

Drug Class Review on Oral Hypoglycemics



Update #3: Preliminary Scan Report #4

September 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Washington State Health Care Authority with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with the Washington State Health Care Authority's consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Washington State Health Care Authority ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews and actions taken by the FDA or Health Canada on serious harms since the last report. Other important studies could exist.

Date of Last Update:

Update #2 Final Report was completed in May of 2005.

Date of Previous Preliminary Update Scans

Preliminary Update Scan #1: January 2007

Preliminary Update Scan #2: February 2008

Preliminary Update Scan #3: May 2009

SCOPE AND KEY QUESTIONS:

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide committee of experts. Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Question 1. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in the progression or occurrence of clinically relevant outcomes?

Key Question 2. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in the ability to reduce HbA1C levels?

Key Question 3. For adult patients with Type 2 diabetes, do oral hypoglycemics (sulfonylureas and short-acting secretagogues) differ in safety or adverse effects?

Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one oral hypoglycemic (sulfonylureas and short-acting secretagogues) is more effective or associated with fewer adverse effects?

Inclusion Criteria

Population

Adult patients with Type 2 diabetes. Subgroups of interest will include, but are not limited to differences by race, age (older adult versus younger adult), gender and patients with chronic stable angina.

Intervention

- Sulfonylureas: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide (both immediate and extended release formulations included)
- Short-acting secretagogues: repaglinide and nateglinide

Effectiveness outcomes

- Lowering of HbA1c
- Clinically relevant outcomes:
 - Time to requiring insulin
 - Progression or occurrence of long-term microvascular disease (nephropathy as evidenced by proteinuria/dialysis/transplant/end-stage renal disease, retinopathy including proliferative retinopathy and blindness, and neuropathy)
 - Progression or occurrence of macrovascular disease (cardiovascular disease and mortality, myocardial infarction, stroke, coronary disease, angioplasty/CABG, amputation)
 - Exercise tolerance
 - Complications of diabetes
 - All-cause mortality
 - Quality of life

Safety outcomes:

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (e.g., hypoglycemia, weight gain, or effects on lipids)

Study designs

1. For effectiveness, study is a double-blind, randomized controlled trial in an outpatient setting (including emergency department) or good quality systematic reviews. Crossover trials will be included.
2. For safety, controlled clinical trial, observational study, or drug-drug interaction study.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (January 2009 to August 2010). We used terms for included drugs and limits for humans, English and controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality, AHRQ, (www.ahrq.gov) and the Canadian Agency for Drugs and Technologies in Health, CADTH, (www.CADTH.ca). We searched FDA and Health Canada websites for identification of new drugs, indications, and alerts for serious harms. All citations were imported into an electronic database (EndNote X2).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

None

New Indications

None

New Black Box Warnings

None

New Studies

Our Medline search identified 59 potentially relevant citations. Of those, there are 4 new potentially relevant controlled clinical trials (Appendix A). Table 1 below summarizes the comparisons addressed in each new trial. All focused on glycemic control and did not report any 'clinically relevant outcomes'.

Table 1. New head-to-head trials for Update Scan #4

Author Year	Comparison
Dimic 2009	Glimepiride vs repaglinide
Gonzalez-Ortiz 2009	Glimepiride vs glibenclamide, both in combination with metformin
Li 2009	Nateglinide vs repaglinide
Li 2010	Glimepiride vs repaglinide

In addition, Table 2 provides a cumulative list of the 13 head-to-head trials identified in the previous preliminary update scans, none of which reported any ‘clinically relevant outcomes’. Therefore, taken together, now there are a total of 17 head-to-head trials that would likely be added in a full update of this review.

Table 2. Head-to-head trials identified in previous scans

Author Year	Comparison
Anwar 2006	Glimepiride vs repaglinide
Cesur 2007	Glimepiride vs repaglinide vs insulin glargine
DeRosa 2007	Nateglinide vs glibenclamide
Derosa 2009	Nateglinide vs glibenclamide, both in combination with metformin
Go 2004	Glipizide GITS vs glibenclamide
Karadas 2005 (DIACOM)	Gliclazide MR vs glibenclamide bid
Li 2007	Nateglinide vs repaglinide
Papa 2006	Repaglinide vs glibenclamide
Ristic 2007	Nateglinide vs gliclazide, both in combination with metformin
Rizzo 2005	Repaglinide vs glimepiride
Rosenstock 2004	Repaglinide vs nateglinide
Sari 2004	Glimepiride vs gliclazide vs repaglinide
Schwartz 2008	Nateglinide vs glyburide, both in combination with metformin

Our searches of the AHRQ and CADTH websites identified 1 relevant comparative effectiveness review. The title of the review is “Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes” and it was originally completed by the Johns Hopkins Evidence-based Practice Center in July 2007 for the AHRQ Effective Healthcare Program. Appendix B provides the Key Questions used to conduct the review and the abstract from the associated publication in *Annals of Internal Medicine*. An update of this review is currently in progress.

