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## Drugs for Type 2 Diabetes

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*.

Expected A1C Drop When Added to Metformin <sup>23</sup> MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Alpha-glucosidase inhibitors:</b> acarbose ( <i>Precose</i> , generics) and miglitol ( <i>Glyset</i> , generics)			
0.7% to 0.8% (acarbose)  0.7% (miglitol, when added to sulfonylurea, not metformin) <sup>36</sup>  MOA: slows intestinal carbohydrate digestion/absorption. <sup>21,24</sup>	<b>Acarbose</b> 300 mg, divided TID (~\$55)  <b>Miglitol</b> 300 mg, divided TID (~\$200)	<ul style="list-style-type: none"> <li>GI (e.g., abdominal pain, flatulence, diarrhea).<sup>23,24</sup></li> <li>Low risk of hypoglycemia when used as monotherapy.<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>Weight neutral.<sup>23</sup></li> <li>Taken with meals.<sup>24</sup></li> <li>Reduces postprandial glucose.<sup>21</sup></li> <li>Requires frequent dosing (e.g., TID).<sup>21</sup></li> <li>Beneficial in the treatment of prediabetes (acarbose).<sup>9</sup></li> </ul>
<b>Amylin analog:</b> pramlintide ( <i>Symlin</i> )			
~0.36% when added to insulin with or without metformin and/or a sulfonylurea <sup>33</sup>  MOA: slows gastric emptying, increases the feeling of fullness, and reduces postprandial glucagon secretion. <sup>21,24</sup>	<b>Pramlintide</b> 120 mcg/dose (usually 360 mcg/day; divided, prior to major meals) (~\$2,250)	<ul style="list-style-type: none"> <li>GI (e.g., nausea, vomiting).<sup>21</sup></li> <li>Hypoglycemia rare, unless insulin dose not reduced.<sup>21</sup></li> </ul>	<ul style="list-style-type: none"> <li>Weight loss.<sup>21</sup></li> <li>Increased feeling of fullness after meal.<sup>21</sup></li> <li>Injectable.<sup>21</sup></li> <li>Taken immediately before meals.<sup>24</sup></li> <li>Reduces postprandial glucose.<sup>21</sup></li> <li>Requires frequent dosing.<sup>21</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup>  MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Biguanide:</b> metformin ( <i>Glucophage, Glucophage XR</i> , generics). Available in combination with alogliptin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, glipizide, glyburide, linagliptin, pioglitazone, repaglinide, saxagliptin, and sitagliptin. See specific agents.			
1% as monotherapy  MOA: inhibits production of glucose, intestinal absorption of glucose, and increases insulin sensitivity in muscle and fat. <sup>21,24</sup>	<b>Metformin</b> 2,000 to 2,550 mg, divided BID to TID (~\$10)  <b>Metformin XR</b> 2,000 mg to 2,500 mg, divided BID (~\$20)	<ul style="list-style-type: none"> <li>• B12 deficiency.<sup>23,49</sup></li> <li>• GI (e.g., diarrhea, nausea, cramping).<sup>21,23</sup></li> <li>• Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction.<sup>21,24</sup></li> <li>• Low risk of hypoglycemia when used as monotherapy.<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Weight neutral.<sup>21,23</sup></li> <li>• Ameliorates insulin-associated weight gain.<sup>23</sup></li> <li>• First-line after diet and exercise for most patients.<sup>21</sup></li> <li>• Beneficial in the treatment of prediabetes.<sup>10</sup></li> <li>• May reduce cardiovascular mortality.<sup>42</sup></li> <li>• Safe in patients with stable heart failure and moderate renal impairment:<sup>3,16,25,26</sup> <ul style="list-style-type: none"> <li>○ Can be initiated in patients with an eGFR &gt;45 mL/min/1.73m<sup>2</sup>.<sup>24</sup></li> <li>○ Discontinue if eGFR falls below 30 mL/min/1.73m<sup>2</sup>.<sup>24</sup></li> </ul> </li> </ul>
