

Wyoming Drug Utilization Review

Type 2 Diabetes Mellitus and Pharmacological Therapies

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Type 2 diabetes mellitus (T2DM), previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes¹. This form encompasses individuals who have relative insulin deficiency and have peripheral insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need exogenous insulin treatment to survive¹. The risk factors of T2DM include increased age, obesity, lack of physical activity, hypertension, dyslipidemia, certain racial or ethnic subgroups (African American, American Indian, Hispanic/ Latino, and Asian American), and prior gestational diabetes mellitus¹.

The treatment goal for T2DM is to reach the glycemic target and to prevent cardiovascular (CV) diseases and microvascular complications. Treatment regimens of T2DM include lifestyle modification and pharmacological treatment. First-line therapy of T2DM is metformin and comprehensive lifestyle changes, including weight management and physical activity².

There are multiple classes of medications indicated for T2DM, and a summary is provided in table 1. Subsequent newsletter articles are planned to discuss the classes in further detail. Other FDA-approved agents for T2DM include meglitinides (nateglinide and repaglinide), alpha-glucosidase inhibitor acarbose (Precose[®], and generics) and miglitol (Glyset[®], and generics), the immediate-release formulation of the ergot-derived dopamine agonist bromocriptine mesylate (Cycloset[®]), the bile acid sequestrant colestevlam (Welchol[®], and generics), and the subcutaneously injected amylin mimetic pramlintide (Symlin[®]). None of these agents are recommended as monotherapy and they are minimally effective at reducing A1C (~0.5% reduction)³.

Pharmacological Treatment

2020 American Diabetes Association (ADA) Guidelines recommendations²

1. Metformin should be started when T2DM is diagnosed and continued as long as it is tolerated and not contraindicated.
2. Early combination therapy can be considered in some patients presenting with A1C levels 1.5–2.0% above target.
3. The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or with very high A1C levels (>10%) or blood glucose levels (300 mg/dL).
4. Among patients with T2DM who have established atherosclerotic cardiovascular disease (ASCVD) or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated CV disease and/or kidney disease benefits (Table 2) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors.
5. In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible.

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2020 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Guidelines recommendations⁴

1. Independent of glycemic control, for patients with established ASCVD or high risk, chronic kidney disease, or heart failure with reduced ejection fraction (HFrEF), long acting GLP-1 receptor agonists or SGLT-2 inhibitors with proven efficacy (Table 2) are recommended.
2. For patients with recent-onset T2DM or mild hyperglycemia (A1C <7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.
3. Patients who present with an A1C >7.5% (whether newly diagnosed or not) and who are not already taking any anti-hyperglycemic agents should be started initially on metformin plus another agent in addition to lifestyle therapy.
4. Patients with A1C >9.0% who are symptomatic (presenting with polyuria, polydipsia, or polyphagia) would likely derive the greatest benefit from the addition of insulin, but if presenting without significant symptoms, these patients may initiate therapy with maximum doses of two or three other medications.

Conclusion:

First-line therapy of T2DM is metformin plus lifestyle therapy. Metformin is the preferred initial glucose-lowering medication for most people

with T2DM and should be continued as long as it is tolerated and not contraindicated. Since there are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events, heart failure events, or renal events in patients with T2DM treated with SGLT-2 inhibitors or GLP-1 receptor agonists, these two classes of medications with proven efficacy are recommended to add to treatment regimens for patients with T2DM and indicated diseases.

