Oregon Health Resources Commission

Oral Hypoglycemics
Subcommittee Report

Update #2, May 2005

This report is an update of the initial
Oral Hypoglycemic Subcommittee Report of April, 2003.
All revisions are highlighted.

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan. Statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

In November of 2002 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of oral hypoglycemics. Members of the subcommittee consisted of physicians, research administrator, other health care professionals and consumer. The subcommittee had five meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Oregon Health and Science University's Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the Oregon Evidence-based Practice Center reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU's Oregon Evidence-based Practice Center draft report, "Drug Class Review on Oral Hypoglycemics" was completed the week of March 17, 2003, circulated to subcommittee members and posted on the web. The subcommittee met on April 7, 2003, to review the document and additional evidence. By consensus, the subcommittee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. The subcommittee's final meeting was held on April 21, 2003 to review the draft subcommittee report. All available sources of information; the Oregon Evidence-based Practice Center report which includes information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the Oral Hypoglycemic Subcommittee comprise the body of this report.

The HRC appointed a Standing Update Committee to perform evidence-based reviews of the Drug Class Review on Oral Hypoglycemics every year based on new information or changes in the FDA package inserts. This report is the second update of the initial June 2002 Opioid Subcommittee Report. All new revisions are highlighted. Members of the Standing Update Committee consisted of one HRC member, two subcommittee physicians, one Oregon State University (OSU) pharmacist, one OHPR physician, one OHSU-EPC physician, one nurse practitioner, and one PharmD. The committee had one meeting held in public with appropriate notice provided.

The OHSU-EPC's Drug Class Review on Oral Hypoglycemics update final report # 2, was completed April 2005, circulated to the Standing Update Committee members and posted on the OHPR website at: http://www.ohpr.state.or.us/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

The Update Committee met on May 10, 2005, to review the document and additional evidence. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony, were considered. The Update Committee presented its findings to the HRC and the revisions were approved at its meeting on May 20, 2005.

This report is prepared to facilitate the HRC in providing recommendations to OMAP for the plan drug list (PDL). This update report does not recite or characterize all the evidence that was discussed by the OHSU-EPC, the Standing Update Committee, or the HRC. For further information provided during the committee process readers are encouraged to review the source materials on the website.

The Standing Update Committee of the HRC, working together with the EPC, OMAP, and the OSU College of Pharmacy, will continue to monitor medical evidence for new developments in this drug class. Every year emerging pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PDL will be made. Significant new evidence for pharmaceuticals already on the PDL will be assessed and Federal Drug Administration (FDA) changes in indications and safety recommendations will be evaluated. The Oral Hypoglycemic Subcommittee Report will be amended if indicated. Substantive changes will be brought to the attention of the HRC, who may choose to approve the report, or reconvene the OPIOID Subcommittee.

This report and the OHSU-EPC's update final report are all available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: www.oregonrx.org. Information regarding the HRC and its subcommittee policy and process can be found on the OHPR website: http://www.ohpr.state.or.us/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml More information, copies of the report, or minutes and tapes of the meetings can be requested from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

John Santa, MD
Assistant Director for Health Projects
OHSU, Center for Evidence-based Policy
2611 SW 3rd Avenue, MQ280
Portland, OR 97201-4950
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There will be a charge for copying and handling documents both from the Office of Oregon Health Policy & Research and from the Center for Evidence-based Policy.

Critical Policy:

- *Senate Bill 819*
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."
- *Health Resources Commission*
  - "Clinical outcomes are the most important indicators of comparative effectiveness";
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Inclusion Criteria:

- *Scope*
  - Patients: Adult patients with Type 2 diabetes. Subgroups of interest will include, but are not limited to differences by race, age (older adult vs. younger adult), and gender.
- *Interventions include either:*
  - Sulfonylureas: chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide (both immediate and extended release formations included). For short-acting secretagogues; repaglinide and nateglinide.
- *Effectiveness*
  - For effectiveness (lowering of HbAlc), study is a double-blind, randomized controlled trial in an outpatient setting (including emergency department). Crossover trials will be included.
- *Outcomes*
  - Time to requiring insulin.
  - Progression or occurrence of long-term microvascular disease (nephropathy as evidenced by proteinuria/dialysis/transplant/end-state 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).
- Complications of diabetes.
- All-cause mortality.
- Quality of life.

- *Adverse Effects*
  - Adverse effects will be based on total withdrawals or withdrawals due to specific adverse events such as hypoglycemia, weight gain, or effects on lipids. The study will be a controlled clinical trial, observational study, or drug-drug interaction.