<b>Dipeptidyl peptidase-4 (DPP-4) inhibitor (“gliptins”) or incretin enhancer:</b> <ul style="list-style-type: none"> <li>• alogliptin (<i>Nesina</i>, generics, with metformin [<i>Kazano</i>], with pioglitazone [<i>Oseni</i>])</li> <li>• linagliptin (<i>Tradjenta</i>, with metformin [<i>Jentadueto, Jentadueto XR</i>], with empagliflozin [<i>Glyxambi</i>], with metformin and empagliflozin [<i>Trijardy XR</i>])</li> <li>• saxagliptin (<i>Onglyza</i>, with metformin [<i>Kombiglyze XR</i>], with dapagliflozin [<i>Qtern</i>])</li> <li>• sitagliptin (<i>Januvia</i>, with metformin [<i>Janumet, Janumet XR</i>], with ertugliflozin [<i>Steglujan</i>])</li> </ul>			
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. <sup>21,24</sup>	<b>Alogliptin</b> 25 mg (~\$195)  <b>Linagliptin</b> 5 mg (~\$460)  <b>Saxagliptin</b> 5 mg (~\$425)  <b>Sitagliptin</b> 100 mg (~\$475)	<ul style="list-style-type: none"> <li>• May be associated with pancreatitis.<sup>6,21</sup></li> <li>• New or worsening heart failure (saxagliptin and alogliptin).<sup>7,8,13,17,21,43</sup></li> <li>• May cause severe joint pain.<sup>12</sup></li> <li>• Low risk of hypoglycemia when used as monotherapy.<sup>21,23</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Dosage modification with renal impairment needed (sitagliptin, saxagliptin, alogliptin).<sup>24</sup></li> <li>• CYP3A4 interactions (saxagliptin, linagliptin).<sup>24</sup></li> <li>• Reduces postprandial glucose.<sup>44</sup></li> <li>• Weight neutral.<sup>23</sup></li> <li>• Generally, well tolerated.<sup>21</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup>  MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic:</b> <ul style="list-style-type: none"> <li>dulaglutide (<i>Trulicity</i>)</li> <li>exenatide (<i>Byetta</i>) and exenatide extended-release (<i>Bydureon, Bydureon BCise</i>)</li> <li>liraglutide (<i>Victoza</i>, with insulin degludec [<i>Xultophy</i>])</li> <li>lixisenatide (<i>Adlyxin</i>, with insulin glargine [<i>Soliqua</i>])</li> <li>semaglutide (<i>Ozempic, Rybelsus</i>)</li> </ul>			
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. <sup>21,24</sup>	See our chart, <i>Comparison of GLP-1 Agonists</i> , for dosing and cost info.	<ul style="list-style-type: none"> <li>GI (diarrhea, nausea).<sup>21</sup></li> <li>May be associated with pancreatitis (rare).<sup>6,21</sup></li> <li>May be associated with gallbladder disease (liraglutide, exenatide).<sup>18,19</sup></li> <li>Low risk of hypoglycemia when used as monotherapy.<sup>21</sup></li> <li>May lead to retinopathy complications (semaglutide).<sup>41</sup></li> </ul>	<ul style="list-style-type: none"> <li>Weight loss.<sup>21</sup></li> <li>Injectable.<sup>21</sup></li> <li>Linked to thyroid cell cancer in rats.<sup>21</sup></li> <li>Avoid if eGFR &lt;45 mL/min/1.73m<sup>2</sup> (extended-release exenatide), &lt;30 mL/min/1.73m<sup>2</sup> (immediate-release exenatide), or &lt;15 mL/min/1.73m<sup>2</sup> (lixisenatide).<sup>24</sup></li> <li>Reduces postprandial glucose.<sup>21</sup></li> <li>CV benefit (albiglutide, dulaglutide, liraglutide, semaglutide).<sup>19,22,39,40,62</sup></li> <li>Renal benefit (liraglutide, semaglutide).<sup>19,40,53</sup></li> <li>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.<sup>1</sup></li> </ul>
<b>Insulin:</b> various			
