects on beta-cell function.[78]

Many patients with type 2 diabetes are overweight or obese, therefore, changes in body weight caused by anidiabetes therapy may be important for both patients and clinicians. Our analysis demonstrated that addition of insulins or TZDs to metformin and sulfonylurea resulted in a statistically significant increase

in body weight relative to treatment with metformin and sulfonylurea combination therapy alone. By contrast, addition of DPP-4 inhibitors, α-glucosidase inhibitors, and GLP-1 analogues were not associated with statistically significant weight gain. There is evidence that the distribution of weight gain observed with antihyperglycemic agents is not identical between drug classes, such that TZDs are associated with subcutaneous fat deposition while insulins are associated with visceral fat deposition.[79-81] The latter is thought to be more metabolically detrimental[82] and because of possible distinct pathophysiologic consequences the absolute differences in weight gain between different drug classes should be interpreted with caution. Furthermore, there is no universally accepted minimal clinically important difference for body weight, although 5% is the smallest change cited as being of clinical importance in the literature.[83-85] Based on the estimated average weight of the patients included in the MTC analysis (weighted mean 87.0 kg), only bolus insulins were associated with a weight increase exceeding 5% relative to placebo. Differences in weight between GLP-1 analogues and TZDs or biphasic insulins also exceeded the 5% threshold.

Definitions of hypoglycemia were variable and often not reported in the included clinical trials, making it difficult to accurately compare hypoglycemia risk across drug classes.[86] Insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators. Biphasic and bolus insulins were associated with a significantly greater risk of hypoglycemia than basal insulin. When given in combination with metformin and sulfonylureas, TZDs, GLP-1 analogues, and DPP-4 inhibitors were associated with a significantly greater number of patients experiencing hypoglycemia than placebo. In contrast, our prior analysis of second-line therapy found no increased risk of hypoglycemia when these agents are administered in combination with metformin alone, suggesting that combined use with sulfonylureas may potentiate risk.[13] Events of severe hypoglycemia were infrequent in most trials, limiting the statistical power to make comparisons across drug classes.

Strengths and Limitations

Unlike previous systematic reviews of therapies for type 2 diabetes,[65,66,78,87,88] this review included newer drug classes available for the treatment of type 2 diabetes after inadequate control with metformin and sulfonylurea combination therapy. The results from MTC meta-analyses were consistent with those from direct pair-wise comparisons across all outcomes, a finding that adds validity to the analysis. Finally, the results of a variety of sensitivity analyses, meta-regressions, and alternative modelling approaches were aligned with the reference case, a finding that demonstrates the robustness of the analysis.

Apart from the short duration of trials and lack of adequate data on diabetes-related complications, a number of other limitations of the available evidence warrant discussion. A majority of RCTs were assessed as having significant methodological limitations. There was significant variability in the reporting of metformin and sulfonylurea dosing at baseline, with most RCTs failing to report this information. Furthermore, several studies only required half-maximal dosing of sulfonylureas before subjects were considered to have failed therapy, which may not be reflective of clinical practice since higher doses are may be tried before adding third-line therapy. Finally, the glycemic targets used in individual trial protocols varied somewhat between RCTs. It is possible that trials with more aggressive glycemic targets achieved larger effect sizes than those with more modest glycemic targets.

CONCLUSION

DPP-4 inhibitors, GLP-1 analogues, TZDs, and all forms of insulin produced statistically significant reductions in HbA_{1c} of a similar magnitude in combination with metformin and sulfonylurea combination therapy while α-glucosidase inhibitors and meglitinides did not produce as large a reduction in HbA_{1c}. Key distinguishing features between treatments were weight gain and the risk of hypoglycemia. Insulin and TZDs were associated with a statistically significant increase in body weight; whereas DPP-4 inhibitors, α-glucosidase inhibitors, and GLP-1 analogues were not. Treatment regimens containing insulin were associated with increased hypoglycemia relative to other active comparators, although events of severe

hypoglycemia were rare for all treatments. Longer studies adequately powered to measure possible differences in macrovascular and microvascular complications are required.

