

## Sugar How Do You Get So High? Pharmacologic Approaches for Diabetes Mellitus

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### Disclosures

- Nothing to disclose

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### Learning Objectives

- Review the different types of insulins and dosing strategies
- Compare pharmacologic treatment options for patients with type 2 diabetes
- Identify when it is appropriate to intensify therapy or use combination therapy

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### Overview

- Insulin Therapy
- Treatment of Type 1 Diabetes
- Non-insulin Therapies
- Treatment of Type 2 Diabetes

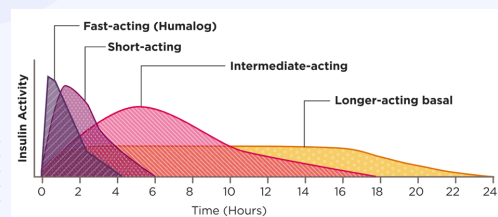
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### Overview

- Insulin Therapy
- Treatment of Type 1 Diabetes
- Non-insulin Therapies
- Treatment of Type 2 Diabetes

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### Comparison of Insulins



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### Rapid-Acting (Fast-Acting) Insulins

Generic	Brand	Onset (min)	Peak (hr)	Duration
Aspart	Novolog	10-15	1-3	3-5
Aspart	Fiasp	2.5	1-3	4
Glulisine	Apidra	5-15	1	4
Lispro	Humalog, Admelog	10-15	1-2	4-6
Lispro-aabc	Lyumjev	15	1-3	4-5
Human Insulin	Afrezza	12	1	1.5-3

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### Short-Acting and Intermediate-Acting Insulins

Generic	Brand	Onset (min)	Peak (hr)	Duration (hr)
Regular	Humulin R, Novolin R	30-60	2-3	6
Regular U500	Humulin R U-500	30	1-3	Up to 8
NPH	Humulin N, Novolin N	2-4 hours	4-6	14-16

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### Long-Acting Insulins

Generic	Brand	Onset (hr)	Peak (hr)	Duration (hr)
Detemir	Levemir	1-3	3-14	18-24
Glargine	Lantus, Basaglar	4-6	-	Up to 24
Glargine-yfgn	Semglee	4-6	-	Up to 24
Glargine U300	Toujeo	6	-	Up to 36
Degludec	Tresiba	>1	-	Up to 42

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### Administration Techniques



#### Inhalation

Cartridge must be inserted into inhaler  
Inhaler must be kept level to avoid loss of drug powder  
Patient exhales first, then inhales into device, holding breath as long as comfortable  
May result in decline in lung function over time



#### Subcutaneous

Avoid intramuscular injection  
Use of 4mm pen needles  
Sites: abdomen, outer thigh, upper buttock, upper arm  
Site rotation to prevent lipohypertrophy

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### Which supplies to prescribe?

<p>BD Nano 2nd Gen Pen Needles</p> <p>Use with insulin pens #100 needles in a box New technology</p>	<p>BD Veo Insulin Syringes with Ultra-Fine needle</p> <p>Use with insulin vials #100 syringes in a box 31G 6mm (15/64") 3/10mL (max 30 units per injection)</p>	<p>BD Veo Insulin Syringes with Ultra-Fine needle</p> <p>Use with insulin vials #100 syringes in a box 31G 6mm (15/64") 1/2mL (max 50 units per injection)</p>	<p>BD Veo Insulin Syringes with Ultra-Fine needle</p> <p>Use with insulin vials #100 syringes in a box 31G 6mm (15/64") 1mL (max 100 units per injection)</p>
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### Overview



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## Treatment Strategies

### Basal-Bolus Injections

- Includes basal, mealtime, and correctional doses
- Basal: long-acting insulin
- Mealtime: rapid-acting analogues, ultra-rapid acting analogues, inhaled insulin
- Greater flexibility, lower risk of hypoglycemia

### NPH with Regular

- Lower cost
- Simpler plan (2 injections) without carbohydrate counting
- Potentially 4-5 injections daily
- Increased risk of nocturnal hypoglycemia
- Requires consistent mealtimes and carbohydrate intake