Exclusions:

- No original data: Paper does not contain original data (e.g., non-systematic review, editorial, letter with no original data). Good quality systematic reviews will be used as appropriate to inform the current review.
- Studies of multiple oral hypoglycemic drugs (e.g., sulfonylurea/metformin) where the effect of the sulfonylurea cannot be delineated.

Oral Hypoglycemic Drugs

Generic	*Brand*
– Chlorpropamide	Diabenase
– Glimepiride	Amaryl
– Glipizide	Glucotrol, Glucotrol XL
– Glyburide	DiaBeta, Micronase, Glynase PresTab, Glycron
– Tolazamide	Tolinase
– Tolbutamide	Orinase
– Repaglinide	Prandin
– Nateglinide	Starlix

Key Questions:

1. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbAlC levels?

2. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the progression or occurrence of clinically relevant outcomes?

3. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse effects?

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

New Findings Update #2, May 2005:

- OH&SU EPC reported there were no new oral hypoglycemics marketed in the U.S. since April, 2003 and there have been no FDA labeling changes.

- A recent fair quality systematic review evaluated the effects of different oral agents for diabetes including sulfonyoureas and short-acting secretagogues on lipid profiles.[1]

Amended Summary of Results

Key Question 1. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbAlC levels?

Eight randomized, multi-center fair-to-good quality trials directly compared oral sulfonylureas or non-sulfonylurea secretagogues. There were no head-to-head trials comparing tolazamide and tolbutamide to other sulfonylureas or non-sulfonylurea secretagogues. Results were similar in all trials: there was a small absolute change in HbA1C with these agents, but no clinically significant difference between them.

The UKPDS was the largest head-to-head trial involving 4,209 patients and its major goal was tight glycemic control. It found no significant difference in HbA1c lowering between chlorpropamide and glyburide after three years or between chlorpropamide and glipizide after six years. After ten years chlorpropamide had a small but significant lowering of HbA1c

[1] Buse JB, Tan MH, Prince MJ, et al. The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism* 2004;6(2):133-156.

compared to glyburide, however by that time in the trial over 60% of both groups were on more than one agent to control blood sugars and many patients were on insulin.

"Good" trials imply that chlorpropamide, glyburide and glipizide are similar in HbA1c lowering. "Fair trials suggest that glimepiride, glipizide, micronized glyburide and repaglinide have similar efficacy compared to glyburide. One fair trial showed repaglinide to be superior to glipizide, however the highest dose of glipizide used was 15mg (less than half the maximum dose) and this dose was only used in half of the patients.

A fair-quality systematic review of 63 trials of oral agents showed no difference in efficacy within or between the sulfonylureas and the non-sulfonylurea secretagogues.

The Standing Update Committee agrees by consensus that:

- *for all the agents in these two classes (oral sulfonylureas and non-sulfonylurea secretagogues) current evidence shows no clinically significant difference between any of these agents in ability to lower HbA1c.*

Key Question 2.

For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the progression or occurrence of clinically relevant outcomes?

Only the UKPDS study provides head-to-head evidence to answer this question. There is good evidence that there are no significant differences between chlorpropamide, glyburide and insulin in combined diabetes endpoints, diabetes related deaths, all cause mortality, myocardial infarctions, strokes, amputation or death from peripheral vascular disease and microvascular complications excluding retinopathy. For progression of retinopathy, there is a significant benefit for tight control of blood sugars and a trend favoring glyburide over chlorpropamide. For the combined microvascular endpoint (which is driven by the difference in progression of retinopathy), the number needed to treat (NNT) for glyburide vs. conventional treatment was 27 (relative risk reduction [RR] 0.66, confidence interval [CI] 0.47-0.93) and for chlorpropamide was 70 (RR 0.86, CI 0.63-1.17). Patients assigned to chlorpropamide had a lesser risk reduction in progression of retinopathy than patients assigned to glyburide or insulin at 12 years irrespective of HbA1c.

There are not yet outcome data on other sulfonylureas or non-sulfonylurea secretagogues, although there may be data on glipizide from the UKPDS eventually reported.

The Standing Update Committee agrees by consensus that:

- *there is no statistically significant difference between glyburide and chlorpromide in progression or occurrence of clinically relevant outcomes with the exception of retinopathy.*
- *Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.*
- *There is insufficient evidence to comment on other sulfonylureas and non-sulfonylureas secretagogues.*

Key Question 3.

For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse effects?