Competing interests: RH has received honoraria for educational lectures from Merck Frosst, Eli Lilly, AstraZeneca, Novo Nordisk, Sanofi-aventis, Pfizer, and Boehringer Ingelheim. She has also received research grants from GlaxoSmithKline, Medtronic, Pfizer, AstraZeneca, and Eli Lilly. CC, BM, CY, LD and SS report no conflict of interest.

Contributors: All of the authors contributed to the conception and design of the study. BM and CY extracted data from primary studies, CC performed the Bayesian MTC meta-analyses, BM and CY conducted the frequentist pair-wise meta-analyses. CC, BM, and CY interpreted the results. SS provided oversight for data extraction, analysis and interpretation. BM with the help of SS, CC, AC, and RH, LD and LM drafted the manuscript. All of the authors critically reviewed the manuscript and approved the final version submitted for publication.

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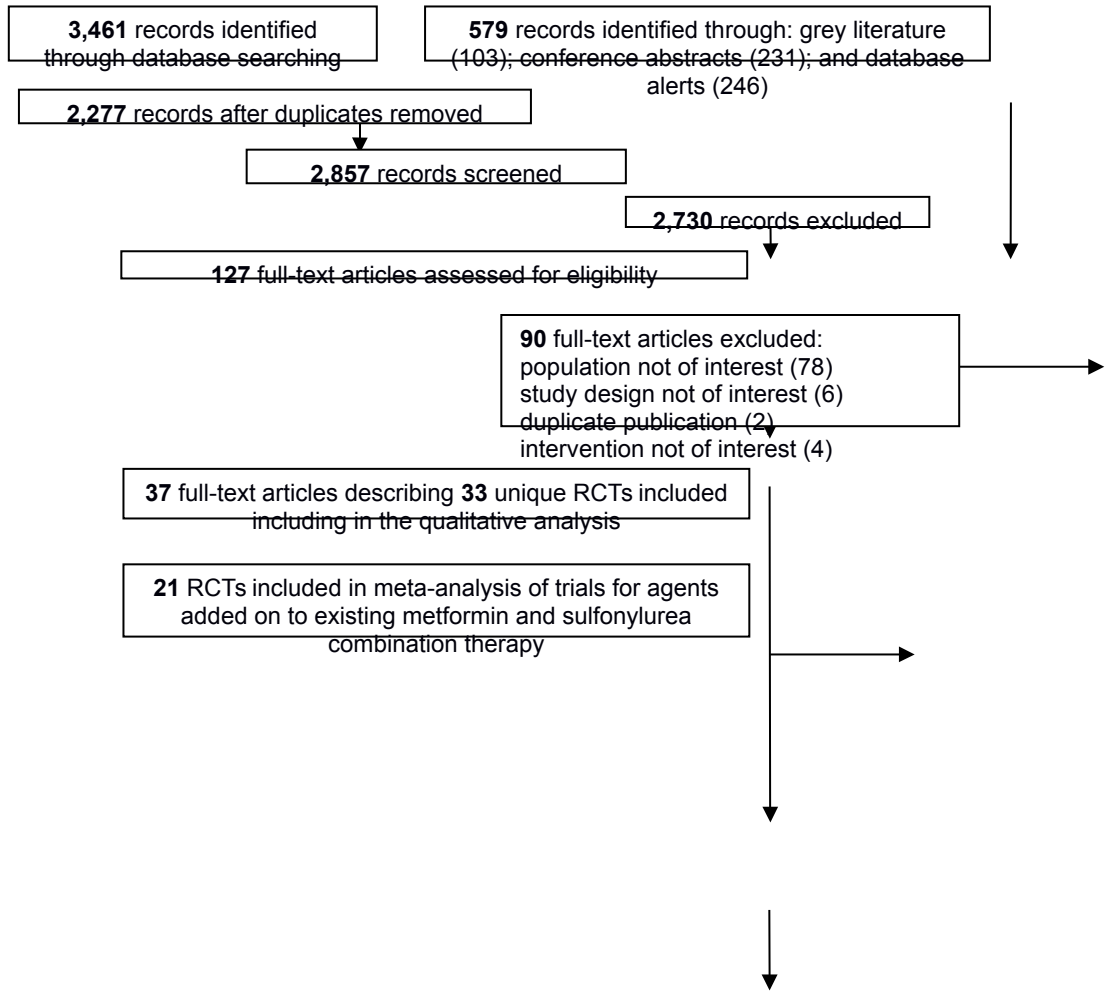
Figure 1: PRISMA diagram of study selection results



