

Oral Hypoglycemic Agents

Clinical Pearls for Washington Rx Therapeutic Interchange Program (TIP)

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Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared glipizide and glyburide to be the “preferred” oral hypoglycemic agents for patients covered by their prescription insurance. Patients currently using “non-preferred” agents” must be evaluated for conversion to glipizide and glyburide. Furthermore, once the TIP program is operational, patients presenting with prescriptions for non-preferred agents from “endorsing practitioners” (i.e., providers that have signed the TIP agreement) may be automatically converted to preferred agents by pharmacists.

Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agents.

First Generation Oral Sulfonylureas	Second Generation Oral Sulfonylureas	Non-Sulfonylurea Secretagogues
1. Chlorpropamide (Diabenase®) 2. Tolazamide (Tolinase®) 3. Tolbutamide (Orinase®)	1. Glimepiride (Amaryl®) 2. Glipizide (Glucotrol®) 3. Glyburide (Diabeta®, Micronase®) 4. Glyburide Micronized (Glynase®)	1. Nateglinide (Starlix®) 2. Repaglinide (Prandin®)

Washington State Evidence Based Preferred Drugs for Insulin Secretagogue-type Oral Hypoglycemics class:

- Glipizide (generic)
- Glyburide (generic)

Overview of Sulfonylureas (SU):

- Effective when used as monotherapy or combination with other hypoglycemics or insulin
- Most effective in patients with normal or slightly increased weight
- Lowers blood glucose concentrations by about 20 percent
- Manufacturers recommend doses as high as 20mg/day for glyburide and 40 mg/day for glipizide. However, doses above 10 mg/day glyburide or 20mg/day glipizide usually provide little further benefit and may be associated with increased side effects (i.e., dizziness).

Overview of Meglitinides:

- Short-acting, glucose-lowering agents indicated for treatment of Type 2 diabetes
- Structurally different than SU, but act similarly which thereby increases insulin secretion
- May be used alone or combination with metformin
 - Generally administered three times a day prior to meals (15 min)

Comparative efficacy of oral hypoglycemics for Type 2 diabetic patients in:

1. Reducing HbA_{1c} levels

Current evidence reveals no difference between any agents in the classes of oral SUs and non-SU secretagogues. All agents demonstrate small absolute change in HbA_{1c}. Limited data exists for comparing first-generation SU tolazamide and tolbutamide to other SUs or non-SU secretagogues.

2. Progression or occurrence of clinically relevant outcomes

Only the United Kingdom Prospective Diabetes Study (UKPDS 33, Lancet 1998; 352: 837-58.), the largest head-to-head diabetes study to date, provides this evidence, comparing chlorpropamide and glyburide. Results indicate no difference between glyburide and chlorpropamide for intensive treatment in preventing vascular complications except for progression of retinopathy, for which glyburide demonstrated greater risk reduction. Insufficient evidence exists for other SUs and non-SUs.

Safety and adverse effects comparisons for oral hypoglycemics:

The UKPDS trial revealed adverse effects with long-term use of chlorpropamide and glyburide: chlorpropamide had fewer hypoglycemic events compared to glyburide, but was associated with more weight gain, 2.6kg vs. 1.7kg ($p < 0.001$). At this time, there are no reported results for glipizide. Other head-to-head trials have not demonstrated significant differences in weight and lipid changes between:

- Glyburide vs. Micronized glyburide
 - Glyburide vs. Glipizide
 - Glyburide vs. Glimpiride
 - Repaglinide vs. Micronized glyburide
 - Repaglinide vs. Glyburide
 - Repaglinide vs. Glipizide
- Insufficient evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.

Cost Considerations:

Meglitinides are considerably more expensive than SU agents and have not been shown to offer any significant therapeutic outcomes advantages. It is recommended that pharmacists contact physicians for newly diagnosed patients with prescriptions for meglitinides to discuss the interchange for glyburide or glipizide.

Oral Hypoglycemic Cost Comparisons

Hypoglycemic Agent	Dose & Frequency	Cost*
First Generation SU		
Chlorpropamide	250mg qd	\$10
Second Generation SU		
Glimpiride (Amaryl)	4mg qd	\$26
Glipizide (generic)	20mg qd	\$18
Glyburide (generic)	10mg qd	\$20
Glyburide micronized (generic)	6mg qd	\$16
Meglitinides		
Nateglinide (Starlix)	60 – 120mg tid	\$83
Repaglinide (Prandin®)	2mg tid	\$76

*Cost for 30-day supply based on DSHS reimbursement formulas

Other significant considerations:

1. Age, particularly elderly

Diagnoses of Type 2 diabetes are usually made in adults aged 40 years or older. In 2002, the prevalence of total diabetes among people aged 60 years or older in the United States was 8.6 million, or approximately 18.3% of this demographic. This population is at risk for serious hypoglycemic episodes ($< 50\text{mg/dL}$). UKPDS indicated fewer events with chlorpropamide vs. glyburide, yet glyburide and glipizide did not differ in adverse events or efficacy in patients (Clin Ther 1993;15(6):1031-40).

2. Renal insufficiency and renal failure

In patients with significant renal insufficiency ($\text{CrCl} < 50\text{ml/min}$) glipizide should be given consideration as the preferred agent to avoid accumulation and resultant hypoglycemia and other adverse events. (Refer to renal dosing parameter chart.)

