



What is the Best Medicine?

The question is often posed about what the best treatment is for diabetes? The foundation of successful diabetes treatment is EXERCISE. It is the best medicine. Tremendous health benefits are seen with even low levels of exercise. The amount of exercise needed to benefit health is much lower than amount needed for fitness. Physical Activity Guidelines published in 2008 by the U.S. Department of Health & Human Services tell us the correct “dosage” of physical activity necessary for health benefits. For most, **150 minutes per week of moderate-intensity physical activity is what the provider should order.** Patients can choose their own schedule. For example: 30 minutes of moderate-intensity exercise, five days per week OR three 10-minute sessions per day, five days per week.

Regular physical activity can:

- Reduce the risk of heart disease by 40%.
- Lower the risk of stroke by 27%.
- Reduce the incidence of diabetes by almost 50%.
- Reduce the incidence of high blood pressure, by almost 50%.
- Can reduce mortality and the risk of recurrent breast cancer by almost 50%.
- Can lower the risk of colon cancer by over 60%.
- Can reduce the risk of developing Alzheimer’s disease by one-third.
- Can decrease depression as effectively as medications or behavioral therapy.

“If we had a pill that gave all those benefits and was readily available, we would find a way to make sure every patient took it.”

-Robert E. Sallis, M.D.

Why isn’t this happening with exercise?

–Providers may lack the proper training to effectively counsel patients about exercise.

–There is no national reimbursement policy for referrals to exercise experts.

–Lack of media advocacy.

–No tangible success measures.

–Providers are lacking the time to effectively counsel patients.

“What if there was **one prescription** that could **prevent and treat** dozens of diseases, such as diabetes, hypertension and obesity?”



Robert E. Sallis, M.D., M.P.H., FACSM,
Exercise is Medicine™ Task Force Chairman

Every treatment has side effects, but these are very minimal with exercise. The most common side effects associated with increased physical activity include overuse injuries. These can often be avoided by starting low and going slow. The evidence is overwhelming on the health burden of physical inactivity. We cannot continue to ignore this evidence when formulating treatment plans for patients. No patient should leave a provider’s office or educator visit without an assessment of his/her physical activity and a prescription for an exercise regimen or a referral to a qualified fitness professional.

continued on page 4

Inside this issue:

Selecting a Sulfonylurea	2-3
What is the best medicine? <i>continued</i>	4

Objectives:

- ◆ Discuss the impact physical activity can have on chronic diseases.
- ◆ Recognize the correct “dosage” of activity for most patients.
- ◆ Identify differences in the half live, metabolism and side effect profile of the most common sulfonylureas.

Selecting a Sulfonylurea

By Celeste Vinluan and Mark Nulty, PharmD Candidates 2012

Sulfonylureas have been available for the treatment of type 2 diabetes since the early 1950s. When lifestyle interventions and metformin can no longer maintain glycemic control, the joint statement provided by the American Diabetes Association and European Association for the Study of Diabetes recommends adding a sulfonylurea to the patient's regimen in preference to utilizing a different class of oral diabetes medications. Sulfonylureas are the most widely prescribed medications for the treatment of type 2 diabetes. The three most commonly prescribed sulfonylureas are glyburide, glipizide, and glimepiride. The joint statement specifically recommends sulfonylureas other than glyburide or chlorpropamide. This article will explore the subtle yet important differences between the sulfonylureas (1).

The first sulfonylureas developed were chlorpropamide, acetohexamide, tolazamide, and tolbutamide. Better safety profiles demonstrated by second-generation sulfonylureas have mostly replaced these first-generation sulfonylureas. Today, glyburide, glipizide, and glimepiride are the more commonly prescribed sulfonylureas. All sulfonylureas stimulate insulin secretion from β -cells in the pancreas. Sulfonylureas are equally effective at decreasing blood sugars when administered in equipotent doses, lowering the hemoglobin A_{1c} on average approximately 1.5%. Although, glyburide, glipizide, and glimepiride are placed in the same pharmacological class, there are some differences among them that should be considered before selecting a sulfonylurea.

