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Drugs for Type 2 Diabetes

Glucose control is the mainstay of diabetes management. In recent years, a variety of new agents with novel mechanisms of action have been approved for the treatment of type 2 diabetes. While this provides more options for the treatment of these patients, it may lead to confusion as to which agents should be used. In general, both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend that in addition to lifestyle modification, metformin is first-line for the treatment of type 2 diabetes in most patients.[1,2,49] The target A1C concentrations are 7% (ADA) or 6.5% (AACE), but the goal may be individualized in patients with other illnesses and in those at risk for hypoglycemia.[1,2,21] Therapy can be started with more than one agent in patients with an A1C ≥9% (ADA) or ≥7.5% (AACE). However, for patients who fail metformin monotherapy, a broad variety of agents can be used in combination with metformin, or as monotherapy in those who cannot use metformin.[1,2,49] The choice of second-line and third-line agents varies based on patient characteristics, patient preferences, potential adverse effects (e.g., hypoglycemia, weight gain), and cost.[49] The table below summarizes the agents available in the U.S. for the treatment of type 2 diabetes, including expected A1C reduction when added to metformin, cost, adverse effects, and other pertinent information (e.g., frequency of dosing, cardiovascular benefits). For additional details on cardiovascular benefits associated with drugs for type 2 diabetes, see our chart, *Diabetes Medications and Cardiovascular Impact*.

Abbreviations: BID = two times daily; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; MOA = mechanism of action; TID = three times daily; UTI = urinary tract infection.

Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Alpha-glucosidase inhibitors Acarbose (*Precose*, generics) Miglitol (*Glyset*, generics)	0.7% to 0.8% (acarbose) 0.7% (miglitol, when added to sulfonylurea, not metformin)[36] MOA: slows intestinal carbohydrate digestion/absorption.[21,24]	**Acarbose** 300 mg, divided TID (~$50) **Miglitol** 300 mg, divided TID (~$200)	• GI (e.g., flatulence, diarrhea).[23] • Low risk of hypoglycemia when used as monotherapy.[23]	• Weight neutral.[23] • Taken with meals.[24] • Reduces postprandial glucose.[21] • Requires frequent dosing (e.g., TID).[21] • Beneficial in the treatment of prediabetes (acarbose).[9]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Amylin analog Pramlintide (*Symlin*)	~0.36% when added to insulin with or without metformin and/or a sulfonylurea[33] MOA: slows gastric emptying, increases the feeling of fullness, and reduces postprandial glucagon secretion.[21,24]	**Pramlintide** 120 mcg/dose (usually 360 mcg/day; divided, prior to major meals) (~$2,200)	• GI (e.g., nausea, vomiting).[21] • Hypoglycemia rare, unless insulin dose not reduced.[21]	• Weight loss.[21] • Increased feeling of fullness after meal.[21] • Injectable.[21] • Taken immediately before meals.[24] • Reduces postprandial glucose.[21] • Requires frequent dosing.[21]

Biguanide
Metformin (*Glucophage*, *Glucophage XR*, generics)
 	
Available in combination with alogliptin, canagliflozin, dapagliflozin, glimepiride, glipizide, glyburide, linagliptin, pioglitazone, repaglinide, rosiglitazone, saxagliptin, and sitagliptin. See specific agents.
	1%
	
	MOA: inhibits production of glucose, intestinal absorption of glucose, and increases insulin sensitivity in muscle and fat.[21,24]
		Metformin
		2,000 to 2,550 mg, divided BID to TID
		(~$10)
		
