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INTRODUCTION

In the United States, approximately 16 million persons have type 2 diabetes mellitus. Diabetes is associated with increased morbidity from vascular disease. Hyperglycemia is thought to increase the risk of these vascular complications and, in the United Kingdom Prospective Diabetes Study, intensive treatment with diet, insulin, or oral hypoglycemic medications reduced the risk of microvascular complications by about 25%. While the optimal level of glycemic control is not known, most practice guidelines recommend that pharmacologic treatment be initiated in patients who have a fasting glucose level >140 mg/dL or a HbA1c value >8% despite efforts at dietary control.

The oral hypoglycemics addressed in this review are listed in Table 1. Sulfonylureas are a class of oral drugs that reduce blood glucose levels by stimulating insulin secretion. The elevated insulin levels reduce hepatic glucose production and increase muscle glucose uptake. First-generation sulfonylureas available in the U.S. include chlorpropamide, tolazamide, and tolbutamide. Second-generation sulfonylureas available in the U.S. are glipizide, glimepiride, and glyburide (also called glibenclamide). An extended release form of glipizide is also available. In the U.S., glyburide is available under several trade names, including Micronase, DiaBeta, and Glynase. Glynase, a micronized form of glyburide, has different dosage and duration of action than the nonmicronized preparations. Because these products are labelled differently by the FDA, for the purposes of this review we considered them to be different drugs. Two other oral antidiabetic drugs that work by stimulating insulin secretion, repaglinide and nateglinide, are available in the U.S. These drugs have been called “non-sulfonylurea secretagogues.”

Table 1. Oral hypoglycemic agents included in this review.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>USUAL / MAXIMAL DOSE and INTERVAL</th>
<th>DURATION</th>
<th>ACTIVE METABOLITES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>250-500 mg po qd</td>
<td>24-72</td>
<td>yes</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>250-500 mg po bid</td>
<td>12-24</td>
<td>yes</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500-1500 mg po bid</td>
<td>6-12</td>
<td>no</td>
</tr>
<tr>
<td>2nd generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>4-8 mg po qd</td>
<td>≥24</td>
<td>yes</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>10-20 mg po bid</td>
<td>≥24</td>
<td>no</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5-20 mg po qd</td>
<td>16-24</td>
<td>weak</td>
</tr>
<tr>
<td>Glyburide micronized</td>
<td>3-12 mg po qd</td>
<td>12-24</td>
<td>weak</td>
</tr>
<tr>
<td><strong>Non-sulfonylurea secretagogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>120-180 mg tid before meals</td>
<td>1.5 hours</td>
<td>yes</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>2-4 mg tid before meals</td>
<td>1 hour</td>
<td>yes</td>
</tr>
</tbody>
</table>

Source: Drug Facts and Comparisons

* may be split bid above 10 mg/qd

In 2002, the Oregon Health Resources Commission (OHRC) and the Washington State DUEC requested a review of the sulfonylureas and non-sulfonylurea secretagogues available in the U.S. as of March 1, 2003.
Specifically, the OHRC requested information about whether there is evidence that one or more of these drugs is superior to others in terms of efficacy and safety.

**Scope and Key Questions**

The Oregon Evidence-based Practice Center developed the scope of the review by writing preliminary key questions, identifying the populations, interventions, and outcomes of interest and based on these, the eligibility criteria for studies. These were reviewed by an Oregon Health Resources Commission subcommittee comprised of local experts (pharmacists, physicians, and consumers) in public meetings and refined based on their input. In consultation with the subcommittee, we selected the following key questions to guide this review:

1. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbA1C 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?

**METHODS**

**Literature Search**

To identify articles relevant to each key question, we searched the Cochrane Library (2002, Issue 1), MEDLINE (1966-2002), EMBASE (1980-2001), and reference lists of review articles. In electronic searches, we combined terms for and relevant research designs (see Appendix A for complete search strategy). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohprr.state.or.us/index.htm). All citations were imported into an electronic database (EndNote 6.0).