The sulfonylurea receptor is a component of the ATP-dependent potassium channel in the pancreatic beta cells. Sulfonylurea binding leads to inhibition of these channels, which alters the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion. The net effect is more insulin being released at all blood glucose concentrations. So, sulfonylureas are useful only in patients that have some beta cell function. Some of the differences among the three sulfonylureas may originate from their affinity for three isoforms of the sulfonylurea receptor (SUR1, SUR2A, and SUR2B). The SUR1 receptor is found in the ATP-sensitive potassium channels in the pancreas, while SUR2A and SUR2B are found in cardiac and vascular smooth muscle (2-6). Sulfonylureas specific for SUR1 receptor, such as glipizide, act primarily on the β -cells in the pancreas and stimulate insulin secretion (7). In addition to affinity for SUR1 receptor, glyburide has affinity for SUR2A and SUR2B (8;9). Since these receptors are found on the cardiac cells and coronary vessels there have been concerns around the cardiac effects of sulfonylureas. Conflicting studies make it uncertain whether sulfonylureas increase cardiovascular mortality (11;12;13). This is an area that warrants further investigation.

The second generation sulfonylureas vary in their potency per milligram, duration of action, hypoglycemic activity of the metabolites, extent of hepatic metabolism, and renal excretion. For example, the risk for hypoglycemia is associated directly with the duration of action of each sulfonylurea, with the highest potential for hypoglycemia occurring with glyburide (11). Therapy with glipizide and glimepiride appears to have a lower risk for hypoglycemia than glyburide, possibly because the presence of active metabolites with glyburide causes a longer hypoglycemic effect that persists for 24 hours (11). Although, glyburide, glipizide, and glimepiride are metabolized in the liver, glyburide is metabolized to active metabolites while glipizide and glimepiride are metabolized to inactive metabolites. These characteristics of each individual sulfonylurea become important when initiating sulfonylureas in the elderly and in patients with renal dysfunction. Table 1 provides general considerations, Table 2 details the major differences between glyburide, glipizide, and glimepiride. When comparing glyburide, glipizide, and glimepiride, we should consider renal impairment, liver function, risk for hypoglycemia, age, weight gain, and drug interactions before selecting a sulfonylurea for treatment of patients with type 2 diabetes. In most cases the sulfonylurea selected should be glipizide or glimepiride.

Table 1. Sulfonylurea considerations at a glance.

	Glyburide	Glipizide	Glimepiride
Recommended for elderly	No	Yes	Yes
Active metabolites	Yes	No	No
Renal adjustment suggested	Yes (CrCl<50ml/min)	No (CrCl<10ml/min)	Yes (CrCl<25ml/min)
Weight gain	Yes (++)	Yes (+)	Yes (+)
Hepatic adjustment suggested	Yes	Yes	No

Table 2. Comparison of glyburide, glipizide, and glimepiride (13;14;15).

Sulfonylurea	Recommended Starting Dosage		Maximum Daily Dose	Half-life elimination	Duration of Action	Therapeutic Notes
	Nonelderly	Elderly				
Glyburide (Diabeta, Micronase)	2.5-5 mg daily	1.25-5mg daily	20 mg daily (>10 mg divide doses)	10 hours	Up to 24 hours	Metabolized in liver; metabolites have hypoglycemic potency. Elimination is 50% excreted in urine and 50% in feces; may accumulate in patients with renal insufficiency.
Glyburide Micronized (Glynase)	1.5-3 mg daily	1.5-3 mg daily	12 mg daily (>6 mg divide doses)	4 hours	Up to 24 hours	Metabolized in liver; metabolites have hypoglycemic potency. Elimination is 50% excreted in urine and 50% in feces; may accumulate in patients with renal insufficiency.
Glipizide (Glucotrol)	5 mg daily	2.5-5 mg daily	40 mg (>15 mg divide doses)	2-5 hours	Up to 20 hours	Absorption delayed with food; take 30 min before meals. Metabolized in liver to inactive metabolites; may be significantly affected by drugs that induce/inhibit CYP2C9 liver enzyme. Not dependent on renal function. Less weight gain.
Glipizide Extended release (Glucotrol XL)	5 mg daily	2.5-5 mg daily	20 mg daily	2-5 hours	24 hours	Absorption delayed with food; take 30 min before meals. Metabolized in liver to inactive metabolites; may be significantly affected by drugs that induce/inhibit CYP2C9 liver enzyme. Not dependent on renal function. Less weight gain.
Glimepiride (Amaryl)	1-2 mg daily	1 mg daily	8 mg daily	5-9 hours	24 hours	Meals only have a modest effect on absorption. Metabolized in liver to inactive metabolites; may be significantly affected by drugs that induce/inhibit CYP2C9 liver enzyme. Safer option for patients with renal impairment. PK not affected by significant liver disease. Less weight gain.