		Metformin XR
		2,000 mg to 2,500 mg, divided BID
		(~$15)
			• B12 deficiency.[23,49]
			• GI (e.g., diarrhea, nausea, cramping).[21,23]
			• Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction.[21,24]
			• Low risk of hypoglycemia when used as monotherapy.[23]
				• Weight neutral.[21,23]
				• Ameliorates insulin-associated weight gain.[23]
				• First-line after diet and exercise for most patients.[21]
				• Beneficial in the treatment of prediabetes.[10]
				• May reduce cardiovascular mortality.[42]
				• Safe in patients with stable heart failure and moderate renal impairment:[3,16,25,26]
				  ○ Can be initiated in patients with an eGFR >45 mL/min/1.73m^2.[24]
				  ○ Discontinue if eGFR falls below 30 mL/min/1.73m^2.[24]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Dipeptidyl peptidase-4 (DPP-4) inhibitor ("gliptins") or incretin enhancer Alogliptin (*Nesina*, others, with metformin [*Kazano*], with pioglitazone [*Oseni*]) Linagliptin (*Tradjenta*, with metformin [*Jentadueto*, *Jentadueto XR*], with empagliflozin [*Glyxambi*]) Saxagliptin (*Onglyza*, with metformin [*Kombiglyze XR*], with dapagliflozin [*Qtern*], with metformin and dapagliflozin [*Qternmet XR*]) Sitagliptin (*Januvia*, with metformin [*Janumet*, *Janumet XR*])	0.5% to 0.7% MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, increases sense of fullness, and slows gastric emptying.[21,24]	**Alogliptin** 25 mg (~$195) **Linagliptin** 5 mg (~$440) **Saxagliptin** 5 mg (~$410) **Sitagliptin** 100 mg (~$450)	• May be associated with pancreatitis.[6,21] • New or worsening heart failure (saxagliptin and alogliptin).[7,8,13,17,21,43] • May cause severe joint pain.[12] • Low risk of hypoglycemia when used as monotherapy.[21,23]	• Dosage modification with renal impairment needed (sitagliptin, saxagliptin, alogliptin).[24] • CYP3A4 interactions (saxagliptin, linagliptin).[24] • Reduces postprandial glucose.[44] • Weight neutral.[23] • Generally, well tolerated.[21]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic Dulaglutide (*Trulicity*) Exenatide (*Byetta*) and exenatide extended-release (*Bydureon, Bydureon BCise*) Liraglutide (*Victoza*, with insulin degludec [*Xultophy*]) Lixisenatide (*Adlyxin*, with insulin glargine [*Soliqua*]) Semaglutide (*Ozempic*)	1% (See GLP-1 agonist chart for individual agents) MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, leading to reduced hepatic glucose production and slowed gastric emptying.[21,24]	See our chart, *Comparison of GLP-1 Agonists*, for dosing and cost info.	• GI (diarrhea, nausea).[21] • May be associated with pancreatitis (rare).[6,21] • May be associated with gallbladder disease (liraglutide, exenatide).[18,19] • Low risk of hypoglycemia when used as monotherapy.[21] • May lead to retinopathy complications (semaglutide).[41]	• Weight loss.[21] • Injectable.[21] • Linked to thyroid cell cancer in rats.[21] • Avoid if eGFR <45 mL/min/1.73m^2 (extended-release exenatide) or <30 mL/min/1.73m^2 (immediate-release exenatide).[24] • Reduces postprandial glucose.[21] • CV benefit (albiglutide, liraglutide, semaglutide).[19,22,40] • In patients who need more than one or two diabetes meds, combination therapy with basal insulin and a GLP-1 agonist is an emerging strategy.[1]
Insulin Various	0.9% to 1.2% or more MOA: promotes storage of glucose in muscle and fat tissues, and inhibits production of glucose.[21,24]	No maximum dose[23] See our chart, *Comparison of Insulins*, for cost info.	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] • Highest risk of weight gain.[21,23]	• Consider initial therapy with insulin plus metformin if blood glucose is ≥300 mg/dL and/or A1C is ≥10%.[21]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Meglitinide Nateglinide (*Starlix*, generics) Repaglinide (*Prandin*, others, with metformin [*PrandiMet*])	0.7% to 1.1% MOA: stimulates pancreatic insulin secretion.[21,24]	**Nateglinide** 360 mg, divided TID (~$130) **Repaglinide** 16 mg, divided TID (~$80)	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] • Weight gain.[21]	• Requires frequent dosing.[21] • Reduces postprandial glucose.[21] • Provides flexible dosing (e.g., can hold dose if skipping meal).[21,24] • Consider over sulfonylureas (less hypoglycemia, better postprandial control).[2]
Sodium-glucose co-transporter 2 (SGLT2) inhibitors Canagliflozin (*Invokana*, with metformin [*Invokamet*, *Invokamet XR*]) Dapagliflozin (*Farxiga*, with metformin [*Xigduo XR*], with saxagliptin [*Qtern*], with saxagliptin and metformin [*Qternmet XR*]) *Continued…*	0.4% to 0.7% MOA: blocks glucose reabsorption in the kidney, and increases urinary excretion of glucose.[21,24]	**Canagliflozin** 300 mg (~$495) **Dapagliflozin** 10 mg (~$495) **Empagliflozin** 25 mg (~$495) **Ertugliflozin** 15 mg (~$280)	• Genital fungal (yeast) infections (male/female).[2] • UTI (may be severe), ketoacidosis (rare).[14] • Dizziness, hypotension, hypoglycemia (rare), increased LDL/urination.[21] • Hyperkalemia, especially in patients with renal impairment.[35] • Fractures (rare, in susceptible patients).[4] • Decrease in BMD (canagliflozin).[11] • May be associated with increased risk of bladder cancer (dapagliflozin).[39] • Acute kidney injury, may require dialysis (canagliflozin, dapagliflozin).[15] • May be associated with **acute** pancreatitis (rare).[46,48]	• Weight loss.[21] • Do not use if eGFR <45 mL/min/1.73m^2 (canagliflozin, dapagliflozin, empagliflozin) or <60 mL/min/1.73m^2 (ertugliflozin).[24] • CV benefit (canagliflozin, empagliflozin).[20,37] • Renal benefit (canagliflozin).[50]