**Study Selection**

We applied the following eligibility criteria to identify eligible articles:

**Exclusion criteria:**
1. No original data: Paper does not contain original data (e.g., non-systematic review, editorial, letter with no original data).
2. Studies of multiple oral hypoglycemic drugs (e.g., sulfonylurea/metformin) where the effect of the sulfonylurea cannot be delineated.
3. Non-English title and abstract.
4. Article published in abstract form only.
Inclusion criteria: Good-quality and fair-quality studies in which

1. The patients were adults with Type 2 diabetes. Subgroups of interest will include, but are not limited to, different races, ages (older adult versus younger adult), and gender.

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

3. For efficacy (lowering of HbA1c), study is a fair-or-better-quality systematic review or double-blind, randomized controlled trial (including crossover trials) in an outpatient setting (including emergency department).

4. Clinically relevant outcomes include:
   - Progression or occurrence of 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)
   - Other complications of diabetes
   - Quality of life
   - All-cause mortality

5. To be included, reports about safety or adverse events had to report total withdrawals, withdrawals due to specific adverse events such as hypoglycemia, weight gain, or effects on lipids; or the frequency and severity of these specific adverse events. Controlled clinical trials, longitudinal cohort studies, and drug-drug interaction studies were eligible for inclusion.

When properly designed, direct comparator (“head-to-head”) trials provide the best-quality evidence to compare the efficacy and safety of different drugs. Direct comparator trials were available for some drug-drug comparisons.

Observational studies were eligible for the review of adverse events. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up.
Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK). We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality and were excluded from the review; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

We summarized our results in evidence tables and in a narrative summary.

RESULTS

Overview

We identified a total of 1,108 citations, of which 27 were head-to-head trials of the included drugs. Twenty of these trials were excluded because they did not report any of the outcome measures selected for this review or because of poor- or poor-to-fair quality (internal validity.) (Appendix C) Most of the excluded poor-quality studies were small, did not compare baseline data or had major baseline differences, had high losses to followup, or excluded dropouts or nonresponders from the analysis and did not report enough information to calculate intention-to-treat results.

United Kingdom Prospective Diabetes Study

The largest head-to-head trial was the UK Prospective Diabetes Study. Unlike the other studies we found, the UKPDS addressed three of our key questions (glycemic control, outcomes, and adverse events),
permitting a more complete comparison of the advantages and disadvantages of the compared drugs. Although it was an open study, it used adequate methods of randomization, was analyzed as an intention-to-treat study, had few dropouts, and examined several important clinical endpoints. Moreover the drugs it compared were not new to the market, reducing the chance of bias due to the lack of blinding.

The UKPDS was designed to address four questions:
1. Will improved blood glucose control by increasing insulin supply be beneficial or harmful?
2. Will insulin therapy or sulphonylurea therapy be particularly beneficial or harmful?
3. Will first- or second-generation sulphonylurea be particularly beneficial or harmful?
4. Will improving glucose control by enhancing insulin sensitivity with metformin be beneficial or harmful?

The first two questions are outside the scope of our review, but were examined in a recent, good-quality systematic review conducted for the US Preventive Services Task Force. That review concluded that the UKPDS was the best evidence available to support “intensive treatment” to control blood glucose in patients who have Type 2 Diabetes Mellitus. In the UKPDS, “intensive treatment,” or “tight control,” refers to a policy of increasing drug therapy to achieve a goal of normal fasting blood glucose levels. The UKPDS found that treatment with a sulfonylurea or insulin over the first 10 years after diagnosis of diabetes decreased the risk of microvascular disease. For all hypoglycemic drugs combined (insulin or a sulfonylurea), intensive glycemic control was associated with a 25% reduction in all microvascular endpoints combined, corresponding to a number needed to treat of 42 patients to prevent one event in 10 years. This difference was due primarily to a difference in the risk of having retinal laser photocoagulation (RR for intensive treatment 0.71, NNT=37 to prevent one event over 10 years.) No other clinical endpoints in the UKDPS reached statistical significance, but intensive treatment improved several intermediate endpoints (progression of retinopathy, proteinuria, two-fold increase in creatinine.) The number needed to treat to prevent one clinical endpoint was 19.6 (CI 10-500). The confidence interval indicates that intense glycemic control for 10 years prevents one or more complications of diabetes for every 10 to 500 patients treated.

The parts of the UKPDS of most interest in this review are described in Table 2 and in Figure 1. The largest, most important part of the UKPDS was the “main randomization” study, which is shown in bold in the figure. The UKPDS also provided data to compare the efficacy and safety of first- and second-generation sulphonylureas in a separate trial, called the “primary diet failure randomization.” (Table 2).