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A: Hemoglobin A1C **B: Body weight**

Figure 2: Network diagrams showing the distribution of evidence for each of the mixed-treatment comparison meta-analyses. (A) 21 RCTs reported the change from baseline in hemoglobin A1c; and (B) 16 RCTs reported change from baseline in body weight. Abbreviations: AGI – alpha glucosidase inhibitor; DPP-4 – dipeptidyl peptidase-4 inhibitor; GLP-1 – glucagon-like peptide-1 analogue; Ins – insulin; Met – metformin; RCT – randomized controlled trial; SU – sulfonylurea; TZD – thiazolidinediones.

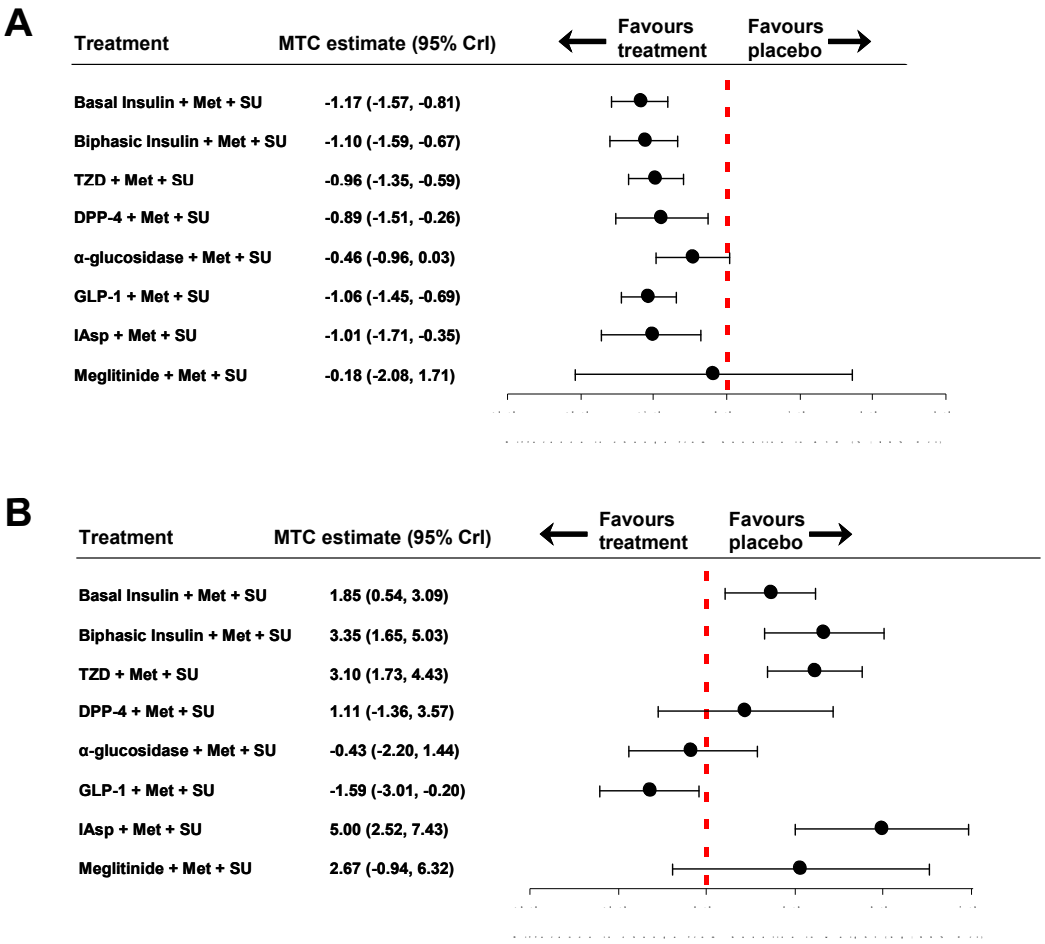

Figure 3: MTC results showing the effect of adding third-line antihyperglycemic agents versus placebo in adults taking metformin and a sulfonylurea; (A) change from baseline in hemoglobin A1c; (B) change from baseline in body weight. Abbreviations: CrI – credible interval; DPP – dipeptidyl peptidase; GLP – glucagon-like peptide; IAsp – insulin aspart; MET – metformin; MTC – mixed treatment comparison; SU – sulfonylurea; TZD – thiazolidinediones.