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## Treatment Strategies

### Insulin pumps

- Standard of care
- Can lower A1c by 0.3%
- Accommodates varying insulin sensitivity by time of day, exercise, and illness
- Reduces severe hypoglycemia rates, especially when used with CGM
- Much greater flexibility
- Improves quality of life
- Higher cost
- Decision to use a pump over basal/bolus is individualized

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## Hypoglycemia

- All patients with type 1 diabetes should be prescribed glucagon (IM or inhaled)
- Family and those in close contact should be educated on use and administration

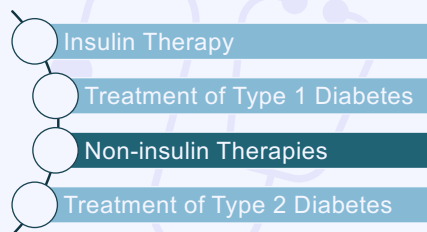
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## Non-insulin Treatment for Type 1 Diabetes



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## Overview



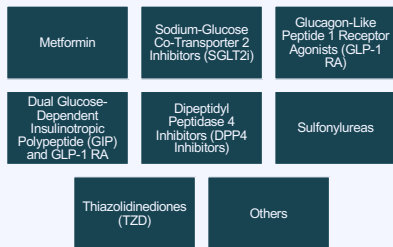
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## Lifestyle Modifications

- Diabetes Prevention Program (DPP)
- Diabetes education
- Social support
- Weight management

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### Medication Classes



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### Non-Insulin Agents for Diabetes

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
Biguanide	Metformin	1.0-2.0%	- / ↓	Neutral	Neutral	\$87-1884
SGLT2-i	Empagliflozin, dapagliflozin, etc	0.7-1.0%	↓	Benefit	Benefit	\$408-718
GLP1-RA	Semaglutide, dulaglutide, etc	0.5-2.0%	↓↓↓	Benefit	Benefit	\$964-1340
GIP/ GLP1-RA	Tirzepatide	2.0-2.4%	↓↓↓	Unknown	Unknown	\$1228
DPP4-i	Linagliptin, sitagliptin, etc	0.5-0.7%	-	Neutral	Neutral	\$234-657
SU	Glipizide, etc	1.0-2.0%	↑	Neutral	Neutral	\$48-82
TZD	Pioglitazone	1.0-1.2%	↑	Inc risk	Neutral	\$348

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### Metformin

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
Biguanide	Metformin	1.0-2.0%	- / ↓	Neutral	Neutral	\$87-1884

- MoA: decrease gluconeogenesis in the liver, increases insulin sensitivity
- Hypoglycemia – No
- Monitor eGFR
  - Half dose if eGFR 30 – 45, no initiation
  - Contraindicated with eGFR <30
- Clinical Considerations:
  - GI side effects common: bloating, abdominal discomfort, diarrhea
  - Monitor GFR, LFTs, and B12 levels

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### SGLT-2 Inhibitors

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
SGLT2-i	Empagliflozin, dapagliflozin, etc	0.7-1.0%	↓	Benefit	Benefit	\$408-718

- Drugs: canagliflozin, empagliflozin, dapagliflozin, ertugliflozin, bexagliflozin
- MoA: inhibits SGLT-2 which blocks glucose reabsorption by the kidneys and promotes renal excretion of glucose
- Hypoglycemia – No
- Cardiac benefit – Yes
  - Effect on MACE: canagliflozin, empagliflozin
  - HF: canagliflozin, empagliflozin, dapagliflozin, ertugliflozin, bexagliflozin
- Renal benefit – canagliflozin, empagliflozin, dapagliflozin, ertugliflozin
  - Glucose lowering effect is lower at lower eGFR

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### SGLT-2 Inhibitors

- Clinical Considerations:
  - Euglycemic DKA risk (rare)
    - Hold 3 days before scheduled surgery, during critical illness, or during prolonged fasting
  - Increased risk of genital mycotic infections
  - Necrotizing fasciitis of the perineum (rare reports)
  - Attention to volume status, blood pressure
  - Canagliflozin may increase risk of leg and foot amputations