Table 2. UKPDS trial populations relevant to this review.

<table>
<thead>
<tr>
<th>Population</th>
<th>Comparison*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. “Main randomization” Subjects who had fasting plasma glucose values between 6 mmol/l and 15 mmol/l after 3 months of diet therapy.</td>
<td>Intensive treatment with chlorpropamide vs. intensive treatment with glyburide or glipizide. vs. conventional therapy</td>
<td>Stratified by body weight (&gt;20 lb over ideal body weight vs. &lt;20 lbs over)</td>
</tr>
<tr>
<td>2. “Primary diet failure randomization.” Subjects who had fasting plasma glucose values above 15 mmol/l despite 3 months of diet therapy.</td>
<td>Intensive treatment with chlorpropamide vs. intensive treatment with glyburide or glipizide.</td>
<td>Stratified by body weight (&gt;20 lb over ideal body weight vs. &lt;20 lbs over)</td>
</tr>
</tbody>
</table>

* Insulin and metformin were also comparators, but are excluded from the table because our focus is on comparisons among sulfonylureas.

Main randomization.
In the “main randomization” population, 4,209 subjects who had fasting plasma glucose values between 6 mmol/l and 15 mmol/l were randomized to intensive treatment (70%) or to conventional therapy (30%). In patients randomized to intensive treatment, the goal of management was to get the fasting glucose below 6 mmol/l. At the first 15 sites, intensive treatment patients were randomized to insulin, chlorpropamide (up to 500 mg daily), or glyburide (up to 10 mg bid.) At the last 8 sites, patients were randomized to insulin, chlorpropamide or to glipizide (up to 20 mg bid.).

Many subjects initially assigned to intensive treatment with a sulfonylurea eventually developed a fasting blood glucose level higher than 6 mmol/l despite maximal doses. Until 1989, these subjects were maintained on monotherapy with the sulfonylurea unless their fasting glucose exceeded 15 mmol/l (if it did, insulin was added). From 1990 on, subjects who had fasting glucose levels ≥6 mmol/l despite maximal sulfonylurea therapy were re-randomized to either continue the sulfonylurea or to add metformin.

The goal of conventional treatment was to keep the fasting plasma glucose ≤15 mmol/l. If this could not be accomplished after one year or more of diet alone, the subject was re-randomized to one of the drug therapies, still with the goal of keeping the fasting plasma glucose ≤15 mmol/l. Most patients originally assigned to diet alone eventually required drug therapy.

Glycemic control. After 3 years of follow-up, there was no significant difference in HbA1c lowering between patients taking chlorpropamide (-0.4% change in HbA1c) and glyburide (-0.3% change). Fewer chlorpropamide patients required addition of a second drug (9% vs. 13%) but more chlorpropamide patients refused treatment or discontinued due to side effects (13% vs. 7%). As a result, the actual number of patients maintained on their assigned therapy was the same for both drugs (78% vs. 79%).

After 6 years, there was no significant difference in HbA1c between chlorpropamide (-0.3% change in HbA1c) and glipizide (-0.2% change) in HbA1c. (Wright UKPDS)

At the 10 year followup assessment, patients who had been assigned to any intensive treatment (insulin or sulfonylurea) had lower HbA1c levels than conventionally treatment patients (7.0% and 7.9%, p<0.0001). After 10 years the net change in HbA1c was –0.38% for chlorpropamide and +0.11% for glyburide (p=0.008). Note that these results are based on an intention-to-treat analysis: By ten years, most patients in both groups were taking combination therapy (the original sulfonylurea plus metformin) or insulin.

Need for additional therapy. At 6 years, of 1305 patients randomized to intensive therapy with a sulfonylurea, 44% were on combination therapy with a second agent. More patients assigned to intensive treatment with chlorpropamide (72%, CI 66% to 77%) were on monotherapy than patients assigned to intensive treatment with glyburide (60%, CI 54% to 66%).