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Drug or Drug Class	Expected A1C Drop When Added to Metformin[23] MOA	Maximum Daily Dose[24] (Cost/30 Days)[a]	Notable Adverse Effects	Comments
SGLT2 inhibitors, continued Empagliflozin (*Jardiance*, with linagliptin [*Glyxambi*], with metformin [*Synjardy*, *Synjardy XR*]) Ertugliflozin (*Steglatro*, with metformin [*Segluromet*], with sitagliptin [*Steglujan*])			• Rare cases of Fournier's gangrene in men and women, with onset early (days) and late (~2 years) in therapy.[47] • Amputations may occur in about 6 of every 1,000 patients treated with canagliflozin over 1 year, compared to about 3 in every 1,000 patients on other diabetes meds.[27,37] • Canagliflozin use in patients at high CV risk for about 3.5 years may increase risk of amputations, NNH ~77 [Evidence level A-1].[37,38]	
Sulfonylurea–first generation Chlorpropamide (*Diabinese* [discontinued], generics) Tolazamide (*Tolinase* [discontinued], generics) Tolbutamide (*Orinase* [discontinued], generics)	1% to 1.5% as monotherapy[45] MOA: stimulates pancreatic insulin secretion.[21,24]	**Chlorpropamide** 750 mg[24] (~$70) **Tolazamide** 1,000 mg (doses >500 mg divide BID)[24] (~$170) **Tolbutamide** 3,000 mg (given once daily or divided up to TID)[24] (~$170)	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] ○ More common than with second-generation sulfonylureas.[5] • Weight gain.[5] • Increased CV mortality (tolbutamide).[29]	• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.[1] • Second-generation sulfonylureas preferred over first-generation sulfonylureas, due to lower risk of hypoglycemia.[5] • Relatively short-lived efficacy.[1] • Avoid chlorpropamide in patients with renal dysfunction or the elderly.[24]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**

Sulfonylurea-second generation
Glyburide (*DiaBeta* [discontinued], *Glynase*, *Micronase*, generics, with metformin [*Glucovance*])
 	
Glipizide (*Glucotrol*, *Glucotrol XL*, generics, with metformin [*Metaglip*])
 	
Glimepiride (*Amaryl*, generics, with pioglitazone [*Duetact*], with rosiglitazone [*Avandaryl*])
	0.7% to 1.3%
	
	MOA: stimulates pancreatic insulin secretion.[21,24]
		Glimepiride 8 mg (~$15)
		
		Glipizide IR 40 mg (doses >30 mg should be divided BID) (less than $10)
		
		Glipizide XL 20 mg (~$20)
		
		Glyburide 20 mg (standard formulation; doses >10 mg can divide BID);
		12 mg (micronized product; once daily or in divided doses) (~$20)
			• Hypoglycemia, especially with renal dysfunction (educate patient to prevent, recognize, and manage).[21]
			  ○ Less with glimepiride versus glyburide.[5] Avoid both in the elderly.[51]
			• Weight gain.
			  ○ Less with glipizide and glimepiride versus glyburide.[5]
				• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.[1]
				• Relatively short-lived efficacy.[1]
				• For the elderly and those with hepatic or renal dysfunction, start with low doses and titrate up.[21]

Thiazolidinedione (TZD) Pioglitazone (*Actos*, generics, with metformin [*ACTOplus Met* or *ACTOplus Met XR*], with glimepiride [*Duetact*], with alogliptin [*Oseni*]) *Continued…*	0.8% to 0.9% MOA: increases insulin sensitivity in muscle and fat.[21,24]	**Pioglitazone** 45 mg (less than $10) **Rosiglitazone** 8 mg (~$340)	• Low risk of hypoglycemia when used as monotherapy.[21] • Edema.[21] • Weight gain.[21] • Heart failure.[21] • Increased fracture risk.[21] • Increased LDL (rosiglitazone).[21]	• Glycemic control better sustained over diabetes course than metformin or sulfonylureas.[21] • Pioglitazone may improve lipid profile (e.g., lowers triglycerides).[21] • Avoid in patients with symptomatic heart failure.[21] • CV benefit (pioglitazone).[30]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Thiazolidinedione, continued Rosiglitazone (*Avandia*, with metformin [*Avandamet*])			• Possible increased risk of bladder cancer (pioglitazone). Assess risk factors and counsel patients to report hematuria.[31,34]	
Others – bile acid sequestrant Colesevelam (*Welchol*, generic)	0.5%[32] MOA: may reduce hepatic glucose production, increase incretin levels, and decrease glucose absorption.[21]	**Colesevelam** 3.75 gm, given once daily or divided BID (~$550 [powder for suspension]; ~$260 [tablets])	• GI (e.g., constipation, nausea, bloating).[21] • May increase triglycerides.[21] • Rare hypoglycemia.[21]	• Lowers LDL cholesterol.[21] • May decrease absorption of other meds.[21]
Others – dopamine agonist Bromocriptine (*Cycloset*)	0.5% when added to metformin and a sulfonylurea[28] MOA: may centrally regulate metabolism, increases insulin sensitivity.[21]	**Bromocriptine** 4.8 mg (~$750)	• Fatigue.[21] • Dizziness/syncope.[21] • Nausea.[21] • Rare hypoglycemia.[21]	• Weight neutral.[28] • CYP3A4 interactions.[24]

a. Pricing (for generic when available) based on wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed May 2019.

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In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
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C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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