Oral Medication Options for Type 2 Diabetes

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Biguanides – decreases hepatic glucose production and intestinal absorption of glucose and improve insulin sensitivity. Advantage: inexpensive.

Examples & A1c Reduction	Side Effects	Precautions	Dosing	Considerations
-Metformin (Glucophage® XR, Glumetza® – VERY expensive) generic ER formulations available in 500 mg ER only (use ER, $4 WalMart #60) *Potential A1c decrease ~1.5%*	GI upset 9.6-12.5%; start at lower doses and increase as patient tolerates), vitamin B-12 depletion with long-term use can occur	-Heart Failure, contrast dye, alcoholism, >80 years old, lactic acid predisposition especially in CKD, hepatic disease.	-Initiation: 500-850 mg ER once daily to BID with food -Titration: 500 mg, every 7 days; 850 mg, every 14 days -Max dose 2000 mg -Use half dose for CrCl 30-60 mL/min	-Requires patient have adequate endogenous insulin -Low risk of hypoglycemia -Weight neutral -Positive CVD association

Sulfonylureas & Meglitinides – stimulates insulin release from the pancreatic β cells. Advantage: low cost. Meglitinides - short half-life and less hypoglycemia.

Examples & A1c Reduction	Side Effects	Precautions	Dosing*	Considerations
-Glyburide (Micronase®, -Diabeta®) – avoid in elderly -Glipizide (Glucotrol®) -Glimepiride (Amaryl®) *(long duration of action)* -Nateglinide (Starlix®) -Repaglinide (Prandin®) *(short duration of action)* *Potential A1c decrease ~1%*	Dizziness 2-7%, hypoglycemia 3.4%, more frequent in elderly, headache 8%, photosensitivity < 1%, constipation, diarrhea, flatulence 3%, nausea, tremor 3-4%, nervousness 3-4%	-Hypoglycemia unawareness may occur (pts. taking beta-blockers at increased risk) -Caution with renal or hepatic impairment	-Glipizide: initial 2.5 mg (5 mg for XL formulation), 20 mg -Glyburide: initial 1.25-5 mg -Glimepiride: initial 1-2mg, max 8 mg -Max dose: minimal benefit & higher risk of unexpected hypoglycemia -Starlix®: 60-120 mg before meals -Prandin®: 0.5, 1, 2 mg before meals dose 1 to 30 minutes prior to meal	-Glyburide: avoid due to long duration of action & drug accumulation further worsened with poor CrCl -CV side effects linked with undetected hypoglycemia -May overwork beta cell

DPP-4 Inhibitor* – inhibits dipeptidyl peptidase from breaking down GLP (some refer to as "gliptins"). Advantage: well tolerated, works at a unique mechanism of GLP but is a relatively weak GLP agonist compared to injectable GLP agents. Some concern about hospitalization for heart failure with alogliptin and saxagliptin.

Examples & A1c Reduction	Side Effects	Precautions	Dosing	Considerations
-Sitagliptin (Januvia®) -Alogliptin (Nesina®) -Linagliptin (Tradjenta®) -Saxagliptin (Onglyza®) *Combo*s Metformin (Met): -Sitagliptin/Met (Janumet® & Janumet XR) -Alogliptin/Met (Kazano®) -Linagliptin/Met (Jentadueto®) -Saxagliptin/Met (Kombiglyze® XR), Sitagliptin/Ertugliflozin (Steglujan®) *Potential A1c decrease ~0.5 to 1.0%*	Headache 1.1-5.9%, infection (urinary 3.1%, respiratory 4.5%) Rare cases of pancreatitis (2.3%) reported with these meds, do not use if previous pancreatitis or very high triglyceride levels	-Use lower doses in renal insufficiency for Sitagliptin, Saxagliptin, and Alogliptin, -Linagliptin is hepatically metabolized and does not need adjustment for renal insufficiency -Warnings added to PI for alogliptin & saxagliptin for increased hospitalizations for HF, particularly in patients who already have CVD or CKD	-Sitagliptin: 100 mg daily, 50 mg daily in CrCl 30-50 ml/min, 25 mg <30 ml/min Saxagliptin: 5 mg daily, 2.5 mg daily if CrCl ≤50 ml/min - ESRD -Linagliptin: 5 mg daily, ESRD (no adjustment needed) -Alogliptin: 25 mg daily, 12.5 mg in CrCl 30-60, 6.25 mg daily if CrCl <30 ml/min - ESRD -Janumet®: 50 mg/500, 50 mg/1000 mg BID, XR dose daily -Kazano®: 12.5 mg/500, 12.5 mg/1000 mg -Jentadueto® 2.5/500, 2.5/850, 2.5/1000 BID, XR dose daily 2.5/1000 or 5/1000 mg -Kombiglyze® XR: 5 mg/500 mg, 5 mg/1000 mg, 2.5 mg/1000 mg daily	-Expensive without insurance), works better early in disease state -Check for manufacturer coupon cards -Dosing available for End Stage Renal Disease (ESRD) – dose after dialysis

Over the Counter – Cinnamon 2 to 4 grams and Chromium 200 to 400 mcg daily in divided doses (combo products available) used in early type 2 diabetes close to A1c goal. No data available of effects on anticoagulation in patients on warfarin using high dose Cinnamon.