Outcomes. The UKPDS investigators also compared outcomes after 10 years of intensive treatment with chlorpropamide (n=619) or glyburide (n=615). No direct comparisons of outcome for chlorpropamide vs. glyburide were statistically significant, but chlorpropamide had less favorable results than glyburide when compared to conventional therapy. For example, compared with conventional therapy, the NNT to prevent any diabetes-related endpoint was 17 for intensive treatment with glyburide (RR 0.82; 0.69-0.97, p=0.018), but it was 57 for intensive chlorpropamide (RR 0.93; 0.79-1.99, p=36). For the combined microvascular endpoint, the NNT for glyburide vs. conventional therapy was 27 (RR 0.66, CI 0.47 to 0.93, p=0.017), but it was 70 for chlorpropamide vs. conventional therapy (RR 0.86, CI 0.63 to 1.17, p=0.33). Patients assigned to chlorpropamide also did not have the same risk reduction in progression to retinopathy as glyburide or insulin at 12 years (p=0.0056).

No outcome data have been reported for glipizide.

Adverse events. In the UKPDS (UKPDS 13) intensive treatment group, 13% of chlorpropamide patients refused treatment or discontinued due to side effects, versus 7% of glyburide patients. Weight gain and hypoglycemic episodes were significantly raised by any intensive drug treatment. Patients assigned to chlorpropamide gained more weight than those assigned to glyburide. Over 10 years,
compared with the conventional therapy group, chlorpropamide patients gained 2.6 kg more (1.6-4.9, p<0.0001), glyburide patients gained 1.7 kg more (0.7-2.7, p<0.001). and insulin patients gained 4.0 kg more (3.1-4.9, p<0.0001).

Identical proportions of patients had hypertension before entering the study, but after 10 years, chlorpropamide subjects were more likely to be on therapy for hypertension (43% vs. 36%, p=0.022). Patients assigned chlorpropamide also had significantly higher systolic and diastolic blood pressure at 6 years (143/82 mm Hg vs. 138/80 mm Hg on other therapies, p<0.001). Adjusting for the difference in mean systolic or diastolic blood pressure by logistic regression analysis did not change this finding.

In the intention-to-treat population (UKPDS 33), major (severe) hypoglycemic episodes at 10 years with chlorpropamide and glyburide were 1.0% and 1.4%, respectively, compared to 0.7% for diet. Compared with chlorpropamide, glyburide was associated with a higher frequency (16% vs. 21%) and a higher annual rate of hypoglycemic episodes (0.4% for chlorpropamide, 0.6% for glyburide, 0.1% for diet therapy.)The UKPDS was designed to re-examine whether intensive treatment increases the risk of cardiac events, as had been reported in an earlier trial for tolbutamide (University Group Diabetes Program UGDP)6, 7 and in a VA cooperative study of intensive insulin therapy. In the UKPDS, there was no adverse effect of tight control on cardiovascular outcomes.

For glipizide, adverse event data from the UKPDS have not been reported fully. A partial report of glycemic control at six years found no difference in the annual rate of hypoglycemic episodes between chlorpropamide (1.8%) and glipizide (1.4%). Weight gain with chlorpropamide was significantly higher at +4.0 kg compared to glipizide +2.8 kg (p=0.048), but was not significantly different when adjusted for initial weight.

**Primary diet failure randomization.**

This trial compared insulin, sulfonylureas, and metformin in patients who had fasting blood glucose levels greater than 15 mmol/l despite up to 3 months of diet therapy. A partial report of the results of this part of the UKPDS was published in 1998.8 By 6 years, 62% of patients assigned to chlorpropamide and 69% patients assigned to glyburide required additional therapy (addition of metformin, addition of insulin, or change to insulin.) More major hypoglycemic episodes occurred in this population than in the “main randomization” population. By 6 years, the annual rate of serious (major) hypoglycemic episodes was 2.5% (0.0-6.7) for glyburide and 1.5% (0.0-2.6) for chlorpropamide.

1. **For adult patients with Type 2 diabetes, do oral hypoglycemics differ in the ability to reduce HbA1c levels?**

**Head-to-head trials.** There was a great gap in quality and relevance between the UK Prospective Diabetes Study and the other 6 head-to-head trials that assessed efficacy, summarized in Table 3 and in Appendix D. Although the studies varied in baseline plasma glucose levels, prior treatments, and length of followup, the results were consistent: there was a small absolute change in HbA1c with these agents, only apparent after at least 8 weeks of therapy, and diminishing in time. There were no significant differences in 6 of the 7 trials that followed patients for 15 months or less. The non-sulfonylurea secretagogue repaglinide was found to be superior to glipizide in one fair study,9 but the dosage of glipizide was maximized at 15 mg, while it is labeled for use up to 40mg. Additionally, only 50% of patients received the 15 mg dose.