AGENT	CREATININE CLEARANCE	RECOMMENDATION
Chlorpropamide	<50mL/min	Avoid use
Glimepiride	<22mL/min	Initial starting dose 1mg and increase dose based on fasting BG level
Glipizide	<10ml/min	Not recommended
Glyburide	<50ml/min	Not recommended
Nateglinide	Mild to severe renal disease	No specific dosage adjustment recommended
Repaglinide	Any degree of impairment, even with more severe degree	Safely titrated (Max dose of 4mg, 3 times daily)

3. Concomitant medications/ Drug interactions:

No significant differences between preferred agents and most of the other SU.

4. Co-morbidities: Obese patients

No evidence supports that any particular SU is more effective or associated with fewer side effects. The current drug of choice for obese Type 2 diabetics is metformin, which promotes modest weight reduction or at least weight stabilization (UKPDS 34, Lancet1998; 352: 854–65)

Steps in Converting Patient to Preferred Agents: Considerations for agent and dose selection, counseling, education, monitoring, and follow-up:

#1. Determine if there is any rationale or justification for use of the current, non-preferred agent.

- Does the patient have any history of allergy, intolerance or adverse reactions to glipizide or glyburide that would preclude them for using these preferred agents?
 - If yes, then obtaining DSHS prior authorization to continue the current non-preferred agent is advised.
- It is recommended that pharmacists contact physicians for newly diagnosed patients with prescriptions for meglitinides to discuss the interchange for glyburide or glipizide.

#2. Determine which preferred agent is most appropriate and then select the conversion dose based on the current hypoglycemic agent and dose (using the conversion guide below or other tools).

- Since there are no perfect, equivalent conversion doses for these agents, it is crucial that the patient be counseled regarding the possibility of a hyper- or hypoglycemic reactions and possible changes in glucose control. Hypoglycemic reactions are the most concerning risk with these conversions and would be more likely in diabetics with tighter glucose control, the elderly, and in patients with less severe diabetes whose average blood sugars run closer to normal levels. (See the patient consultation considerations below.)

#3. Patient Education and Consultation

- The patient should be counseled on the rationale behind this conversion.
- The patient should be specifically instructed to stop the previous hypoglycemic agent and begin taking the new agent with emphasis on the risk of using both medications concomitantly.
- Counseling should include advising the patient on adverse reactions that may occur with all hypoglycemic medications and what to do should they experience any significant reactions.
 - Classic signs and symptoms of HYPERglycemia are thirst, polyuria, weight loss, and visual blurring.
 - Early stages of a HYPOglycemic episode (blood sugar < 60 mg/dL), symptoms may include sweating, tremor, hunger, and anxiety.
 - Here are some key questions to cover with your diabetic patients to assure a safe and effective transition to the new hypoglycemic medication.
 - Are you monitoring your blood sugars at home?
 - Do know how to interpret your blood glucose readings (ie, hyper- and hypoglycemic results, goal ranges)?

- Do you know the signs and symptoms of hypo/hyperglycemia?
- What would you do if you experienced these signs and symptoms?
- If you experience any of these symptoms, especially in the in the next few days or weeks after this change is made, you should contact your physician for possible follow-up or dose adjustments, or call the pharmacy if you have any medication-related questions.

#4. Notification of Prescriber Regarding Conversion

- The pharmacist/pharmacy is legally obligated to communicate information regarding medication changes that occur via the TIP for all patients to ensure continuity of care.

Dosing Conversion Guide for Sulfonylureas and SU-secretagogues*

Glyburide	Glipizide	Glyburide Micronized	Chlorpropamide [#]	Tolbutamide	Tolazamide	Nateglinide	Repaglinide
2.5mg qd	5mg qd	1.25mg qd	125mg qd	500mg qd	100mg qd	60mg ac tid	0.5mg ac tid – qid
2.5mg bid or 5mg qd	5mg bid or 10mg qd	3mg qd	250mg qd	1000mg qd	250mg qd	60mg ac tid	1-2mg ac tid – qid
5mg bid or 10mg qd	10mg bid or 20mg qd	3mg bid or 6mg qd	500mg qd	2000mg qd	500mg qd	120mg ac tid	3mg ac tid – qid
10mg bid or 20mg qd	20mg bid or 40mg qd	6mg bid or 12mg qd	750mg qd	3000mg qd	750 -1000mg divided bid	120mg ac tid	4mg ac tid - qid

*This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials. Practitioners should exercise common sense in the practical application of this guide, including consideration for a patient’s current glycemic control, risk for hypoglycemia and other clinical variables. Patient education and professional follow-up after drug conversions have been made are vital to ensure patient safety and desired therapeutic outcomes.

[#] If the patient is transferred from chlorpropamide to another hypoglycemic agent, extreme caution is necessary during the first two weeks since chlorpropamide has a long half-life and may precipitate hypoglycemia.

References and Resources:

- American Diabetes Association “Standards of Care” (Diabetes Care (27), Suppl 1, Jan 2004) (<http://care.diabetesjournals.org/>)
- American Diabetes Association: (<http://www.diabetes.org/home.jsp>) patient and professional information
- National Diabetes Information Clearing House (<http://diabetes.niddk.nih.gov/>)
- Life Clinic (<http://www.lifeclinic.com/focus/diabetes/default.asp>): great patient education and some professional info.
- Lexi-Comp Online (<http://www.lexi.com/web/index.jsp>)
- Oregon Health Sciences University (OHSU) and the Office for Oregon Health Policy and Research (http://www.oregonrx.org/oregon_health_plan_drug_list)
- UpToDate (<http://www.uptodate.com/>)
- UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-58.
- Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854–65