

Wyoming Drug Utilization Review

Type 2 Diabetes Mellitus: Metformin and Alpha-Glucosidase Inhibitors

WRITTEN BY MEGAN MEIER, PHARM D CANDIDATE, 2021

Type 2 Diabetes Treatment Approach

Type 2 diabetes mellitus (T2DM) is characterized as a loss of insulin secretion from β -cells (1). Insulin deficits and peripheral insulin resistance are hallmarks of this disease. T2DM accounts for 90-95% of all diabetic cases. Once diagnosed, treatment goals will be set for each patient that aim to delay complications and enhance quality of life. These include individualized lifestyle changes, weight loss, hemoglobin A1c (HbA1c) targets, and adherence to pharmacological regimens (1).

Wyoming Medicaid requires that all patients diagnosed with T2DM begin therapy on metformin before initiating other agents (2). If metformin treatment is failed after a 90-day trial, then alternative agents may be considered. Wyoming Medicaid uses other classes as second line treatment including meglitinides, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, incretin mimetics (GLP-1 receptor agonists), sodium glucose cotransporter-2 (SGLT-2) inhibitors and alpha-glucosidase inhibitors.

Pharmacological Therapy

Metformin:

Metformin is considered the first line treatment for T2DM (1). It inhibits gluconeogenesis to decrease hepatic glucose output (3). Serum insulin concentrations are decreased slightly by the ability of metformin to increase glucose utilization in peripheral tissues (4). Both extended and immediate release metformin are available and are equally effective (5).

At the time of diagnosis, lifestyle modifications such as exercise, weight loss, smoking cessation and psychological support are recommended in addition to metformin (1). Contraindications to metformin include: impaired renal function (glomerular filtration rate <30 mL/min/1.73m²), concurrent liver disease, present alcohol abuse, hypoperfusion risk with acute heart failure, past history of lactic acidosis while using metformin, and hemodynamic instability due to infection (6). Concurrent administration of iodinated contrast and metformin is contraindicated (7). There is debate regarding how long metformin should be held once iodinated contrast is administered; however, the Canadian Association of Radiologists suggests patients should wait 48 hours before restarting metformin (7). Without contraindications, metformin is the preferred initial agent because of the safety profile, low cost, glycemic efficacy, tolerability, and reduced risk of weight gain and hypoglycemia (1).

WY-DUR Manager
Aimee Lewis, PharmD, MBA

WY-DUR Board Members
Robert Monger, MD, Chair
Scot Schmidt, PharmD, Vice Chair
Hoo Feng Choo, MD
Paul Johnson, MD
Scott Johnston, MD
Chris Mosier, RPh
Garrett Needham, RPh
Patrick Yost, MD
Kristen Lovas, PharmD
Melinda Carroll, PharmD
Alissa Aylward, PA
Danae Stampfli, MD

WY-DUR Board Ex-Officios
Patrick Johnson, PharmD, MPH
James Bush, MD
Cori Cooper, PharmD
Melissa Hunter, PharmD

WY-DUR Program Assistant
Karly Bentz

WY-DUR
University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Ave
Laramie, WY 82071
307-766-6750
www.uwyo.edu/DUR

Edited by
Aimee Lewis, PharmD, MBA
Karly Bentz

Gastrointestinal side effects are common with metformin (8). These include nausea, diarrhea, metallic taste in mouth, anorexia, and abdominal discomfort (8). Another metformin side effect is vitamin B12 deficiency, which occurs in up to 30% of patients (9). A large concern during the use of metformin is lactic acidosis; however, the incidence is very low (10).

Drug interactions do exist with metformin, but most only require monitoring of pharmacologic therapy (11). A few interactions may require therapy modification. Certain interactions should be completely avoided. Table 1 categorizes drug interactions with metformin (11).

Table 1: Metformin Drug Interactions Requiring Therapy Modification or Avoidance¹¹

Therapy Modification	Completely Avoid
Cimetidine Dolutegravir Iodinated Contrast Agents Patiromer Ranolazine Tafenoquine	Alcohol

Laboratory monitoring should occur during the use of metformin (1). A patient's HbA1c should be measured at least biannually for patients with stable glucose levels and quarterly for those who do not meet glucose level goals. Serum creatinine and vitamin B12 should be routinely measured (1).

Alpha-glucosidase inhibitors:

Two alpha-glucosidase inhibitors available in the United States are acarbose and miglitol (12). These agents lower blood glucose by inhibiting upper gastrointestinal enzymes, known as alpha-glucosidases; therefore, carbohydrate and fat absorption in the intestines is altered (12).

Alpha-glucosidase inhibitors are not considered first line agents (1). These agents are not included in the American Diabetes Association overall approach for glucose-lowering therapy in type 2 diabetes (1). Many other agents are recommended for use before considering an alpha-glucosidase inhibitor in a diabetic patient's regimen (1). Both acarbose and miglitol are shown to have a measureable effect at lowering HbA1c with minimal effects on fasting blood glucose levels (12). While acarbose and miglitol are used rarely, contraindications exist for both medications including: hypersensitivity, history of diabetic ketoacidosis, inflammatory bowel disease, cirrhosis, colonic ulceration, and intestinal obstruction (15,16).