References:

- Nathan, D M, Buse, J B, Davidson, M B, et al. (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American diabetes association and the European association for the study of diabetes. *Diabetes care*, 32(1), 193-203.
- The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of phenformin therapy. *Diabetes* 1975; 24 Suppl 1:65-184;65-184.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 3). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):837-853.
- Klepzig H, Kober G, Matterer C, Luus H, Schneider H, Boedeker KH et al. Sulfonylureas and ischaemic preconditioning: a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; 20(6):439-446.
- Tomai F, Crea F, Gasparidone A, Versaci F, De Paulis R, Penta dP et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. *Circulation* 1994; 90(2):700-705.
- Gribble FM, Tucker SJ, Seino S, Ashcroft FM. Tissue specificity of sulfonylureas: studies on cloned cardiac and beta-cell K(ATP) channels. *Diabetes* 1998; 47(9):1412-1418.
- Ashcroft FM, Gribble FM. ATP-sensitive K+ channels and insulin secretion: their role in health and disease. *Diabetologia* 1999; 42(8):903-919.
- Gribble FM, Reimann F. Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 2003; 46(7):875-891.
- Song DK, Ashcroft FM. Glimepiride block of cloned beta-cell, cardiac and smooth muscle K(ATP) channels. *Br J Pharmacol* 2001; 133(1):193-199.
- Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* 2001; 103(25):3111-3116.
- Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004; 64(12):1339-1358.
- Evans JM, Ogston SA, Reimann F, Gribble FM, Morris AD, Pearson ER. No differences in mortality between users of pancreatic-specific and non-pancreatic-specific sulphonylureas: a cohort analysis. *Diabetes Obes Metab* 2008; 10(4):350-352.
- Khalangot M, Tronko M, Kravchenko V, Kovtun V. Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. *Diabetes Res Clin Pract* 2009; 86(3):247-253.
- Sulfonylurea dose comparison. *Pharmacist's Letter/Prescriber's Letter* 2009; 25 (8): 250801
- Lexicomp Online
- DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York, NY: McGraw-Hill; 2005

What is the Best Medicine? *(continued)*

All health care providers can assess how much physical activity patients are getting and explore reasons that they aren't more active. A recent study found that only half of all adults were asked about their exercise habits by their healthcare provider. Patients who had been asked reported being more active than those who were never asked. The most promising interventions in primary care practices include patient goal setting, written exercise prescriptions, individually tailored physical activity regimens, and mailed or telephone follow-up. What can you incorporate into your current practice to help patients achieve increased physical activity?

Table 1. Summary of the 2008 Physical Activity Guidelines for Americans published by the U.S. Department of Health and Human Services.

Age	No Chronic Conditions	Chronic Conditions
Children & Adolescents (6-17)	60 minutes or more of physical activity every day (moderate*- or vigorous**-intensity aerobic physical activity). Vigorous-intensity activity at least 3 days per week. Muscle-strengthening and bone-strengthening activity at least 3 days per week.	Develop a physical activity plan with your health care professional. Avoid inactivity. Aerobic activity examples include; bicycling, running and swimming. Strength building examples include; resistance training, sit ups, team sports.
Adults (18-64)	150 minutes a week of moderate-intensity, or 75 minutes a week of vigorous-intensity aerobic physical activity Muscle-strengthening activities that involve all major muscle groups performed on 2 or more days per week.	Develop a physical activity plan with your health care professional. Be as physically active as possible. Avoid inactivity Aerobic activity examples include; hiking, tennis, bicycling and swimming. Strength building examples include; push ups, sit ups and weight training. People with diabetes must monitor their blood sugar and avoid injury to their feet.
Older Adults (65+)	Follow the adult guidelines, or be as physically active as possible. Avoid inactivity. Exercises that maintain or improve balance if at risk of falling.	Develop activity plan with health care professional. Aerobic examples include walking, swimming, aerobic exercise classes, gardening. Strength building examples include hand held weights, calisthenics, and yoga. People with diabetes must monitor their blood sugar and avoid injury to their feet.

References:

1. Exercise as Medicine, <http://exerciseismedicine.org/>
2. Physical Activity Guidelines published in October 2008 by the U.S. Department of Health & Human Services, <http://www.health.gov/paguidelines/pdf/paguide.pdf>
3. AHRQ, Physical Activity and Older Americans , Benefits and Strategies <http://www.ahrq.gov/ppip/activity.htm> accessed September 14, 2011.