0.9% to 1.2% or more  MOA: promotes storage of glucose in muscle and fat tissues, and inhibits production of glucose. <sup>21,24</sup>	No maximum dose. <sup>23</sup> See our chart, <i>Comparison of Insulins</i> , for cost info.	<ul style="list-style-type: none"> <li>Hypoglycemia (educate patient to prevent, recognize, and manage).<sup>21</sup></li> <li>Highest risk of weight gain.<sup>21,23</sup></li> </ul>	<ul style="list-style-type: none"> <li>Consider initial therapy with insulin plus metformin if blood glucose is <math>\geq 300</math> mg/dL and/or A1C is <math>\geq 10\%</math>.<sup>21</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup>  MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Meglitinide:</b> nateglinide ( <i>Starlix</i> , generics) and repaglinide ( <i>Prandin</i> [discontinued], generics, with metformin [ <i>PrandiMet</i> (discontinued), generics])			
0.7% to 1.1%  MOA: stimulates pancreatic insulin secretion. <sup>21,24</sup>	<b>Nateglinide</b> 360 mg, divided TID (~\$65)  <b>Repaglinide</b> 16 mg, divided TID (~\$35)	<ul style="list-style-type: none"> <li>• Hypoglycemia (educate patient to prevent, recognize, and manage).<sup>21</sup></li> <li>• Weight gain.<sup>21</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Requires frequent dosing.<sup>21</sup></li> <li>• Reduces postprandial glucose.<sup>21</sup></li> <li>• Provides flexible dosing (e.g., can hold dose if skipping meal).<sup>21,24</sup></li> <li>• Consider over sulfonylureas (less hypoglycemia, better postprandial control).<sup>2</sup></li> </ul>
<b>Sodium-glucose co-transporter 2 (SGLT2) inhibitors:</b> <ul style="list-style-type: none"> <li>• canagliflozin (<i>Invokana</i>, with metformin [<i>Invokamet</i>, <i>Invokamet XR</i>])</li> <li>• dapagliflozin (<i>Farxiga</i>, with metformin [<i>Xigduo XR</i>], with saxagliptin [<i>Qtern</i>])</li> <li>• empagliflozin (<i>Jardiance</i>, with linagliptin [<i>Glyxambi</i>], with metformin [<i>Synjardy</i>, <i>Synjardy XR</i>], with linagliptin and metformin [<i>Trijardy XR</i>])</li> <li>• ertugliflozin (<i>Steglatro</i>, with metformin [<i>Segluromet</i>], with sitagliptin [<i>Steglujan</i>])</li> </ul>			
0.4% to 0.7%  MOA: blocks glucose reabsorption in the kidney, and increases urinary excretion of glucose. <sup>21,24</sup>	<b>Canagliflozin</b> 300 mg (~\$520)  <b>Dapagliflozin</b> 10 mg (~\$520)  <b>Empagliflozin</b> 25 mg (~\$520)  <b>Ertugliflozin</b> 15 mg (~\$295)	<ul style="list-style-type: none"> <li>• Genital fungal (yeast) infections (male/female).<sup>2</sup></li> <li>• UTI (may be severe), ketoacidosis (rare).<sup>14</sup></li> <li>• Dizziness, hypotension, hypoglycemia (rare), increased LDL/urination, volume depletion.<sup>21,54</sup></li> <li>• Hyperkalemia (canagliflozin), especially with high baseline potassium and renal impairment.<sup>35</sup></li> <li>• Fractures (rare, in susceptible patients).<sup>4</sup></li> <li>• Decrease in BMD (canagliflozin).<sup>11</sup></li> <li>• Acute kidney injury, may require dialysis.<sup>15,24</sup></li> <li>• May be associated with acute pancreatitis (rare).<sup>46,48</sup></li> <li>• Fournier's gangrene (rare; in men and women). Onset: days to years into therapy.<sup>47</sup></li> <li>• May be associated with rare amputations (canagliflozin).<sup>27</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Weight loss.