The main side effects of alpha-glucosidase inhibitors are flatulence and diarrhea (13). Flatulence occurs in 74% of patients taking acarbose, while diarrhea occurs in 31% and abdominal pain in 19% (15). In patients taking miglitol, flatulence occurs in 42%, diarrhea in 29%, and abdominal pain in 12% (16). These side effects tend to be mild, but can affect compliance to the therapeutic regimen (13). Decreasing an alpha-glucosidase inhibitor dose can decrease side effects (13). Another approach to decreasing side effects is to exchange the immediate release version with the extended release formulation (6).

Similar to metformin drug interactions, alpha-glucosidase inhibitors have interactions requiring therapeutic modification (15,16). The most concerning reactions occur when alpha-glucosidase inhibitors are combined with insulin or sulfonylureas. These combinations require providers to consider therapy modification in their patient's regimens (15,16).

In patients taking alpha-glucosidase inhibitors who have stable glycemic levels and meet treatment goals, HbA1c should be monitored biannually (1). For those patients who do not meet goals, HbA1c should be monitored quarterly (1).

Type 2 diabetes is a difficult disease state to manage. Lifestyle management along with pharmacological therapy allows patients to gain control of blood glucose levels. Initially, metformin is recommended. If this therapy is not successful in lowering glycemic levels other agents, such as alpha-glucosidase inhibitors are considered. Effective treatment of diabetes is highly individualized to each patient.

References:

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2020;43(suppl 1):S1-S110.
2. Preferred drug list. Wyoming Department of Health website. Cheyenne (WY). Wyoming Department of Health; 2020. Available from: <http://wymedicaid.org/pdl>. Accessed: June 22, 2020.
3. Jackson R, Hawa MI, Jaspan JB, et al. Mechanism of metformin action in non-insulin-dependent diabetes. *Diabetes*. 1987;36:632-640.
4. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333:550-554.
5. Pala L, Rotella CM. The “slower” the better. *J Endocrinol Invest*. 2014;37:497-498.
6. Huang W, Castelino RL, Peterson GM. Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to? *Intern Med J*. 2014;44:266-272.
7. Baerlocher MO, Asch M, Myers A. Metformin and intravenous contrast. *CMAJ*. 2013;185:E78.
8. Bailey CJ, Turner RC. Metformin. *N Engl J Med*. 1996;334:574-579.
9. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. *J Clin Endocrinol Metab*. 2016;101:1754-1761.
10. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;2010:CD002967.
11. Metformin. Lexi-Comp Online™. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available from: <http://online.lexi.com> Accessed: June 21, 2020.
12. Meneilly GS, Ryan EA, Radziuk J, et al. Effect of acarbose on insulin sensitivity in elderly patients with diabetes. *Diabetes Care*. 2000;23:1162-1167.
13. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemc control over 3 years (U.K. prospective diabetes study 44). *Diabetes Care*. 1999;22:960-964.
14. Mitrakou A, Tountas N, Raptis AE, et al. Long-term effectiveness of a new alpha-glucosidase inhibitor (BAY m1099-miglitol) in insulin-treated type 2 diabetes mellitus. *Diabet Med*. 1998;15:657-660.
15. Acarbose. Lexi-Drugs. Lexi-Comp Online™. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available from: <http://online.lexi.com>. Accessed: June 22, 2020.
16. Miglitol. Lexi-Drugs. Lexi-Comp Online™. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available from: <http://online.lexi.com>. Accessed: June 22, 2020.

The P&T Committee met for its quarterly business meeting on May 13, 2021

Highlights of this meeting include:

- Dr. Danae Stampfli was chosen by the Committee to replace Dr. Joseph Horam.
- Buprenorphine products will require a diagnosis of opioid dependence or abuse. Doses above 16 mg per day will require prior authorization. All other PA requirements will be removed.
- Gabapentin and pregabalin will be approved for perioperative pain for a maximum of 14 days.
- Orladeyo, Zokinvy, Verquvo, Evkeeza, Lupkynis, Xolair, Fasentra, Nucala and Dupixent will be limited to indication. Amondys-45 will be held to the same criteria as other drugs for Duchenne's muscular dystrophy.

The proposed prior authorization criteria are open for public comment. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board
Dept. 3375, 1000 E. University Avenue
Laramie, WY 82071.

Comments should be received prior to June 15, 2021.

The next P&T Committee meeting will be held August 12, 2021 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Wyoming Drug Utilization Review
University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Avenue
Laramie, WY 82071

June 2021
In This Issue

Type 2 Diabetes Mellitus: Metformin and Alpha-Glucosidase Inhibitors
P&T Committee Meeting Update

Please contact WY-DUR at 307-766-6750 to have your name added or removed from our mailing list, or if you need to update your address. The WY-DUR newsletter is also available on-line at www.uwyo.edu/DUR/newsletters.