Table 1: Summary of results from direct pairwise and MTC meta-analyses

Treatment Vs. Placebo + Met + SU	Difference in change from baseline in A1C (%)		Difference in change from baseline in body weight (kg)	
	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)	Direct Estimates WMD (95% CI)	MTC Estimates (95% CrI)
Basal Insulin + Met + SU	-1.22 (-2.33, -0.10)	-1.17 (-1.57, -0.81)	0.88 (-1.39, 3.15)	1.85 (0.54, 3.09)
Biphasic Insulin + Met + SU	———	-1.10 (-1.59, -0.67)	———	3.35 (1.65, 5.03)
TZD + Met + SU	-1.16 (-1.36, -0.96)	-0.96 (-1.35, -0.59)	3.54 (2.43, 4.64)	3.10 (1.73, 4.43)
DPP-4 + Met + SU	-0.89 (-1.11, -0.66)	-0.89 (-1.51, -0.26)	1.10 (0.28, 1.29)	1.11 (-1.36, 3.57)
α-glucosidase + Met + SU	-0.43 (-0.72, -0.14)	-0.46 (-0.96, 0.03)	-0.88 (-1.63, -0.14)	-0.43 (-2.20, 1.44)
GLP-1 + Met + SU	-0.96 (-1.14, -0.89)	-1.06 (-1.45, -0.69)	-0.88 (-1.29, -0.47)	-1.59 (-3.01, -0.20)
IAsp + Met + SU	———	-1.01 (-1.71, -0.35)	———	5.00 (2.52, 7.43)
Meglitinide + Met + SU	———	-0.18 (-2.08, 1.71)	———	2.67 (-0.94, 6.32)
No. of studies included in MTC meta-analysis	21 RCTs [20,24,25,27,29-32,35,37-41,45,47,48,50-52,54]		16 RCTs [20,24,25,29-32,35,38,41,45,48,50-52,54]	

A1C – glycosylated hemoglobin, Met – metformin, SU – sulfonylurea, NPH – neutral protamine Hagedorn, IAsp – insulin aspart, GLP – glucagon-like peptide, DPP – dipeptidyl peptidase, CI – confidence interval, CrI – credible interval, WMD – weighted mean difference, TZD – thiazolidinedione, MTC – mixed treatment comparison

Table 2: Sensitivity analyses, meta-regression analyses, and model comparisons for HbA1C

MTC estimate of effect (95% CrI) for change from baseline in A1C (%) (vs. metformin + sulfonylurea + placebo)						
Analysis	**Basal insulin**	**Biphasic insulin**	**TZDs**	**DPP-4 Inhibitors**	**AG inhibitors**	**GLP-1 analogues**
Random effects model vs. fixed effects model						
Reference case – random effects model	-1.17 (-1.57, -0.81)	-1.10 (-1.59, -0.67)	-0.96 (-1.35, -0.59)	-0.89 (-1.51, -0.26)	-0.46 (-0.96, 0.03)	-1.06 (-1.45, -0.69)
Reference case – fixed effects model	-1.07 (-1.20, -0.95)	-0.94 (-1.09, -0.78)	-0.99 (-1.14, -0.85)	-0.89 (-1.09, -0.69)	-0.42 (-0.71, -0.14)	-1.01 (-1.14, -0.88)
Meta-regression adjusting for:						
Baseline A1C	-1.19 (-1.57, -0.84)	-1.09 (-1.55, -0.67)	-0.91 (-1.28, -0.53)	-0.89 (-1.49, -0.29)	-0.29 (-0.83, 0.25)	-1.06 (-1.44, -0.70)
Baseline duration of diabetes	-1.18 (-1.59, -0.80)	-1.10 (-1.62, -0.65)	-0.96 (-1.39, -0.54)	-0.89 (-1.55, -0.23)	-0.46 (-0.98, 0.05)	-1.06 (-1.47, -0.67)
Sensitivity analyses - removal of:						
Cross-over studies	-1.13 (-1.51, -0.76)	-1.07 (-1.55, -0.61)	-0.94 (-1.33, -0.56)	-0.89 (-1.52, -0.26)	-0.45 (-0.97, 0.06)	-1.03 (-1.42, -0.64)
Studies using A1C thresholds less than 7.0% to define inadequate control	-1.19 (-1.60, -0.83)	-0.98 (-1.54, -0.51)	-0.99 (-1.37, -0.61)	-0.89 (-1.52, -0.27)	-0.46 (-0.95, 0.04)	-1.02 (-1.43, -0.64)
Studies in which SU dose at baseline was not reported	-1.31 (-2.03, -0.69)	-1.16 (-2.18, -0.26)	-1.09 (-1.83, -0.43)	-0.89 (-1.87, 0.11)	-0.58 (-1.51, 0.37)	-1.03 (-1.90, -0.20)
Studies < 1 year in duration	-1.19 (-1.59, -0.84)	-1.00 (-1.54, -0.54)	-0.98 (-1.36, -0.61)	-0.89 (-1.51, -0.26)	-0.46 (-0.95, 0.03)	-1.03 (-1.42, -0.66)