<sup>21</sup></li> <li>• Do not use if eGFR &lt;45 mL/min/1.73m<sup>2</sup> (not recommended: <b>dapagliflozin</b> and <b>empagliflozin</b> [for diabetes; contraindicated &lt;30 mL/min/1.73m<sup>2</sup>], or &lt;30 mL/min/1.73m<sup>2</sup> (<b>dapagliflozin</b> [for heart failure, due to insufficient data], <b>canagliflozin</b> [may continue at 100 mg/day in patients with albuminuria &gt;300 mg/day when NOT using for glycemic control], <b>ertugliflozin</b>).<sup>24</sup></li> <li>• CV benefit (canagliflozin, dapagliflozin, empagliflozin).<sup>18,20,37,38,50,55,56,59-61</sup></li> <li>• Renal benefit (canagliflozin, dapagliflozin, empagliflozin).<sup>50,55,57,58</sup></li> <li>• Consider using with caution in patients with a history of amputation or an active peripheral arterial ulcer, especially canagliflozin.<sup>27,52</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup>  MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Sulfonylurea–first generation:</b> <ul style="list-style-type: none"> <li>chlorpropamide (<i>Diabinese</i> [discontinued], generics)</li> <li>tolazamide (<i>Tolinase</i> [discontinued], generics)</li> <li>tolbutamide (<i>Orinase</i> [discontinued], generics)</li> </ul>			
1% to 1.5% as monotherapy <sup>45</sup>  MOA: stimulates pancreatic insulin secretion. <sup>21,24</sup>	<b>Chlorpropamide</b> 750 mg <sup>24</sup> (~\$100)  <b>Tolazamide</b> 1,000 mg (daily doses >500 mg divide BID) <sup>24</sup> (~\$170)  <b>Tolbutamide</b> 3,000 mg (given once daily or divided up to TID) <sup>24</sup> (~\$170)	<ul style="list-style-type: none"> <li>Hypoglycemia (educate patient to prevent, recognize, and manage).<sup>21</sup> <ul style="list-style-type: none"> <li>More common than with second-generation sulfonylureas.<sup>5</sup></li> </ul> </li> <li>Weight gain.<sup>5</sup></li> <li>Increased CV mortality (tolbutamide).<sup>29</sup></li> </ul>	<ul style="list-style-type: none"> <li>Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.<sup>1</sup></li> <li>Second-generation sulfonylureas preferred over first-generation sulfonylureas, due to lower risk of hypoglycemia.<sup>5</sup></li> <li>Relatively short-lived efficacy.<sup>1</sup></li> <li>Avoid chlorpropamide in patients with renal dysfunction or the elderly.<sup>24</sup></li> </ul>
<b>Sulfonylurea-second generation</b> <ul style="list-style-type: none"> <li>glyburide (<i>DiaBeta</i> [discontinued], <i>Glynase</i>, <i>Micronase</i> [discontinued], generics, with metformin [<i>Glucovance</i>, generics])</li> <li>glipizide (<i>Glucotrol</i>, <i>Glucotrol XL</i>, generics, with metformin [<i>Metaglip</i>, generics])</li> <li>glimepiride (<i>Amaryl</i>, generics, with pioglitazone [<i>Duetact</i>, generics], with rosiglitazone [<i>Avandaryl</i>])</li> </ul>			
0.7% to 1.3%  MOA: stimulates pancreatic insulin secretion. <sup>21,24</sup>  <i>Continued...</i>	<b>Glimepiride</b> 8 mg (~\$15)  <b>Glipizide IR</b> 40 mg (daily doses >30 mg should be divided BID) (less than \$10)  <b>Glipizide XL</b> 20 mg (~\$25)	<ul style="list-style-type: none"> <li>Hypoglycemia, especially with renal dysfunction (educate patient to prevent, recognize, and manage).<sup>21</sup> <ul style="list-style-type: none"> <li>Less with glimepiride versus glyburide.<sup>5</sup> Avoid both in the elderly.<sup>51</sup></li> </ul> </li> <li>Weight gain.             <ul style="list-style-type: none"> <li>Less with glipizide and glimepiride versus glyburide.<sup>5</sup></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.<sup>1</sup></li> <li>Relatively short-lived efficacy.<sup>1</sup></li> <li>For the elderly and those with hepatic or renal dysfunction, start with low doses and titrate up.<sup>21</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup>  MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Sulfonylurea-second generation, continued</b>			