We did not identify any trials comparing the first-generation sulfonylureas tolazamide and tolbutamide to other sulfonylureas or to non-sulfonylurea secretagogues.
Table 3. Fair- or better quality head-to-head trials.

<table>
<thead>
<tr>
<th>Trial Drug/Dose</th>
<th>Trial Design</th>
<th>Length</th>
<th>Difference in efficacy measure (HbA1c)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glyburide vs. chlorpropamide</strong></td>
<td><strong>UKPDS 13 chlorpropamide or glyburide vs. diet, insulin, metformin, or add-on 1995 British Medical Journal UKPDS 33 1998 Lancet</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Newly diagnosed Type 2 DM 3 month diet run-in, 2520 patients. randomized to one of five treatments</td>
<td>3 years</td>
<td>Chlorpropamide-0.4%, Glyburide -0.3% (NS)</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 years</td>
<td>Chlorpropamide -0.38%, Glyburide +0.11% (p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>Micronized glyburide vs. glyburide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carlson 1993 Clinical Therapeutics¹</td>
<td>Type 2 DM on glyburide &gt; 1 month no washout, 206 patients randomized to continue glyburide or take micronized glyburide</td>
<td>8 weeks</td>
<td>Micr. Glyburide +0.3%, Glyburide -0.1% NS</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Glipizide vs. glyburide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitabchi¹⁰ 2000 American J Medical Sciences</td>
<td>Type 2 DM unresponsive to diet, 2-month washout, 18 patients randomized</td>
<td>15 months</td>
<td>Glipizide -1.0%, Glyburide -1.3% NS</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Glimepiride vs. glyburide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Draeger¹¹ 1996 Horm. Metab. Res.</td>
<td>Type 2 DM on glyburide &gt;2 months, 2-week run-in, 1044 patients randomized</td>
<td>12 month</td>
<td>Glimepiride +0.3%, Glyburide +0.3% NS</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Repaglinide vs. glyburide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landgraf² 1999 Eur J Clin Pharm</td>
<td>Type 2 DM on sulfonylurea 1-2 week washout, 194 patients treated</td>
<td>10 week</td>
<td>Repaglinide -0.1%, Glyburide -0.2% NS</td>
<td>Fair</td>
</tr>
<tr>
<td>Wolfenbuttel (micronized) 1999 Diabetes Care¹³</td>
<td>Type 2 DM diet or OH, 1-week washout, 424 patients randomized, 320 completed it. Higher dropout rate in the glyburide group.</td>
<td>12 month</td>
<td>Repaglinide -0.3%, Glyburide -0.4% NS</td>
<td>Fair, high dropout rate</td>
</tr>
<tr>
<td><strong>Repaglinide vs. glipizide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madsbad⁴ 2001 Diabetic Medicine</td>
<td>Type 2 DM requiring diet or oral hypoglycemic drug, 1-week washout, 256 patients randomized. Did not use maximal doses of glipizide.</td>
<td>12 month</td>
<td>Repaglinide +0.2%, Glipizide +0.8% p&lt;0.05</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Placebo-controlled trials. One fair-quality systematic review compared oral hypoglycemic drugs in type 2 diabetics¹⁴. It included 63 trials of oral agents, most of which were comparisons to placebo rather than direct comparator trials. The authors found no difference in the efficacy within or between the sulfonylureas and the non-sulfonylurea secretagogues.

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

Only the UKPDS provides evidence on this question, and only for the comparison of chlorpropamide to glyburide. The results of the UKPDS are discussed above.
3. For adult patients with Type 2 diabetes, do oral hypoglycemics differ in safety or adverse events?

Adverse Events. The UKPDS provides the best available data on adverse effects of long-term use of chlorpropamide or glyburide. So far it has not reported the results for glipizide. Results of the UKPDS were described above.

There are no comparable data for other sulfonylureas or for the newer secretagogues. There were no significant differences in weight and lipid changes in the other head-to-head trials (Table 4), except for a small difference in HDL. One trial found a slight increase in HDL-C.

Table 4. Adverse events in head-to-head trials.