A1C – glycosylated hemoglobin, AG – alpha glucosidase, TZD - thiazolidinediones, DPP-4 – dipeptidyl peptidase-4, GLP-1 – glucagon-like peptide-1, SU – sulfonylurea, CrI – credible interval

Table 3: Summary of results for overall hypoglycemia

Intervention 1	Intervention 2	No. of RCTs	N	Direct Estimates OR (95% CI)	I^2 (%)
Placebo comparisons (intervention 1 versus intervention 2)					
Basal Insulin + Met + SU	Placebo + Met + SU	1[45]	346	2.03 (1.15, 3.58)	——
TZD + Met + SU	Placebo + Met + SU	2[30,32]	664	5.62 (2.81, 11.25)	33
DPP-4 Inhibitors + Met + SU	Placebo + Met + SU	1[52]	229	21.94 (2.88, 167)	——
GLP-1 + Met + SU	Placebo + Met + SU	2[25,45]	1324	2.07 (1.54, 2.77)	
Active comparisons (intervention 1 versus intervention 2)					
Biphasic Insulin + Met + SU	Basal Insulin + Met + SU	1[54]	469	4.01 (2.31, 6.96)	——
Biphasic Insulin + Met + SU	Basal Insulin + Met + SU	1[57]	469	1.29 (0.90, 1.86)	——
TZD + Met + SU	Basal Insulin + Met + SU	4[20,27,41,48]	413	0.40 (0.21, 0.75)	22
GLP-1 + Met + SU	Basal Insulin + Met + SU	1[45]	462	0.93 (0.62, 1.39)	——
Bolus insulin + Met + SU	Basal Insulin + Met + SU	1[54]	402	8.97 (4.34, 18.56)	——
Biphasic Insulin	Basal Insulin + Met + SU	1[21]	236	1.32 (0.86, 2.03)	——
GLP-1 + Met + SU	Biphasic Insulin + Met + SU	1[24]	105	0.33 (0.19, 0.55)	——
Bolus insulin + Met + SU	Biphasic Insulin + Met + SU	1[54]	445	2.24 (0.99, 5.05)	——
Biphasic insulin + Met	Biphasic Insulin + Met + SU	1[24]	248	1.26 (0.76, 2.09)	——
Biphasic insulin + Met	GLP-1 + Met + SU	1[24]	112	3.87 (2.28, 6.58)	——
Biphasic insulin + Met	Basal Insulin + Met	1[34]	56	1.32 (0.40, 4.33)	——
Basal insulin + Meg. + Met	Basal Insulin + Met	1[34]	55	0.57 (0.15, 2.23)	——
Basal insulin + Meg. + Met	Biphasic insulin + Met	1[34]	53	0.43 (0.11, 1.66)	——
Basal insulin	Basal Insulin + Met	1[49]	174	1.08 (0.01, 218.9)	——
Biphasic Insulin	Basal Insulin + Met	1[49]	173	1.12 (0.01, 115.9)	——
Biphasic Insulin	Basal insulin	1[49]	175	1.04 (0.09, 12.34)	——