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### GLP-1 RAs

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
GLP1-RA	Semaglutide, dulaglutide, etc	0.5-2.0%	↓↓↓	Benefit	Benefit	\$964-1340

- Drugs: semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide
- MoA: hormone mimetic that stimulates insulin secretion in response to carbohydrates, decreases glucagon secretion, slows gastric emptying, and causes early satiety
- Hypoglycemia risk: low
- Contraindications: history of thyroid C cell tumor, MEN2, family history of medullary thyroid cancer
- Lowers A1c by 0.5 – 2.0% but if combined with another non-insulin agent, A1c lowering can be ≥2%

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### GLP-1 RAs

- Cardiac benefit
  - Effect on MACE
    - Benefit: dulaglutide, liraglutide, semaglutide (SQ)
    - Neutral: once-weekly exenatide, lixisenatide
  - Effect on HF: neutral
- Renal benefit
  - Benefit: dulaglutide, liraglutide, semaglutide (SQ)
- Clinical pearls
  - Avoid in patients with gastroparesis
  - No renal adjustments necessary
  - GI side effects, pancreatitis (rare)



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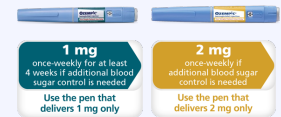
### Ozempic Dosing

#### Getting started



- At week 5, patients may increase to 0.5mg weekly dosing
- Starter pen designed for 6 week dosing period
- If maintaining 0.5mg dosing, pen contains 4 doses

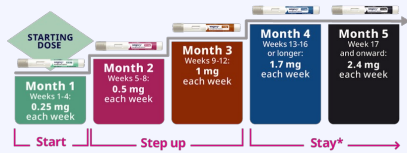
#### Additional control



- 1mg and 2mg pens each deliver 4 respective doses

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### Wegovy Dosing



\*At month 5 and on, you may either stay at 1.7 mg or increase to 2.4 mg. Work with your health care provider to determine which dose is right for you.

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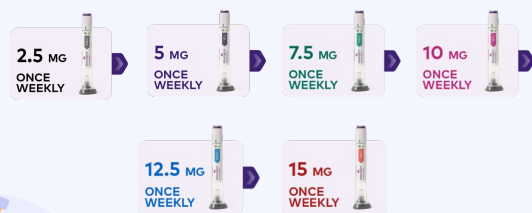
### GIP/GLP-1 RA

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
GIP/GLP-1-RA	Tirzepatide	2.0-2.4%	↓↓↓	Unknown	Unknown	\$1228

- MoA: GIP (gastric inhibitory polypeptide) is another incretin hormone. GIP and GLP-1 RA work similarly on GI tract, pancreas, heart, and brain
- Shown to be superior to Ozempic 1mg (not studied against Ozempic 2mg)
- Cardiac effect
- Renal effect
- A1c reduction (endpoint at 40 – 52 weeks)
  - 1.8 – 2.1% reduction with tirzepatide 5mg
  - 1.7 – 2.4% reduction with tirzepatide 10mg
  - 1.7 – 2.4% reduction with tirzepatide 15mg

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### Mounjaro Dosing



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### DPP-4 Inhibitors

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
DPP-4-I	Linagliptin, sitagliptin, etc	0.5-0.7%	-	Neutral	Neutral	\$234-657

- Drugs: sitagliptin, saxagliptin, linagliptin, alogliptin
- MoA: Inhibits breakdown of endogenous incretin enzymes (GLP-1 and GIP) which inhibits glucagon release and increases insulin secretion
- Hypoglycemia – No
- Cardiac benefit:
  - Effect on MACE: Neutral
  - HF: Neutral (potential risk – saxagliptin, alogliptin)
- Renal benefit: Neutral
  - Renal dose adjustment required for sitagliptin, saxagliptin, alogliptin
  - No dose adjustment required for linagliptin

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### DPP-4 Inhibitors

- Clinical considerations
  - Joint pain
  - History of pancreatitis
  - History of bullous pemphigoid

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### Sulfonylureas

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
SU	Glipizide, etc	1.0-2.0%	↑	Neutral	Neutral	\$48-82