APPENDIX A. RELEVANT NEW TRIALS

Dimic, D., M. Velojic Golubovic, et al. (2009). "Evaluation of the repaglinide efficiency in comparison to the glimepiride in the type 2 diabetes patients poorly regulated by the metformin administration." Bratislavske Lekarske Listy 110(6): 335-9.

OBJECTIVES: An impaired early phase of insulin secretion in the type 2 diabetes mellitus (DM) is very important for the postprandial hyperglycemia. The aim of the study was to compare the efficacy of metformin/repaglinide and metformin/glimepiride regimes in type 2 diabetics uncontrolled with metformin monotherapy. **METHODS:** Totally, 60 type 2 diabetics with haemoglobin A1c \geq 7.5% and 2000 mg of metformin monotherapy for at least three months were divided in the following groups: A-30 patients with metformin+repaglinid (2 mg for each meal) and B metformin+glimepirid (3 mg in the morning). Assessment of the regimes efficacy comprised of haemoglobin A1c, fasting blood glucose (FBG) and postprandial blood glucose (PBG). Assessment of the safety was performed on the basis of recorded hypoglycemia (<4.0 mmol/l). **RESULTS:** In both groups, FBG was significantly lower at the end of the study. In the group A it decreased from 9.03 ± 1.00 to 7.32 ± 0.65 ($p < 0.001$), in the group B from 8.94 ± 1.01 to 7.23 ± 0.70 ($p < 0.001$). There was no statistical difference between the groups. PBG was significantly lower after 12 weeks in both groups. **CONCLUSION:** Metformin/repaglinid is an efficient and safe therapeutic regime in the treatment of the type 2 DM that ensure a better control of PBG levels (Tab. 4, Ref. 18).

Gonzalez-Ortiz, M., J. F. Guerrero-Romero, et al. (2009). "Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus." Journal of Diabetes & its Complications 23(6): 376-9.

AIM: The aim of this study was to compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled type 2 diabetes mellitus. **PATIENTS AND METHODS:** A randomized, double-blind, multicenter clinical trial was performed in 152 uncontrolled type 2 diabetic patients. Serum fasting and postprandial glucose, hemoglobin A1c (A1C), high-density lipoprotein cholesterol, and triglycerides were measured. After random allocation, all patients received two pills of glimepiride (1 mg)/metformin (500 mg) or glibenclamide (5 mg)/metformin (500 mg) po once a day. Dosage was increased to a maximum of four pills in order to reach the glycemic control goals (fasting glucose ≤ 7.2 mmol/l, postprandial glucose <10.0 mmol/l, A1C $<7\%$, or an A1C $\geq 1\%$ reduction). Statistical analyses were carried out using chi-square, ANOVA, or Student's t test. The protocol was approved by an ethics committee and met all requirements needed to perform research in human subjects; all patients gave written informed consent. **RESULTS:** Each study group included 76 patients. No significant differences in basal clinical and laboratory characteristics between groups were found. At the end of the study, A1C concentration was significantly lower in the glimepiride/metformin group ($P=0.025$). A higher proportion of patients from the glimepiride group (44.6% vs. 26.8%, $P<0.05$) reached the goal of A1C $<7\%$ at 12 months of treatment. A higher proportion of hypoglycemic events were observed in the glibenclamide group (28.9% vs. 17.1%, $P<0.047$). **CONCLUSION:** Glimepiride/metformin demonstrated being more efficacious than

glibenclamide/metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus.

Li, C., J. Xia, et al. (2009). "Nateglinide versus repaglinide for type 2 diabetes mellitus in China." Acta Diabetologica 46(4): 325-33.

Li, Y., L. Xu, et al. (2010). "Effects of short-term therapy with different insulin secretagogues on glucose metabolism, lipid parameters and oxidative stress in newly diagnosed Type 2 Diabetes Mellitus." Diabetes Research & Clinical Practice 88(1): 42-7.

AIM: To compare effects of three different insulin secretagogues on early-phase insulin secretion, metabolism of glucose and lipids, and lipid peroxidation in newly diagnosed Type 2 Diabetes Mellitus (T2DM). METHODS: Totally 60 newly diagnosed T2DM outpatients were randomized to three groups with 1-month monotherapy of repaglinide (Rg), glimepiride (Gm) or gliclazide MR (Gli), respectively. Some indexes of early-phase insulin secretion, glucose, lipids, and lipid peroxidation were inspected. RESULTS: Fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and fructosamine (FA) were improved in all groups similarly ($p > 0.05$). Rg group was with the highest early-phase insulin secretion index (DeltaI30/DeltaG30) ($p = 0.026$), lower mean amplitude of glycaemic excursion (MAGE) ($p < 0.05$), lowest mean peak value of post-lunch glucose ($p = 0.043$), and lowest postprandial triglyceride (TG) ($p = 0.039$). Postprandial free fatty acid (FFA) was lower after Rg and Gli treatment ($p < 0.05$). Serum 8-iso prostaglandin F(2alpha) (8-iso PGF(2alpha)) was improved in all groups, but the improvement showed statistically significant only in Rg group ($p = 0.04$). CONCLUSION: Rg, Gm and Gli can all decrease blood glucose effectively in newly diagnosed T2DM patients, while Rg performs outstandingly in the aspects of improving early-phase insulin secretion, glucose excursion, postprandial lipids and 8-iso PGF(2alpha).