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; IAsp = insulin aspart; Meg = meglitinide; Met = metformin; N = total sample size; No. = number; OR = odds ratio; RCTs = randomized controlled trials; SU = sulfonylurea; TZD = thiazolidinediones

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	OVID
Databases:	BIOSIS Previews <1985 to 2009 Week 21>; EMBASE <1980 to 2009 Week 18>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 4, 2009>; Ovid MEDLINE(R) <1950 to April Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	May 4, 2009
Alerts:	Monthly search updates began June 2009 and ran to [DATE].
Study Types:	randomized controlled trials
Limits:	Publication years 1980-present English

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
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	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

Line #	Searches
	MEDLINE / BIOSIS
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 Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.
8 (486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
9 (dpp adj IV adj inhibitor*).ti,ab.
10 (Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
11 DPP-4 inhibitors.ti,ab.
12 dipeptidyl peptidase-4 inhibitors.ti,ab.
13 exp Sulfonylurea Compounds/
14 (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.
15 (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.
16 alpha-Glucosidases/ai [Antagonists & Inhibitors]
17 (acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
18 (56180-94-0 or 72432-03-2 or 83480-29-9).rn.
19 ((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
20 acarbose/ [mesh]
21 Lipase/ai [Antagonists & Inhibitors]
22 (Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
23 (96829-58-2 or 106650-56-0).rn.
24 (lipase adj inhibit*).ti,ab.
25 (repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
26 (135062-02-1 or 105816-04-4).rn.
27 Amyloid/
28 (Pramlintide or symlin).ti,ab.
29 (amylin adj analog*).ti,ab.
30 151126-32-8.rn.
31 exp insulin/
32 (long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
33 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
34 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
35 (nph insulin or humulin or novolin).ti,ab.
36 11061-68-0.rn.
37 (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.

38 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.

39 (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.

40 (Glulisine or 207748-29-6 or Apidra).ti,ab,rn.

41 or/1-40

42 ((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.

43 exp Diabetes Mellitus, Type 2/

44 (Mody or niddm or t2dm).ti,ab.

45 diabetes mellitus/

46 or/42-45

47 41 and 46

48 Randomized Controlled Trial.pt.

49 Randomized Controlled Trials as Topic/

50 Randomized Controlled Trial/

51 Randomization/

52 Random Allocation/

53 Double-Blind Method/

54 Double Blind Procedure/

55 Double-Blind Studies/

56 Single-Blind Method/

57 Single Blind Procedure/

58 Single-Blind Studies/

59 Placebos/

60 Placebo/

61 (random* or sham or placebo*).ti,ab,hw.

62 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

63 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

64 or/48-63

65 Metformin/

66 Metformin.ti,ab.

67 (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.

68 (657-24-9 or 1115-70-4).rn.

69 (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.

70 (apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.

71 (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.

72	or/65-71
73	47 and 64 and 72
74	limit 73 to yr="1980 -Current"
75	limit 74 to english language

Line #	Searches
	EMBASE
1	*Diabetes Mellitus/
2	*Maturity Onset Diabetes Mellitus/
3	*Non Insulin Dependent Diabetes Mellitus/
4	*Lipoatrophic Diabetes Mellitus/
5	((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.
6	(Mody or niddm or t2dm).ti,ab.
7	or/1-6
8	Metformin/
9	Metformin.ti,ab.
10	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.
11	(657-24-9 or 1115-70-4).rn.
12	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
13	(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.
14	(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.
15	or/8-14
16	Antidiabetic agent/
17	Oral Antidiabetic agent/
18	((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.
19	exp *glitazone derivative/
20	(glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab.
21	(122320-73-4 or 155141-29-0).rn.
22	exp *Dipeptidyl Peptidase IV Inhibitor/
23	(Sitagliptin or januvia or Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.
24	(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.
25	(dpp adj IV adj inhibitor*).ti,ab.
26	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.