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>ADVERSE EVENTS AND HYPOGLYCEMIA</th>
<th>WEIGHT</th>
<th>LIPIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlson 1993 Clinical Therapeutics Glyburide(Gly) vs. Micronized Glyburide(Mic Gly)</td>
<td>Any adverse event: 61% (no difference) hypoglycemia: Mic Gly 0.9%; Mic 0.9%</td>
<td>NS change</td>
<td>NS change</td>
</tr>
<tr>
<td>Kitabchi 2000 American J Medical Sciences Glipizide(Glip) vs. Glyburide(Gly)</td>
<td>Any adverse event: NS difference Hypoglycemia: NS difference Severe hypoglycemia: Glip=0 episodes; Gly=0 episodes</td>
<td>NS change</td>
<td>NS change</td>
</tr>
<tr>
<td>Wolffinenbuttell 1999 Diabetes Care Repaglinide(Rep) vs. Micronized Glyburide (Mic Gly)</td>
<td>Any adverse event: 14% Withdrawals: Total: 25% Hypoglycemia: Rep 9%; Mic Gly 9%</td>
<td>NS change</td>
<td>NS change</td>
</tr>
<tr>
<td>Landgraf 1999 Eur J Clin Pharm Repaglinide(Rep) vs. Glyburide(Gly)</td>
<td>Hyperglycemia: Rep=13 episodes; Gly=9 episodes Hypoglycemia: 35 episodes overall; Rep 9.5%,Gly 8.9% (p-value NS) Withdrawals: Total 15% Adverse event: 3% overall; Rep 12%, Gly 23%</td>
<td>NS change</td>
<td>NS change except &gt;HDL-C in Rep (1.15 vs.1.11 mmol/L, p=0.005)</td>
</tr>
<tr>
<td>Madsbad 2001 Diabetic Medicine Repaglinide(Rep) vs.</td>
<td>Severe hypoglycemia: Rep=0 episodes; Glip=0 episodes Hypoglycemia: 15%rep 19%gly</td>
<td>NS decrease</td>
<td>NS changes</td>
</tr>
</tbody>
</table>
Drug Interactions. We did not identify head-to-head comparative studies of drug interactions. Information about drug interactions from trials in healthy volunteers are described in the package inserts for each drug. Some clinically significant drug interactions are described below in Table 5.

Table 5. Clinically significant Drug Interactions*

<table>
<thead>
<tr>
<th>PRECIPITANT DRUG</th>
<th>AFFECTED DRUG</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose, alcohol**, monoamine oxidase inhibitors, metformin, salicylates</td>
<td>sulfonyleureas</td>
<td>Intrinsic hypoglycemic activity</td>
</tr>
<tr>
<td>Chloramphenicol, warfarin</td>
<td>sulfonyleureas</td>
<td>Decreased hepatic metabolism</td>
</tr>
<tr>
<td>Clofibrate, salicylates, sulfonamides, warfarin</td>
<td>sulfonyleureas</td>
<td>Displacement from plasma protein</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors, tricyclic antidepressants</td>
<td>sulfonyleureas</td>
<td>Mechanism unknown</td>
</tr>
<tr>
<td>Probencid, salicylates</td>
<td>sulfonyleureas</td>
<td>Decreased renal excretion</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>CYP2C9 metabolized agents</td>
<td>Nateglinide is a cytochrome P450 isoenzyme CYP2C9 inhibitor</td>
</tr>
<tr>
<td>Inhibitors or inducers of cytochrome P450 CYP3A4 isoenzyme</td>
<td>Repaglinide</td>
<td>may increase or decrease repaglinide action</td>
</tr>
</tbody>
</table>

*Adapted from Facts and Comparisons

**Alcohol may cause a disulfiram-like reaction with chlorpropamide

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?

Cross-sectional data reveal important differences among racial groups in the presentation and course of diabetes.\(^5\) However, there is no direct evidence that any sulfonyleurea or non-sulfonyleurea secretogogue has an advantage in efficacy for any racial group. In placebo-controlled trials presented to the FDA during the approval process for glimeripide, no differences were found in the antihyperglycemic effect between whites (n = 536), blacks (n = 63), and Hispanics (n = 63) who had Type 2 diabetes. Similarly, in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect of repaglinide was comparable between Whites (n=297) and African-Americans (n=33). Repaglinide had similar pharmacokinetics in Whites (n=74) and Hispanics (n=33). Pharmacokinetic data on nateglinide found no differences among several races and ethnic groups.