Judy B. Thompson, Pharm.D., BCPS, CDE
Alaska Native Diabetes Dispatch Reviewers
Terry Raymer, MD, CDE
Denise Ramp, MSN, CNM, NP-C
4315 Diplomacy Drive
Anchorage, AK 99508
Phone: 907-729-2164
Fax: 907-729-2119
Email: jbthompson@anthc.org
Diabetes Office Phone: 907-729-1125
We are on the Web:
www.anthc.org/anmc/services/diabetes/

Goal-The goal of the Diabetes Dispatch is to increase the reader's knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.

ACPE # 0139-9999-11-021-H01-P/T

- Expiration Date 10/18/2014
- ANMC HED Activity # 11-30010

The speakers/authors disclose that they do not have significant financial interests in any product or class of products discussed directly or indirectly in this activity, including research support.

Continuing Education Quiz

Diabetes Dispatch: Fall 2011

1. For most, how many minutes of physical activity per week should a provider recommend?
 - A) 30
 - B) 60
 - C) 90
 - D) 150
2. Regular physical activity can
 - A) Decrease symptoms of depression
 - B) Reduce the risk of heart disease
 - C) Reduce the risk of diabetes
 - D) All of the above
3. What is the most common side effect associated with increased physical activity?
 - A) overuse injuries
 - B) nausea
 - C) diarrhea
 - D) constipation
4. The most promising interventions in primary care practices to increase patient physical activity include all of the following EXCEPT.
 - A) patient goal setting
 - B) calling the patient lazy
 - C) written exercise prescriptions
 - D) individually tailored physical activity regimens
5. According to the 2008 Physical Activity Guidelines for Americans children and adolescents with no chronic conditions should get _____ minutes of physical activity every day
 - A) 30
 - B) 60
 - C) 90
 - D) 120
6. When exercising, people with diabetes should?
 - A) Always eat a snack
 - B) Monitor blood glucose
 - C) Mix aerobic with strength building exercises
 - D) both B and C
7. The sulfonyureas main mechanism of action is?
 - A) Decrease insulin resistance
 - B) Increase insulin secretion
 - C) Decrease hepatic glucose production
 - D) Increase glucagon secretion
8. Which sulfonyurea has active metabolites and the longest duration of action?
 - A) glimeperide
 - B) tolbutamide
 - C) glipizide
 - D) glyburide
9. When choosing a sulfonyurea, the provider should consider?
 - A) Possible weight gain
 - B) The patients renal function
 - C) The patients hepatic function
 - D) All of the above
10. The second generation sulfonylureas _____
 - A) Vary in their ability to decrease blood sugars
 - B) Reduce A1C on average 1.5%
 - C) Require some beta cell function to act.
 - D) both B and C

Pharmacists and Technicians:

To obtain CPE credit for this lesson you must answer the questions on the quiz (70% correct required) return the quiz and evaluation tool. Should you score less than 70%, you will be asked to repeat the quiz. In May and November of each year we will mail a statement of credit, unless otherwise arranged with the AkPhA office. This program furnishes 1.0 hour CPE (0.1 CEU) credit per lesson.

EXPIRATION FOR CREDIT: Pharmacist and technicians may receive credit for completing this course if returned by October 18, 2014 The ALASKA PHARMACISTS ASSOCIATION is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE# 0139-9999-11-021-H01-P/T

For ACPE Credit Mail or Fax to:

AkPhA

203 W. 15th Ave. # 100

Anchorage, AK 99501

Fax to: (907) 563-7880

Circle one: Pharmacist Technician

	Disagree	Agree		Disagree	Agree
1) Activity met learning objectives	1	2 3 4 5	4) Activity learning assessment appropriate	1	2 3 4 5
2) Amount of time was appropriate	1	2 3 4 5	5) Author was knowledgeable in topic	1	2 3 4 5
3) Increased my knowledge of topic	1	2 3 4 5	6) Overall, I was satisfied with the activity	1	2 3 4 5

Name _____ Address _____

E-Mail _____ NABP CPE# _____ DOB: _____ Phone _____

I am a current member of AkPhA _____. I am not a member of AkPhA; enclosed is a check to AkPhA for \$20.00 _____