

What's New in Oral Diabetes Medicines? Non-Insulin Injectables?

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Disclosure to Participants

- Nothing to disclose

Learning Objectives

- Describe the general treatment approaches for glycemic control (hyperglycemia) in people with type 2 diabetes.
- Review the different types of medications people with type 2 diabetes can use for glycemic control.
- Describe the mechanism of action and unique characteristics of the various classes of type 2 diabetes medications.
- Discuss warnings, precautions for use, and side effect profiles of these medications. Describe general dosing principles for the oral and non-insulin injectable medications.
- Review how to tailor a person's medication regimen based on patient-specific factors.

Medication Treatment Options To 2000

- Insulin (human and analogs)
- Sulfonylureas (1950's)
- Biguanides (metformin 12/94)
- Alpha-glucosidase inhibitors (Acarbose 9/95)
- Meglitinides or "Glinides" (Repaglinide 12/97; Nateglinide 12/00)
- Thiazolidinediones (Rosiglitazone 5/99; Pioglitazone 7/99)

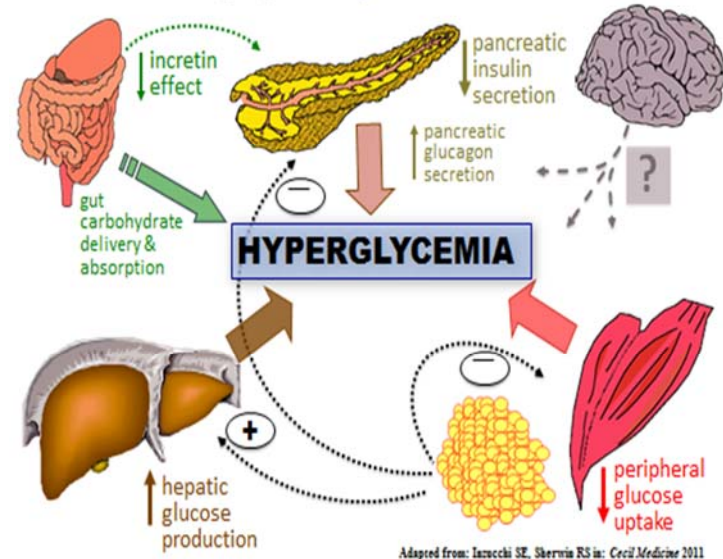
Medication Treatment Options Since 2005

- Amylin (pramlintide)
- **Glucagon-like peptide receptors agonists (GLP-1 RAs)**
- **Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)**
- Bile acid sequestrants (colesevelam)
- Dopamine agonist (bromocriptine)
- **Sodium-glucose cotransporter- 2 inhibitors (SGLT-2 inhibitors)**
- **Combinations of medications**



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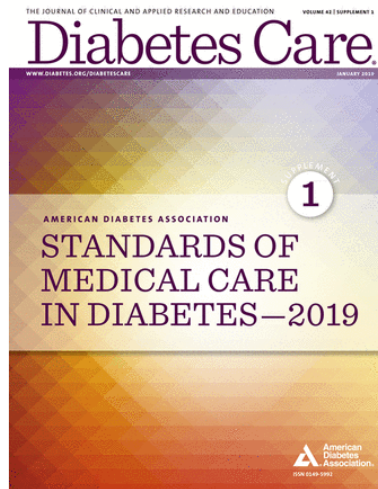
Main Pathophysiological Defects in T2DM



Type 2 Diabetes Pharmacotherapy: Overview and Oral Medications (Part 1)

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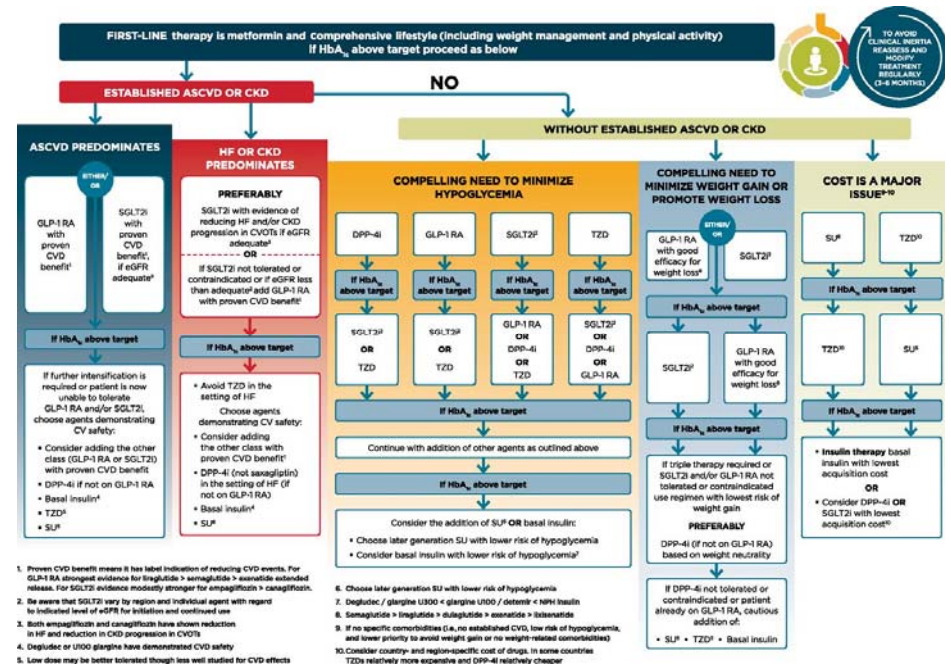
STANDARDS OF MEDICAL CARE IN DIABETES