SGLT-2 Inhibitors* – selectively inhibits sodium glucose transport in proximal tubule, causing reduction in glucose due to glucosuria. Advantages: lowers BP; weight loss; low hypoglycemia, rare cases of euglycemic ketoacidosis reported so careful selection of appropriate patients necessary, hydration very important

Examples & A1c Reduction	Side Effects	Precautions	Dosing	Considerations
-Canagliflozin (Invokana®) -Dapagliflozin (Farxiga®) -Empagliflozin (Jardiance®) -Ertugliflozin (Steglatro®) Combo DPP-4 Linagliptin: Empagliflozin/Linagliptin (Glyxambi®) Dapagliflozin/Saxagliptin (QTERN®) Ertagluflozin/Sitagliptin (Steglujan®) Combos with Metformin: -Empagliflozin/Metformin (Synjardy®) -Canagliflozin/Metformin (Invokamet®) -Dapagliflozin/Metformin XR (Xigduo®), -Metformin/Ertugliflozin (Segluromet®) *A1c decrease ~0.6 to 0.84%, SGLT-2/Metformin combo A1c decrease ~0.8 to 2%*	-Genital mycotic infections women 5.4-12.2% and men 1.6-4.2%, volume depletion 0.3-4.4% -Precaution: Lower limb amputations: canagliflozin (6.3%) and ertugliflozin (0.1-0.5%), continue to monitor literature & risk -SGLT-2/Metformin combo: Lactic acidosis (rare), hypoglycemia (1-2%), GI upset (abdominal pain 2%, constipation 2%, increased thirst 3%, nausea 3%)	-Hypotension – assess volume status, correct hypovolemia in renal impaired, elderly, and low SBP or if on diuretics, ACEI/ ARB are being used, monitor fluid status -Not for use in type 1 diabetes and/or in people with increased ketones in blood or urine	-Invokana® 100 mg daily up to 300 mg if no renal issues, 100 mg in eGFR 30 to 60 ml/min/1.73 m2, if <30 initiation not recommended but dose can be continued -Invokamet®: 50 mg/500 mg, 50 mg/1000 mg, 150 mg/500 mg, 150 mg/1000 mg -Farxiga® 5-10 mg daily, eGFR >25 ml/min. eGFR <25 ml/min do not initiate, Oksy to continue if already on 10 mg daily -QTERN® 5/5 mg daily, eGFR >45 ml/min -Jardiance® 10 mg daily up to 25 mg if eGFR >30 ml/min -Glyxambi® 10 mg/5 mg, 25 mg/5 mg -Synjardy® 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/1000 mg BID, or Synjardy XR daily -Trijardy: Jardiance 5 or 10 mg/Linagliptin 2.5 or 5 mg/Metformin 1000 or 2000 mg -Xigduo® XR 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, 10 mg/1000 mg -Steglatro® 5 mg-15 mg QD -Steglujan® 5mg/100mg, 15mg/100mg QD -Segluromet® 2.5mg/500, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg – BID dosing	-SGLT2 contraindicated in dialysis or hypersensitivity -Invokana® - Approved to reduce risk of ESRD, doubling of SCr, CV death & hospitalization for HF. -Jardiance® approved to reduce risk of CV death & hospitalization for HF, nonfatal MI & stroke in established CVD, diabetic kidney disease can continue up to a eGFR of 30 ml/min. -Farxiga® approved to reduce the risk of sustained eGFR decline, ESRD, CVD death and hospitalization for HF in adults with CKD. decrease HF hospitalizations in CVD or multiple CV risk. Jardiance approved HF w/reduced EF -Avg. wt loss 3.5 to 4.5 lbs.

Thiazolidinedione (TZD) – peroxisome proliferator-activated (PRAR) receptor gamma agonist affects and gene production of insulin receptors. Insulin sensitivity is elevated primarily in the muscle and adipose. Advantage: may beneficially affect lipid profile (decreased triglycerides and increased HDL). Inexpensive.

Examples & A1c Reduction	Major SE's	Precautions	Dosing	Considerations
-Pioglitazone (Actos®) Combo metformin ActosPlus Met® 15/500, 15/850 -Rosiglitazone (Avandia®) *Potential A1c decrease ~0.5 to 1.4%*	-Weight gain, edema 3-5%, CVD risk worrisome, bladder cancer correlations, fractures, and macular edema reported -Avandia not only available on compassionate basis	-Do not use in patients with Class III or IV heart failure due to fluid retention or liver disease (transaminases >2.5 upper limit) -Pioglitazone may increase risk of bladder cancer, do not use in current or past bladder cancer	-Actos® 15 mg daily (more edema with higher dosing) *Generic available* -ActosPlus Met® 15/500 mg daily	Patient weight gain, requires adequate endogenous insulin, may increase plasma volume, takes 6 to 12 weeks to see full effectiveness on glucose lowering

Oral GLP-1: Semaglutide (Rybelsus®), 3 mg titration dose x 30 days, 7 mg and 14 mg for type 2 diabetes in adults. GI side effects - 7 mg 32%, 14 mg 41%, placebo 21%. Take at least 30 minutes before first food, beverage, or other oral medications with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking Rybelsus® with food, beverages (other than plain water) or oral medications will decreasing its absorption. ~5.5 weight loss. Swallow tablets whole. Do not split, crush, or chew tablets and protect from moisture. Contraindicated in patients with history of MTC or in multiple endocrine neoplasia.
Less Frequently Used Rx Agents - Bile acid sequestrant, colesevelam (Welchol®) 625 mg large tablets, 6 daily (potential GI side effect profile). -Bromocriptine (D2 recpetor agonist) dosed 0.8 mg up to 4.8 mg daily (may be some CNS adverse reactions and should not be used in orthostatic hypotension). - Alpha glucosidase inhibitor Acarbose (Precose®), Miglitol (Glyset®) - decreases hydrolysis of ingested complex carbohydrates and disaccharides and absorption of glucose. Can cause abdominal pain, diarrhea (33%) and flatulence (77%), possible increases in liver function tests, TID dosing with meals. Low cost generic.