

Drug Class Review on Oral Hypoglycemics



Update #2: Preliminary Scan Report #2

February 2008

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.

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director
Marian S. McDonagh, PharmD, Principal
Investigator
Drug Effectiveness Review Project

Update Scan conducted by Kim Peterson, MS



OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations 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 Participating Organizations' 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 Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #2 Final Report was completed in May of 2005. First preliminary update scan was performed in January 2007.

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 2007 to February 2008). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

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

RESULTS

Overview

We identified 52 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 and identifies what each would add to the existing body of evidence.

Table 1. New trials for Update Scan #2

Author Year	Comparison	What do they add?
Cesur 2007	Glimepiride vs repaglinide vs insulin glargine	Effects during Ramadan fasting
DeRosa 2007	Nateglinide vs glibenclamide	No previous head-to-head trials involving nateglinide
Li 2007	Nateglinide vs repaglinide	Only 1 previous head-to-head trial from scan #1 (Rosenstock 2004) comparing the two secretagogues
Ristic 2007	Nateglinide or gliclazide in combination with metformin	No previous head-to-head trials involving nateglinide

Taken together with the 16 trials identified in the first preliminary update scan, there are now a total of 20 new trials. As a reminder, in the majority of new trials identified in the previous scan (n=9), the comparators were metformin, placebo or were unclear and wouldn't offer any information about how the sulfonylureas and short-acting secretagogues directly compare to one another. Only the seven remaining trials involved head-to-head comparisons, the details of which are summarized in Table 2. However, there still have not been any new trials reporting health outcomes that would add to the evidence already provided by the large-scale UKPDS trial.

Table 2. Head-to-head trials from Update Scan #1

Author Year	Comparison	What do they add?
Anwar 2006	Glimepiride vs repaglinide	Muslims during Ramadan
Go 2004	Glipizide GITS vs glibenclamide	8-wk HbA1c outcomes
Karadas 2005 (DIACOM)	Glicazide MR vs glibenclamide bid	16-wk HbA1c
Papa 2006	Repaglinide vs glibenclamide	Elderly
Rizzo 2005	Repaglinide vs glimepiride	3-month HbA1c

Author Year	Comparison	What do they add?
Rosenstock 2004	Repaglinide vs nateglinide	First head-to-head trial comparing short-acting secretagogues and provides 16-wk HbA1c outcomes
Sari 2004	Glimepiride vs gliclazide vs repaglinide	Ramadan

New Drugs

None

New Indications

None

New Safety Alerts

None

APPENDIX A

Cesur, M., D. Corapcioglu, et al. (2007). "A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting." Diabetes Research & Clinical Practice **75**(2): 141-7.

Although diabetics may be exempted from Ramadan fasting, many patients still insist on this worship. Aim of the present study is to compare the effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetics during Ramadan fasting on the glucose metabolism. Patients, who were willing to fast, were treated with glimepiride (n=21), repaglinide (n=18), and insulin glargine (n=10). Sixteen non-fasting control type 2 diabetics matched for age, sex, and body mass index were also included. Fasting blood glucose (FBG), post-prandial blood glucose (PBG), HbA1c, and fructosamine as well as lipid metabolism were evaluated in pre-Ramadan, post-Ramadan, and 1-month post-Ramadan time points. There was no significant change from pre-Ramadan in FBG, PBG, and HbA1c variables in fasting diabetics at post-Ramadan and 1-month post-Ramadan. However, PBG was found higher in non-fasting control diabetics at post-Ramadan and 1-month post-Ramadan ($p<0.05$ and $p<0.001$, respectively). In fructosamine levels, a significant increase was noted both in fasting group and non-fasting group at 1-month post-Ramadan ($p<0.01$ for all). However, no significant difference was found in the comparison of the changes in fructosamine levels between fasting group and non-fasting group. Risk of hypoglycemia did not significantly differ between fasting and non-fasting diabetics. There was no significant difference between three drug therapies regarding glucose metabolism and rate of hypoglycemia. No adverse effects on plasma lipids were noted in fasting diabetics. In this fasting sample of patients with type 2 diabetes, glimepiride, repaglinide, and insulin glargine did not produce significant changes in glucose and lipid parameters.

Derosa, G., A. D'Angelo, et al. (2007). "Effects of nateglinide and glibenclamide on prothrombotic factors in naive type 2 diabetic patients treated with metformin: a 1-year, double-blind, randomized clinical trial." Internal Medicine **46**(22): 1837-46.

OBJECTIVE: To evaluate the effect on coagulation and fibrinolysis parameters and on non-conventional cardiovascular risk factors of metformin plus nateglinide or glibenclamide in naive type 2 diabetes patients. **PATIENTS AND METHODS:** A total of 248 type 2 diabetic patients were enrolled and randomly assigned to receive nateglinide or glibenclamide, and metformin for 12 months. We assessed body mass index (BMI), glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), homeostasis model assessment index (HOMA index), lipid profile with lipoprotein (a) [Lp(a)], fibrinogen (Fg), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), homocysteine (Hcy), systolic blood pressure (SBP), diastolic blood pressure (DBP). **RESULTS:** After 9 months of treatment, both tested drug combinations were similarly associated with a significant reduction in FPG (nateglinide, -17.2%; glibenclamide, -16.9%, both $p<0.05$) compared to the baseline, while HbA1c (-17.3%, $p<0.05$) and PPG (-15.2%, $p<0.05$) significantly decreased only in the nateglinide group. After one year of treatment, compared to the baseline the nateglinide group showed a significant reduction in HbA1c (-21%, $p<0.01$), FPG (-20.7%, $p<0.01$), PPG (-21.5%, $p<0.05$), HOMA index (-25.4%, $p<0.05$); the glibenclamide group, showed a significant reduction in HbA1c (-11%, $p<0.05$), FPG (-23.2%, $p<0.05$), PPG (-11.2%, $p<0.05$), and HOMA index (-23.9%, $p<0.05$) but to a minor extent. Moreover, the HbA1c difference value from baseline observed in the nateglinide-treated group was significantly higher than that observed in the glibenclamide group. Therefore the nateglinide-treated patients showed a significant reduction in some prothrombotic parameters (PAI-1=-19%, Lp(a)=-31%, and Hcy=-32.3%, all $p<0.05$), whereas the glibenclamide-treated patients did not. **CONCLUSION:** Nateglinide appears to improve glycemic control as well as the levels of some