<https://professional.diabetes.org/content/page/practice-guidelines-resources>

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2019; 42 (Suppl. 1): S90-S102.

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Medication Considerations



- Existing conditions
 - Atherosclerotic cardiovascular disease/ASCVD (heart disease, peripheral arterial disease, cerebrovascular disease)
 - Heart failure
 - Chronic kidney disease
- What is the A1C goal? How much expected ↓ A1C?
- Mechanism of action (how the medication works)
- Risk of low blood glucose (hypoglycemia)
- Side effect profile (e.g., potential for weight gain/loss)
- Conditions that may preclude use (warning vs. precaution for use) such as liver or kidney disease
- Cost

Why Metformin is 1st Line?



- Shown to have long-term impact on diabetes complications
- Decreases sugar release from the liver (hepatic glucose output)
- Reduce A1C 1-2%
- Advantages: no weight gain; no low blood sugar when used alone; inexpensive

Metformin, cont'd



- Dosing
 - Take with meals and/or at bedtime
 - Taking with food may reduce stomach upset & diarrhea
 - Dose is *increased slowly* generally to target of 1500 mg daily (therapeutic max is 2000 mg)
 - Side effects: diarrhea, nausea, cramping, metallic taste, lactic acidosis (rare), vit B₁₂ deficiency
 - Extended-release formulation available

Metformin, cont'd



- Avoid use in:
 - Severe kidney disease (glomerular filtration rate <30 ml/min)
 - Active liver disease
 - Heart failure, unstable
 - Other serious medical problems (such as severe lung disease, blood infection, conditions of acidosis)
 - Excessive alcohol use or alcoholism

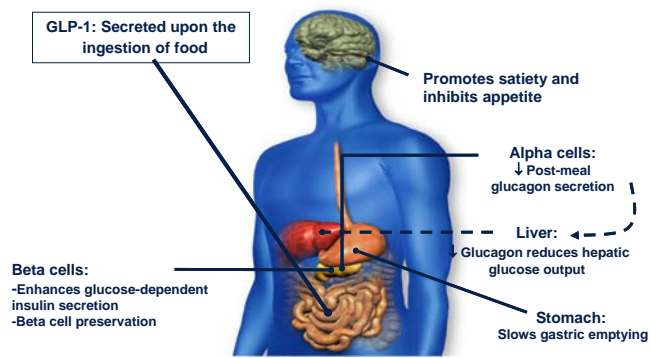
Sulfonylureas (glyburide, glipizide, glimepiride)

- Available for use since the late 1950's
- Stimulate the pancreas to release insulin
- Dosing
 - Taken once or twice daily
 - Start with low dose and increase as required for glucose control
- Side effects: hypoglycemia, weight gain
- Certain SFUs used in elderly or if have kidney disease to lower risk of hypoglycemia: glipizide

Meglitinides (repaglinide, nateglinide)

- Stimulate the pancreas to release insulin
- Fast-acting and help control BG at mealtime
- Taken right before eating a meal (within 30 minutes)
- Effect doesn't last as long as SFUs
- Effect on FBG and A1C similar to SFUs (nateglinide less)
- Option in severe kidney disease or erratic eating habits

Actions of GLP-1 Hormone : Incretins



GLP-1 RAs

	Exenatide (Byetta)	Liraglutide* (Victoza)	Lixisenatide (Adlyxin)	Exenatide XR (Bydureon BCise)	Dulaglutide (Trulicity)	Semiglutide (Ozempic)
FDA Approved	2005	2010	2016	2012	2014	2017
Admin	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly

- Analogs of human GLP-1. Resistant to DPP-4 breakdown.
- Preferential use in ASCVD

*FDA indication: "to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease"



GLP-1 RAs, cont'd



- Reduce A1C ~1-1.2%
- Advantages: weight loss, no hypoglycemia (unless with SFU or insulin)
- SEs: nausea/vomiting/diarrhea (↓ over time; dose slowly increased); injection site reaction
- Avoid in:
 - Severe kidney problems (GFR <30 ml/min)
 - Do not use with severe GI disease (e.g., gastroparesis)
- Do not use if personal or family history of MTC (medullary thyroid cancer) or multiple endocrine neoplasia syndrome type 2 (MEN 2)