- Drugs: glipizide, glimepiride, glyburide
- MoA: stimulates insulin secretion from  $\beta$ -cells in pancreas
- Hypoglycemia risk: HIGH
- FDA warning on increased risk of CV mortality (based on studies of tolbutamide)
- Clinical pearls
  - Caution in patients with sulfa allergies
  - Renally eliminated – caution in renal disease
  - Monitor renal and hepatic function
  - Glyburide recommended in GDM

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### TZDs

Class	Drugs	A1c	Weight	CV Effect	Renal Effect	Avg Cost/mo
TZD	Pioglitazone	1.0-1.2%	↑	Inc risk	Neutral	\$348

- Drugs: pioglitazone, rosiglitazone (dsc)
- MoA: regulates transcription of insulin responsive genes to increase insulin sensitivity, decreases hepatic glucose production
  - Used off-label for NAFLD, NASH
- Hypoglycemia risk: low
- Cardiac benefit
  - HF: increased risk (C/I in NYHA Class III or IV)
- Clinical points
  - Takes 4-6 weeks to reach optimal efficacy
  - Avoid in patients with history of heart failure, osteoporosis
  - Can cause edema/fluid retention, bone fractures
  - Monitor LFTs

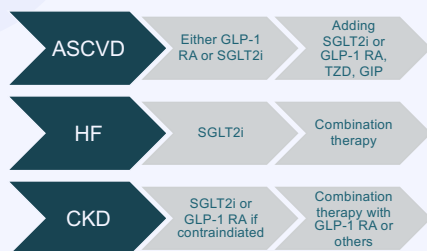
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### Overview



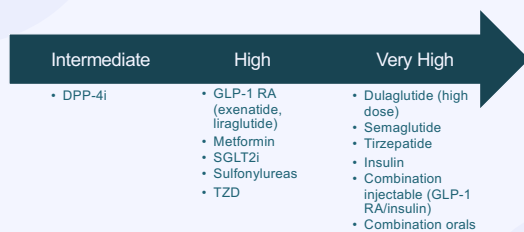
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### DM and Other Pre-existing Conditions



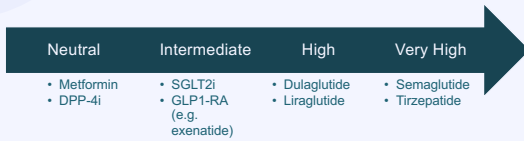
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### Efficacy of Glucose Lowering



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### Efficacy of Weight Loss



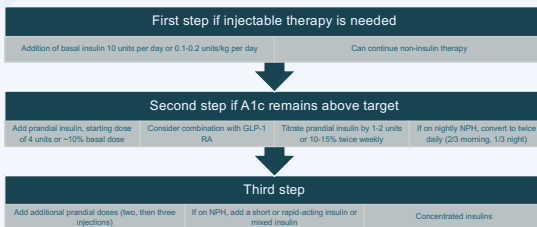
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### Insulin Initiation

	Indications	Patients with unexpected weight loss Patients with symptoms of hyperglycemia A1c > 10% or BG ≥ 300 mg/dL	
	Things to consider	Cost Comorbidities Routine monitoring	Hypoglycemia Education
	Add-on therapy	GLP-1 RA for greater glycemic effectiveness Other oral medications for glycemic and metabolic benefits	

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### Step-wise Approach



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### Combination Injectable Therapy

- When basal insulin has been titrated to an acceptable fasting BG or if dose is greater than 0.5units/kg/day, add GLP-1 RA or combination product
  - Weight loss
  - Less hypoglycemia
- Combination products
  - Insulin glargine 100units/ml + lixisenatide 33mcg/ml (Soliqua)
  - Insulin degludec 100units/ml + liraglutide 3.6mg/ml (Xultophy)

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### Key Points

- Insulin is the main treatment modality of Type 1 Diabetes
- Evaluate patient's comorbidities when considering non-insulin options for Type 2 Diabetes
- Initiate insulin when Hemoglobin A1c greater than 10%
- When recommending insulin, consider patient's health literacy, cost, compliance, and risk for hypoglycemia

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### Questions?

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