Old age is a risk factor for serious hypoglycemic.(Ben-Ami, Arch Int Med 1999) An observational study attempted to make the case that longer-acting sulfonyleureas were associated with a higher risk of suffering hospitalization for hypoglycemia.\(^{15}\) Specifically, the authors noted that, at a time when 23.5% of the population with Type 2 diabetes took a long-acting drug, over 40% of hospitalizations due to hypoglycemia were
associated with long-acting drugs\textsuperscript{15} In the UKPDS trial, however, patients assigned to chlorpropamide had fewer hypoglycemic events than those taking glyburide. In another trial, glipizide and glyburide did not differ in efficacy or adverse events in an elderly population\textsuperscript{16}

**SUMMARY**

Table 6 summarizes the results of this review.
### Table 6. Summary of the Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Overall Quality of the Evidence*</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Comparative Efficacy For adult patients with Type 2 diabetes, do oral</td>
<td>Chlorpropamide vs. glyburide: Good. Glimeripide vs. glyburide or glipizide: Fair Repaglinide vs.</td>
<td>Good quality evidence that chlorpropamide and glyburide are similar in lowering HbA1c, with a small advantage for chlorpropamide. There is fair-quality evidence that repaglinide, glipizide, and micronized glyburide are similar in efficacy to glyburide at equivalent doses. There is no evidence comparing tolbutamide, tolazamide, or nateglinide to other drugs in the class.</td>
</tr>
<tr>
<td>hypoglycemics differ in the ability to reduce HbA1c levels?</td>
<td>Glyburide or glipizide: Fair Repaglinide vs. Glyburide or glipizide: Fair Nateglinide, Tolazamide,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or tolbutamide vs others: Poor</td>
<td></td>
</tr>
<tr>
<td>2: Progression/occurrence of outcomes For adult patients with Type 2 diabetes,</td>
<td>Chlorpropamide vs. Glyburide: Good Others: no data</td>
<td>There is good evidence from 1 trial that chlorpropamide is inferior to glyburide in reducing the progression to retinopathy, irrespective of HbA1c. There are not yet any outcome data on other sulfonylureas or non-sulfonylurea secretagogues, but outcome data from the UKPDS on glipizide may still be reported.</td>
</tr>
<tr>
<td>do oral hypoglycemics differ in the progression or occurrence of clinically</td>
<td></td>
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<td>relevant outcomes?</td>
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<td></td>
</tr>
<tr>
<td>3: Safety/Adverse Effects For adult patients with Type 2 diabetes, do oral</td>
<td>Chlorpropamide vs. glyburide: Good. Glimeripide vs. glyburide or glipizide: Fair Repaglinide vs.</td>
<td>In 1 good-quality long-term trial, chlorpropamide was associated with a lower rate of hypoglycemic episodes that glyburide but was associated with more weight gain and higher blood pressures than glyburide. There is fair evidence that glyburide is similar to micronized glyburide, glimeripide, glipizide, and repaglinide with respect to effects on weight and blood pressure. There is no evidence comparing tolbutamide, tolazamide, or nateglinide to other drugs in the class.</td>
</tr>
<tr>
<td>hypoglycemics differ in safety or adverse effects?</td>
<td>Glyburide or glipizide: Fair Nateglinide, Tolazamide, or tolbutamide vs others: Poor</td>
<td></td>
</tr>
<tr>
<td>4: Subgroups Are there subgroups of patients based on demographics</td>
<td></td>
<td>All of the 2nd generation sulfonylureas and the non-sulfonylurea secretagogues have been shown to have similar efficacy and safety in men and women and in people of different races or ethnicity. We did not identify evidence that one of the included drugs has an advantage over others in any demographic group, in obese diabetics, or in patients who have a history of hypoglycemic episodes.</td>
</tr>
<tr>
<td>(age, racial groups, gender), concomitant medications, co-morbidities (i.e.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>obesity), or history of hypoglycemic episodes for which one oral hypoglycemic</td>
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<td>is more effective or associated with fewer adverse effects?</td>
<td></td>
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</tbody>
</table>
REFERENCES