	<p><b>Glyburide</b> (standard) 20 mg (daily doses &gt;10 mg can be divided BID) (~\$25)</p> <p><b>Glyburide</b> (micronized) 12 mg (once daily or in divided doses) (~\$5)</p>		
<b>Thiazolidinedione (TZD)</b>			
<ul style="list-style-type: none"> <li>pioglitazone (<i>Actos</i>, generics, with metformin [<i>ACTOplus Met</i> or <i>ACTOplus Met XR</i>], with glimepiride [<i>Duetact</i>, generics], with alogliptin [<i>Oseni</i>, generics])</li> <li>rosiglitazone (<i>Avandia</i>, with metformin [<i>Avandamet</i>])</li> </ul>			
<p>0.8% to 0.9%</p> <p>MOA: increases insulin sensitivity in muscle and fat.<sup>21,24</sup></p>	<p><b>Pioglitazone</b> 45 mg (less than \$10)</p> <p><b>Rosiglitazone</b> 8 mg (~\$340)</p>	<ul style="list-style-type: none"> <li>Low risk of hypoglycemia when used as monotherapy.<sup>21</sup></li> <li>Edema.<sup>21</sup></li> <li>Weight gain.<sup>21</sup></li> <li>Heart failure.<sup>21</sup></li> <li>Increased fracture risk.<sup>21</sup></li> <li>Increased LDL (rosiglitazone).<sup>21</sup></li> <li>Possible increased risk of bladder cancer (pioglitazone). Assess risk factors and counsel patients to report hematuria.<sup>31,34</sup></li> </ul>	<ul style="list-style-type: none"> <li>Glycemic control better sustained over diabetes course than metformin or sulfonylureas.<sup>21</sup></li> <li>Pioglitazone may improve lipid profile (e.g., lowers triglycerides).<sup>21</sup></li> <li>Avoid in patients with symptomatic heart failure.<sup>21</sup></li> <li>CV benefit (pioglitazone).<sup>30</sup></li> </ul>

Expected A1C Drop When Added to Metformin <sup>23</sup> MOA	Maximum Daily Dose <sup>24</sup> (Cost/30 Days) <sup>a</sup>	Notable Adverse Effects	Comments
<b>Others – bile acid sequestrant:</b> colesevelam ( <i>Welchol</i> , generics)			
0.5% <sup>32</sup> MOA: may reduce hepatic glucose production, increase incretin levels, and decrease glucose absorption. <sup>21</sup>	<b>Colesevelam</b> 3.75 gm, given once daily or divided BID (~\$450 [powder for suspension]; ~\$160 [tablets])	<ul style="list-style-type: none"> <li>• GI (e.g., constipation, nausea, bloating).<sup>21</sup></li> <li>• May increase triglycerides.<sup>21</sup></li> <li>• Rare hypoglycemia.<sup>21</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Lowers LDL cholesterol.<sup>21</sup></li> <li>• May decrease absorption of other meds.<sup>21</sup></li> </ul>
<b>Others – dopamine agonist:</b> bromocriptine ( <i>Cycloset</i> )			
0.5% when added to metformin and a sulfonyleurea <sup>28</sup> MOA: may centrally regulate metabolism, increases insulin sensitivity. <sup>21</sup>	<b>Bromocriptine</b> 4.8 mg (~\$800)	<ul style="list-style-type: none"> <li>• Fatigue.<sup>21</sup></li> <li>• Dizziness/syncope.<sup>21</sup></li> <li>• Nausea.<sup>21</sup></li> <li>• Rare hypoglycemia.<sup>21</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Weight neutral.<sup>28</sup></li> <li>• CYP3A4 interactions.<sup>24</sup></li> </ul>

a. Pricing (for generic when available) based on wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed October 2020.

**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.

*Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.*

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