27 DPP-4 inhibitors.ti,ab.
28 dipeptidyl peptidase-4 inhibitors.ti,ab.
29 exp *sulfonylurea derivative/
30 (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.
31 (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.
32 exp *"Alpha Glucosidase Inhibitor"/
33 (acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.
34 (56180-94-0 or 72432-03-2 or 83480-29-9).rn.
35 ((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.
36 Lipase inhibitor/
37 *Tetrahydrolipstatin/
38 *Sibutramine/
39 (Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.
40 (96829-58-2 or 106650-56-0).rn.
41 (lipase adj inhibit*).ti,ab.
42 *Meglitinide/
43 *Repaglinide/
44 *Nateglinide/
45 (repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.
46 (135062-02-1 or 105816-04-4).rn.
47 *Pramlintide/
48 (Pramlintide or symlin).ti,ab.
49 (amylin adj analog*).ti,ab.
50 151126-32-8.rn.
51 *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/
52 (long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.
53 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.
54 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.
55 (nph insulin or humulin or novolin).ti,ab.
56 11061-68-0.rn.
57 (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.
58 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.

59	(Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.
60	(Glulisine or 207748-29-6 or Apidra).ti,ab,rn.
61	or/16-60
62	7 and 15 and 61
63	Randomized Controlled Trial.pt.
64	Randomized Controlled Trials as Topic/
65	Randomized Controlled Trial/
66	Randomization/
67	Random Allocation/
68	Double-Blind Method/
69	Double Blind Procedure/
70	Double-Blind Studies/
71	Single-Blind Method/
72	Single Blind Procedure/
73	Single-Blind Studies/
74	Placebos/
75	Placebo/
76	(random* or sham or placebo*).ti,ab,hw.
77	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
78	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
79	or/63-78
80	62 and 79
81	limit 80 to english language

Line #	Searches
	Cochrane Central Register of Controlled Trials
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 Vildagliptin or galvus or gliptin or incretin agent* or Exenatide or byetta or Liraglutide or victoza).ti,ab.
8	[(486460-32-6 or 274901-16-5 or 141758-74-9 or 204656-20-2).rn.]
9	(dpp adj IV adj inhibitor*).ti,ab.
10	(Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab.
11	DPP-4 inhibitors.ti,ab.
12	dipeptidyl peptidase-4 inhibitors.ti,ab.
13	exp Sulfonylurea Compounds/
14	(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.

15 [(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.]

16 alpha-Glucosidases/ai [Antagonists & Inhibitors]

17 (acarbose or glucobay or precose or prandase or akarbose or miglitol* or glyset or diastabol or voglibose).ti,ab.

18 [(56180-94-0 or 72432-03-2 or 83480-29-9).rn.]

19 ((alph* adj glucos* adj inhibit*) or (alf* adj glucos* adj inhibit*)).ti,ab.

20 acarbose/ [mesh]

21 Lipase/ai [Antagonists & Inhibitors]

22 (Orlistat or Xenical or Tetrahydrolipstatin or Sibutramine or meridia).ti,ab.

23 [(96829-58-2 or 106650-56-0).rn.]

24 (lipase adj inhibit*).ti,ab.

25 (repaglinide or nateglinide or Meglitinide* or prandin or gluconorm or starlix or novonorm).ti,ab.

26 [(135062-02-1 or 105816-04-4).rn.]

27 Amyloid/

28 (Pramlintide or symlin).ti,ab.

29 (amylin adj analog*).ti,ab.

30 [151126-32-8.rn.]

31 exp insulin/

32 (long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab.

33 (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn.

34 (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn.

35 (nph insulin or humulin or novolin).ti,ab.

36 [11061-68-0.rn.]

37 (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.

38 (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn.

39 (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn.

40 (Glulisine or 207748-29-6 or Apidra).ti,ab,rn.

41 or/1-40

42 ((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.

43 exp Diabetes Mellitus, Type 2/

44 (Mody or niddm or t2dm).ti,ab.

45 or/42-44

46 41 and 45

47 Metformin/

48 Metformin.ti,ab.

49 (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.