DPP-4 Inhibitors



	Sitagliptin (Januvia)	Saxagliptin (Onglyza)	Linagliptin (Tradjenta)	Alogliptin (Nesina)
FDA Approved	2006	2009	2011	2013
Dosing frequency (dose is not titrated)	daily	daily	daily	daily

- Inhibit DPP-4 and slow breakdown of the body's incretins (GIP, GLP-1). Primary actions:
 - Increase insulin release (glucose-dependent)
 - Reduce post-meal levels of glucagon, which then reduces hepatic glucose output
- Vary with respect to caution in kidney problems and drug-drug interaction potential
- Reduce A1C 0.4-0.8%
- Advantages: oral; weight neutral; little nausea or hypoglycemia
- SEs: nausea; joint pain

Incretin Therapy and Pancreatitis



- Low risk of pancreatitis
 - Difficult to determine due to:
 - Extremely low event rate
 - Type 2 DM associated with 3-fold increased risk
- Do not use if history of pancreatitis; stones in gallbladder, alcoholism, or significantly elevated blood triglycerides
- What to look out for: abdominal pain (persistent, severe, radiating to back, N/V, anorexia) to contact your provider

SGLT-2 Inhibitors



- Inhibit sodium glucose cotransporter-2 in proximal tubules of the kidneys, where responsible for reabsorption of ~90% of glucose filtered through nephron
- Reduce A1C 0.8-1%
- Common side effects: genital yeast infections and UTIs (bladder infections) due to increased glucose in urine
- Increased chance for dehydration, lower blood pressure, dizziness in 1st few months (diuretic effect)
- Risk of bone fractures
- Can promote weight loss
- Preferential use in heart failure, kidney disease and ASCVD

SGLT-2 Inhibitors

	Canagliflozin ² (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin ¹ (Jardiance)	Ertugliflozin (Steglatro)
FDA Approved	2013	2014	2014	2017
Dosing frequency	daily	daily	daily	daily

¹FDA indication: “to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease”

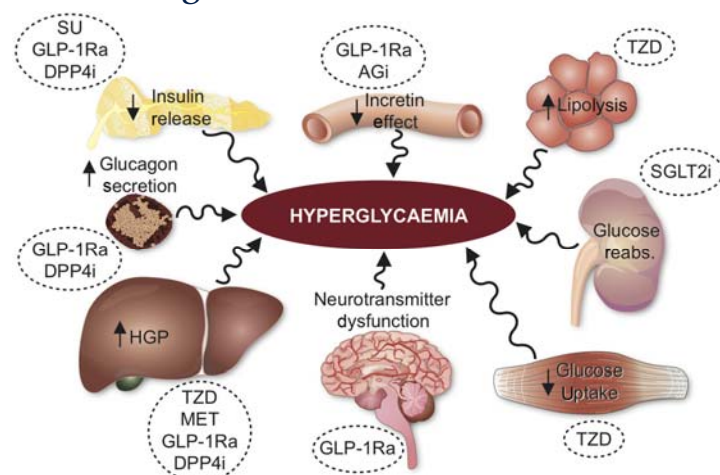
²FDA indication “to reduce the risk of major cardiovascular events such as heart attack, stroke, or death in adults with type 2 diabetes who have known heart disease”

Some are being considered for type 1 diabetes.

Thiazolidinediones (TZDs)

- Pioglitazone (Actos), rosiglitazone (Avandia)
- Improve insulin sensitivity (decrease insulin resistance)
 - enhance glucose uptake by muscle and fat tissue
 - decreases hepatic glucose output
- Slow onset to effect: take 4-6 weeks to have an effect on BG (up to 3 to 4 months)
- Can work well in overweight patients
- Dosing: Taken once or twice daily
- Common side effects: fluid retention, weight gain
- Avoid use in heart failure, osteoporosis, bladder cancer (pioglitazone)

Advancing to Combination Therapy: Combine Agents with Different Actions



General Medication Tips

- Keep an accurate list of all medicines you currently take and carry it with you. Include nonprescription medicines, herbs, vitamins, and dietary supplements.
- Bring and share your medicine list with ALL your health care providers. Bring all your medicine bottles to your visits.
- Try to use only one pharmacy system so the pharmacist has a record of all your medicines (to reduce risk of duplicating medicines and harmful drug interactions).



General Medication Tips, cont'd



- Learn about your medicines
 - Know the purpose of each medicine
 - Read the label carefully
 - Know how to take the medicine and the best time to take it
 - Be familiar with possible side effects
 - Know how to store your medicine
 - Know what to do if you miss a dose

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Taking Medications Consistently



- Take your medicines as instructed. If you are taking a medicine differently, inform your health care provider.
- Devise a system that works for you (such as a pillbox)



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Questions

Thank you!

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