There is good quality evidence from the UKPDS that suggests chlorpropamide was associated with a lower rate of hypoglycemic episodes than glyburide (1.0% vs. 1.4% respectively), but was also associated with more weight gain (+2.6 kg vs. +1.7 kg) and higher blood pressure with increased likelihood of pharmacological therapy than glyburide. At three years, 13% of chlorpropamide patients withdrew because of adverse events compared to 7% of glyburide patients.

Good quality evidence from the UKPDS showed no difference in hypoglycemic events or weight gain for glipizide compared to chlorpropamide.

There is fair evidence from the UKPDS and other studies that there are no significant differences between glimepiride, glipizide, glyburide, micronized glyburide and repaglinide with respect to weight, lipid changes and blood pressure.

A recent fair-quality systematic review evaluated the effects of different oral agents for diabetes (including sulfonylureas and short-acting secretagogues) on lipid profiles.[2] It included only placebo-controlled trials and uncontrolled studies reporting postexposure changes in lipid status. It found no significant changes in lipid profiles associated with any of the drugs included in this report.

There is no evidence comparing tolbutamide, tolazamide or nateglinide to other drugs in these classes of sulfonylureas and non-sulfonylurea secretagogues.

[2] Buse JB, Tan MH, Prince MJ, et al. The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism.* 2004;6(2):133-156.

The Standing Update Committee agrees by consensus that:

- *chlorpropamide has a less favorable adverse effect profile compared to glyburide.*
- *Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile.*
- *No evidence exists for the evaluation of tolbutamide, tolazamide or nateglinide.*

Key Question 4.

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

Based on the EPC's report, package inserts and testimony of the public, there is no difference in efficacy for the sulfonylureas or non-sulfonylurea secretagogues for any gender, racial or ethnic group.

Old age (greater than 60) is known to be a risk for serious hypoglycemia (glucose less than 50) and it had previously been thought that longer-acting sulfonylureas were associated with a higher risk of hypoglycemic episodes. However, in the UKPDS study there were fewer hypoglycemic events in the group on chlorpropamide compared to glyburide and another trial showed no difference in efficacy or adverse events between glipizide and glyburide.

In the UKPDS study when the subgroup of obesity (with 99% of patients having a BMI >25 and 54% having a BMI > 30) was further examined there were no differences in efficacy or adverse side effects between chlorpropamide, glyburide and glipizide.

There were no head-to-head comparative studies of drug interactions but information about drug interactions in healthy volunteers is described in the package inserts for each drug.

No evidence identified suggested any advantage of one included drug over another for any demographic group, or in patients who have a history of hypoglycemia. There were no direct studies comparing effects of these agents on subgroups of patients with other co-morbidities besides obesity, or history of hypoglycemic episodes.

The Standing Update Committee agrees by consensus that:

- *Amongst the demographic subgroups including obesity, currently available evidence does not suggest that any one oral hypoglycemic (sulfonylurea or non-sulfonylurea secretagogue) is more effective or associated with fewer adverse effects than any other oral hypoglycemic agent.*
- *Evidence is lacking in comparative effectiveness and adverse side effects of these agents in the subgroups with concomitant medications, other co-morbidities besides obesity, or history of hypoglycemic episodes.*

Conclusion

In a public meeting with the opportunity for public questions, comment and testimony, the Standing Update Committee of the Health Resources Commission reviewed the medical evidence comparing Oral Hypoglycemics. The Oregon EPC report, "Drug Class Review on Oral Hypoglycemic Drugs," which included appropriate information presented in pharmaceutical manufacturer dossiers, was reviewed and public testimony considered.

Using all of these sources of information, the subcommittee arrived at the following conclusions about the comparative effectiveness and safety of oral hypoglycemic drugs as supported by analysis of the medical literature:

It is the decision of the Standing Update Committee that:

- There is no clinically significant difference between any of the agents in these two drug classes (oral sulfonylureas and non-sulfonylurea secretagogues) in their ability to lower HbAlc.
- There is no statistically significant difference between glyburide and chlorpropamide in the progression or occurrence of clinically relevant outcomes with the exception of retinopathy. Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.
- There is insufficient evidence on other sulfonylureas and non-sulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
- Chlorpropamide has a less favorable adverse effect profile compared to glyburide. There is no difference in safety or adverse effect profiles for other oral sulfonylureas and non-sulfonylureas secretagogues. Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile. No evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.
- There is no evidence that any one oral hypoglycemic is more effective or associated with fewer adverse effects than any other oral hypoglycemic amongst demographic subgroups including obesity. There is no evidence comparing effectiveness and adverse side effects in the subgroups with concomitant medications, other co-morbidities besides obesity, or with a history of hypoglycemic episodes.

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.