Medication Classes	Mechanism of action	Common adverse effects	Severe adverse effects	Black box warning/contraindication	Medications in class
Biguanide	Decreases hepatic glucose production; Increases secretion of GLP-1; Reduces intestinal absorption of glucose; Increases peripheral glucose uptake	Gastrointestinal (GI) side effects (bloating, nausea, abdominal discomfort, and diarrhea); Vitamin B ₁₂ deficiency	Lactic acidosis (very high circulating level)	Lactic acidosis CI: eGFR <30 mL/minute/1.73 m ²	Metformin/ER
GLP-1 receptor agonists	Potentiate glucose-dependent secretion of insulin; Suppress glucagon secretion; Slow gastric emptying; Promote satiety	GI side effects (nausea, vomiting, diarrhea); Injection site reactions	Acute pancreatitis	Thyroid C-cell tumors CI: eGFR <30 mL/minute/1.73 m ² (exenatide) and eGFR <15 mL/minute/1.73 m ² (liraglutide); Severe gastrointestinal disease (exenatide, liraglutide); Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia (liraglutide, dulaglutide, exenatide)	Dulaglutide (Trulicity) [*] ; Exenatide (Byetta [*] , Bydureon [*]) [*] ; Liraglutide (Victoza [*]); [*] , ^{**} , ^{**} ; Lixisenatide (Adlyxin [*]) Semaglutide (Ozempic [*] , Rybelsus [*]) [*]
SGLT-2 inhibitors	Decrease renal glucose reabsorption; Increase urinary glucose excretion	Genitourinary infections; Slightly increased LDL-C levels; Volume depletion (may lead to initial renal impairment, hypotension, syncope, and falls)	DKA (rare in T2DM); Acute kidney injury; Fournier's gangrene (rare); Bladder cancer (dapagliflozin); Bone fractures (canagliflozin)	Risk of amputation (canagliflozin) CI: eGFR <30 mL/minute/1.73 m ²	Canagliflozin (Invokana [*]); ^{**} , ^{**} ; Dapagliflozin (Farxiga [*]); ^{**} , ^{**} ; Empagliflozin (Jardiance [*]); ^{**} , ^{**} ; Ertugliflozin (Steglatro [*]) [*]
DPP-4 inhibitors	Potentiate glucose-dependent secretion of insulin; Suppress glucagon secretion	Joint pain	Acute pancreatitis; Increased risk of heart failure (saxagliptin and alogliptin)		Alogliptin (Nesina [*]) Linagliptin (Tradjenta [*]) Saxagliptin (Onglyza [*]) Sitagliptin (Januvia [*]) [*]
TZDs	Increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver; Reduce hepatic glucose production	Weight gain, edema; Anemia; Increased fracture risk; Increased LDL-C level (rosiglitazone)	Congestive heart failure; Bladder cancer (pioglitazone)	Congestive heart failure CI: Heart failure or fluid overload; History of fracture or at high risk for fracture; Active liver disease; Active or history of bladder cancer; Pregnancy	Pioglitazone (Actos[*]) Rosiglitazone (Avandia [*]) [*]
Sulfonylureas (2 nd generation)	Interact with adenosine triphosphate (ATP)-sensitive potassium channels in the pancreatic beta-cell membrane to increase secretion of insulin	Weight gain; Hypoglycemia		Sulfonamide ("sulfa") allergy	Glimepiride/ER Glipizide/ER Glyburide/ER
Insulin	Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats.	Weight gain; Hypoglycemia Injection sites reactions			Various products

Bold: indicates Medicaid preferred medications; ^{*} indicates Medicaid preferred medications with clinical criteria; ^{*} indicates preferred by guidelines for atherosclerotic cardiovascular diseases (ASCVD); ^{**} indicates preferred by guidelines for heart failure; ^{**} indicates preferred by guidelines for kidney disease

Table 2: Characteristics of medication classes for T2DM ^{2,3}

Medication Classes	Route	Efficacy (A1C reduction)	ASCVD benefits	HF benefits	Nephropathy benefits	Hypo-glycemia	Weight change
Biguanide	Oral	1-1.5%	Potential benefits: metformin	Neutral	Neutral	Low risk	Neutral
GLP-1 receptor agonists	Subcutaneous, oral (Rybelsus [®])	1-1.5%	Benefits: liraglutide* semaglutide dulaglutide	Benefits: liraglutide*	Benefits: liraglutide*	Low risk	Loss
SGLT-2 inhibitors	Oral	0.5-1%	Benefits: empagliflozin* canagliflozin	Benefits: dapagliflozin* empagliflozin* canagliflozin	Benefits: canagliflozin empagliflozin* dapagliflozin*	Low risk	Loss
DPP-4 inhibitors	Oral	0.5-1%	Neutral	Potential risk: saxagliptin	Neutral	Low risk	Neutral
TZDs	Oral	1-1.5%	Potential benefits: pioglitazone	Increased risk	Neutral	Low risk	Gain
Sulfonylureas	Oral	1-1.5%	Neutral	Neutral	Neutral	High risk	Gain
Insulin	Subcutaneous, inhale (Afrezza [®])	Most potent	Neutral	Neutral	Neutral	High risk	Gain

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The P&T Committee met for its quarterly business meeting on February 11, 2021

Highlights of this meeting include:

- Dr. Joe Horam will be leaving the Committee after twelve years of service due to term limits defined in the bylaws. His input has been invaluable and he will be greatly missed. A pediatrician will be sought to fill his open position.
- System changes have been completed to allow pharmacies to bill for administration of the COVID-19 vaccination. The updates will be active February 16, 2021 and pharmacies may back bill for vaccinations administered after January 1, 2021.
- Oxlumo will be limited to indication.
- Montelukast (Singulair) dosages will be limited to the labeled maximums. These are 4 mg for children 0–5 years old, 5 mg for 6–14 years and 10 mg for patients 15 years and older.

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 April 15, 2021.

The next P&T Committee meeting will be held May 13, 2021 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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