50 (apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-

	metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.
51	(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.
52	(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.
53	or/47-52
54	46 and 53
55	limit 54 to yr="1980 -Current"
56	limit 55 to randomized controlled trial

SUPPLEMENTAL SEARCH, SAXAGLIPTIN

OVERVIEW	
Interface:	OVID
Databases:	EMBASE <1980 to 2009 Week 31>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 5, 2009>; Ovid MEDLINE(R) <1950 to July Week 4 2009> * Note: Subject headings have been customized for each database.
Date of Search:	August 5, 2009
Alerts:	Monthly search updates ran to October 2009.
Study Types:	No limits
Limits:	Publication years 1980-present English

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
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	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

Line #	Searches
	MEDLINE
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	or/1-2
4	from 3 keep 1-19
5	limit 4 to (english language and yr="1980 -Current")

Line #	Searches
	EMBASE
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	(361442-04-811 or 945667-22-111).rn.
3	saxagliptin/
4	or/1-3
5	limit 4 to english language

Line #	Searches
	Cochrane Central Register of Controlled Trials
1	(saxagliptin or onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn.
2	[(361442-04-811 or 945667-22-111).rn.]
3	saxagliptin/
4	or/1-3

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 4,	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types. Syntax adjusted for Cochrane Library databases.

Grey Literature and Hand Searches

Dates for Search:	May 2009
Keywords:	metformin, second line therapy, oral anti diabetes agents, anti diabetic agents, type 2 diabetes. All keywords associated with each included drug
Limits:	Publication years 1980-present

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

Institute of Health Economics
http://www.ihe.ca/

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS).
http://www.aetmis.gouv.qc.ca/site/en_publications_liste.phtml

Canadian Agency for Drugs and Technologies in Health
http://www.cadth.ca/index.php/en/hta/reports-publications

Ontario Ministry of Health and Long Term Care. Health Technology Reviews
http://www.health.gov.on.ca/english/providers/program/ohtac/tech/techlist_mn.html

Institute for Clinical Evaluative Sciences (ICES). Ontario.
http://www.ices.on.ca/

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/publications/publications_by_subject/

The Therapeutics Initiative. Evidence-Based Drug Therapy. University of BritishColumbia.
http://www.ti.ubc.ca

Health Quality Council. Saskatchewan.
http://www.hqc.sk.ca/

International Network for Agencies for Health Technology Assessment
http://www.inahta.org

NPS RADAR (National Prescribing Service Ltd)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

Centre for Reviews and Dissemination
www.york.ac.uk/inst/crd/crddatabases.htm

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA).
http://www.hta.ac.uk/ (E)

NHS National Institute for Clinical Excellence (NICE)

http://www.nice.org.uk

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/clinic/techix.htm

AHRQ. Effective Health Care Program. Reports. http://effectivehealthcare.ahrq.gov/index.cfm

ECRI
http://www.ecri.org/
Evidence Based Information on Prescription Drugs for Consumers and Health Care Providers
http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml#Prescription_Drugs

DERP
http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/products.cfm

Veterans Affairs. Drug Class Reviews (U.S.)
http://www.pbm.va.gov/DrugClassReviews.aspx

Saskatoon Health Regions
http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx

Clinical Trials Database (U.S. National Institutes of Health)
http://clinicaltrials.gov/ct/gui

Current Controlled Trials
http://www.controlled-trials.com/

National Research Register. U.K. Dept. of Health.
http://www.update-software.com/national/

WHO - International Clinical Trials Registry Platform
Search Portal
http://www.who.int/trialsearch

Conferences
Societies/Organizations/Associations

Canadian Diabetes Association (CDA)
http://www.diabetes.ca

European Society of Endocrinology
http://www.euro-endo.org/

Society for Endocrinology
http://www.endocrinology.org/

European Society for Paediatric Endocrinology
http://www.eurospe.org/

Endocrine Society (US)

http://www.endo-society.org/

American Association of Clinical Endocrinologists Annual Meeting and Clinical Congress (AACE)
http://www.aace.com

American Diabetes Association (ADA) Scientific Sessions
http://www.diabetes.org/home.jsp

European Association for the Study of Diabetes (EASD)
http://www.easd.org/

Association of British Clinical Diabetologists
www.diabetologists.org.uk

Primary Care Diabetes Europe (PCDE)
http://www.pcdeurope.org

International Diabetes Federation
www.idf.org/home

Search Engines

Google
http://www.google.ca/