prothrombotic parameters compared to glibenclamide when administered in combination with metformin.

Li, J., H. Tian, et al. (2007). "Improvement of insulin sensitivity and beta-cell function by nateglinide and repaglinide in type 2 diabetic patients - a randomized controlled double-blind and double-dummy multicentre clinical trial." *Diabetes, Obesity & Metabolism* 9(4): 558-65.

AIM: To evaluate the efficacy of nateglinide vs. repaglinide in blood glucose (BG) control and the effect on insulin resistance and beta-Cell function in patients with type 2 diabetes.
METHODS: A randomized controlled double-blind and double-dummy multicentre clinical trial was conducted. A total of 230 Chinese patients with type 2 diabetes were enrolled in five clinical centres. The patients were divided randomly into group A [repaglinide 1.0 mg three times daily (t.i.d.), n = 115] or group B (nateglinide 90 mg t.i.d., n = 115). At baseline and end of the 12-week clinical trial, standard mixed meal tolerance tests were performed. **RESULTS:** A total of 223 patients (96.9%) completed the trial. There was no significant difference between repaglinide and nateglinide groups in the effects of reducing fasting blood glucose (FBG), 30-, 60- and 120-min BG during 12 weeks ($p > 0.05$). At week 12, no significant difference was shown between the two groups in BG or haemoglobin A(1c) (HbA(1c)) ($p > 0.05$). However, the effect on HbA(1c) in repaglinide group was stronger than that in nateglinide group ($p < 0.05$). After 12-week treatment, area under the curve (AUC) of BG decreased ($p < 0.05$), and AUC of insulin and C-peptide (CP) increased in both groups ($p < 0.05$). The effects of nateglinide on AUC of BG, insulin and CP were similar to that of repaglinide ($p > 0.05$). There was no significant difference between the two groups in AUC of BG, insulin or CP in week 12 ($p > 0.05$). Furthermore, homeostasis model assessment of insulin resistance (HOMA-IR) and beta-cell function indexes measured by HOMA-beta, DeltaI(30)/DeltaG(30) and (DeltaI(30)/DeltaG(30))/HOMA-IR were improved significantly in both groups during 12 weeks ($p < 0.05$). The effects of improving HOMA-IR and beta-cell function indexes in nateglinide group were comparable with that of repaglinide group ($p > 0.05$). **CONCLUSIONS:** The efficacy of repaglinide and nateglinide in FBG, postprandial glucose excursion and early-phase insulin secretion is similar. But the effect of repaglinide 1.0 mg t.i.d. on HbA(1c) is stronger than that of nateglinide 90 mg t.i.d.. This trial had shown that nateglinide and repaglinide could comparably improve insulin sensitivity and beta-cell function.

Ristic, S., C. Collober-Maugeais, et al. (2007). "Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results." *Diabetes, Obesity & Metabolism* 9(4): 506-11.

AIM: To compare long-term efficacy and safety of nateglinide plus metformin with those of gliclazide plus metformin in patients with type 2 diabetes not adequately controlled with metformin monotherapy. **METHODS:** Double-blind, double-dummy, multicentre study extended to a total of 52 weeks. Patients with inadequate glucose control on maximal doses of metformin were randomized to nateglinide (N = 133) or gliclazide (N = 129) add-on treatment. After the initial 6-month study, the majority of patients in the nateglinide group [n = 112 (93.3%)] and in the gliclazide group [n = 101 (92.7%)] entered a 6-month, double-blind, extension study. **RESULTS:** There was no significant difference between treatment regimens in haemoglobin A1c (HbA1c) change from baseline to 52 weeks (-0.14% for nateglinide vs. -0.27% for gliclazide; $p = 0.396$). Proportions of patients achieving an endpoint HbA1c of $< 7\%$ were similar (40 vs. 47.4%) for nateglinide and gliclazide groups. There was no significant between-treatment difference in fasting plasma glucose change from baseline to 52 weeks (nateglinide: -0.2 mmol/l and gliclazide: -0.7 mmol/l; $p = 0.096$). The decreases in prandial plasma glucose area under the curve(0-4 h) from baseline were -3.26 and -1.86 h x mmol/l in the nateglinide and the gliclazide groups respectively, and the change was statistically significant in the nateglinide group only ($p = 0.006$). Initial insulin response to a meal was augmented with nateglinide treatment only, without

between-treatment difference in 2-h insulin response. The overall rate of hypoglycaemic events was similar with nateglinide and gliclazide combinations with metformin. Nateglinide plus metformin treatment was not associated with weight gain. CONCLUSIONS: No significant difference was seen between nateglinide plus metformin and gliclazide plus metformin in terms of HbA1c. Treatment with nateglinide plus metformin for up to 12 months was not associated with weight gain.