APPENDIX B. RELEVANT COMPARATIVE EFFECTIVENESS REVIEWS

Title: Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes. Comparative Effectiveness Review No. 8. (Prepared by Johns Hopkins Evidence-based Practice Center in July 2007 for the Agency for Healthcare Research and Quality)

Key Questions:

1. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical outcomes: glycated hemoglobin, weight, blood pressure, serum lipid levels, and 2-hour postprandial glucose (PPG) levels?
2. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect distal diabetes-related complications including mortality and the following macrovascular and microvascular complications: coronary artery disease, myocardial infarction, stroke, transient ischemic attack, arrhythmia, coronary artery stenosis and in-stent restenosis, retinopathy, nephropathy, neuropathy, and peripheral arterial disease?
3. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to influence other health outcomes, including quality of life and functional status?
4. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in terms of risk of the following life-threatening adverse events: life-threatening hypoglycemia leading to emergency care or death; liver failure; congestive heart failure (CHF); severe lactic acidosis; cancer; anemia, thrombocytopenia, or leucopenia requiring transfusion; and allergic reactions leading to hospitalization or death?
5. Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their safety for the following adverse events that are not life threatening: hypoglycemia requiring any assistance; elevated aminotransferase levels; pedal edema; hypervolemia; anemia, thrombocytopenia, and leucopenia not requiring transfusion; mild lactic acidosis; and gastrointestinal (GI) problems?
6. Do safety and effectiveness of oral diabetes medications for the treatment of adults with type 2 diabetes differ across particular adult populations, such as those based on demographic factors (e.g., race/ethnicity, age greater than 65 years, or gender) or comorbid conditions (e.g., renal insufficiency, CHF, liver disease, obesity, depression, or schizophrenia)?

Abstract:

From associated publication in *Annals of Internal Medicine* (Bolen, S., L. Feldman, et al. (2007). "Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus." *Annals of Internal Medicine* **147**(6): 386-99

BACKGROUND: As newer oral diabetes agents continue to emerge on the market, comparative evidence is urgently required to guide appropriate therapy. **PURPOSE:** To summarize the English-language literature on the benefits and harms of oral agents (second-generation sulfonylureas, biguanides, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors) in

the treatment of adults with type 2 diabetes mellitus. **DATA SOURCES:** The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched from inception through January 2006 for original articles and through November 2005 for systematic reviews. Unpublished U.S. Food and Drug Administration and industry data were also searched. **STUDY SELECTION:** 216 controlled trials and cohort studies and 2 systematic reviews that addressed benefits and harms of oral diabetes drug classes available in the United States. **DATA EXTRACTION:** Using standardized protocols, 2 reviewers serially abstracted data for each article. **DATA SYNTHESIS:** Evidence from clinical trials was inconclusive on major clinical end points, such as cardiovascular mortality. Therefore, the review was limited mainly to studies of intermediate end points. Most oral agents (thiazolidinediones, metformin, and repaglinide) improved glycemic control to the same degree as sulfonylureas (absolute decrease in hemoglobin A1c level of about 1 percentage point). Nateglinide and alpha-glucosidase inhibitors may have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. Thiazolidinediones were the only class that had a beneficial effect on high-density lipoprotein cholesterol levels (mean relative increase, 0.08 to 0.13 mmol/L [3 to 5 mg/dL]) but a harmful effect on low-density lipoprotein (LDL) cholesterol levels (mean relative increase, 0.26 mmol/L [10 mg/dL]) compared with other oral agents. Metformin decreased LDL cholesterol levels by about 0.26 mmol/L (10 mg/dL), whereas other oral agents had no obvious effects on LDL cholesterol levels. Most agents other than metformin increased body weight by 1 to 5 kg. Sulfonylureas and repaglinide were associated with greater risk for hypoglycemia, thiazolidinediones with greater risk for heart failure, and metformin with greater risk for gastrointestinal problems compared with other oral agents. Lactic acidosis was no more common in metformin recipients without comorbid conditions than in recipients of other oral diabetes agents. **LIMITATIONS:** Data on major clinical end points were limited. Studies inconsistently reported adverse events other than hypoglycemia, and definitions of adverse events varied across studies. Some harms not assessed in trials or observational studies may have been overlooked. **CONCLUSIONS:** Compared with newer, more expensive agents (thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control, lipids, and other intermediate end points. Large, long-term comparative studies are needed to determine the comparative effects of oral diabetes agents on hard clinical end points.