

# Diabetes Mellitus: Optimal Insulin Regimens

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# Learning Objectives

1. Review and discuss various insulin preparations
2. Discuss optimal use of each type of insulin preparation in relation to specific patient parameters
3. Outline strategies to optimize outcomes and reduce common adverse events associated with insulin preparations

# AES Question

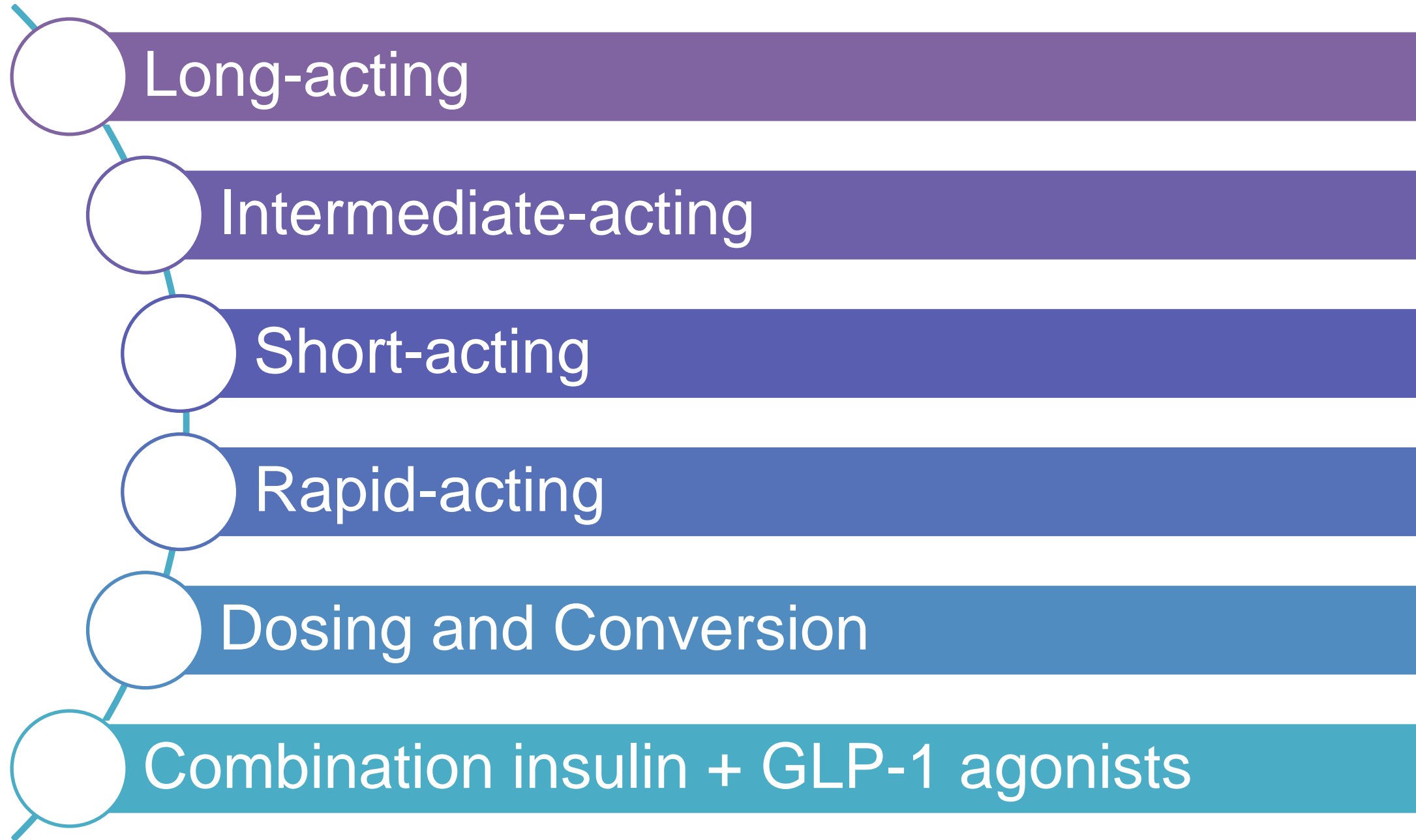


# AES Question 1

True or false? The main difference between insulin types is the pharmacokinetics.

- A. True
- B. False

# Overview of Insulin Types and Dosing





# Long-acting Insulin



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# Lantus, Basaglar (insulin glargine)

- Indication:
  - Type 1 and 2 Diabetes
- Dose:
  - Type 1 insulin-naïve start 30-50% of total dose based on 0.2-0.4u/kg
  - Type 2 insulin-naïve use 10 units/day or 0.1-0.2 u/kg and titrate to 50-75% TDD
  - Converting from Lantus is a 1:1 equivalent
  - Converting from Toujeo reduces dose by 20%
- Efficacy:
  - No difference between insulins
- Adverse Effects:
  - Hypoglycemia, weight gain

- Cost:

Lantus	Lantus Solostar	Basaglar Kwikpen
\$307 (10 mL vial)	\$460 (1 box, 15 mL)	\$380 (1 box, 15 mL)

Insulin Glargine. Lexi-Drugs. Lexicomp Online.



# Toujeo (insulin glargine)

- Long-acting insulin analog but higher concentration of 300u/ml vs 100u/ml of Lantus
- Indication:
  - Type 1 or Type 2 Diabetes
- Dose:
  - Type 1 insulin-naïve start 30-50% of total dose based on 0.2-0.4u/kg
  - Type 2 insulin-naïve start 10u/d or 0.1-0.2u/kg
  - Changing insulin therapy requires a 1:1 conversion if once daily insulin + 10% increase
  - If BID insulin then only use 80% of dose for Toujeo
- Efficacy:
  - Noninferior to Lantus in lowering BS, does have a smaller depot and absorption is slower allowing for a more consistent lowering
  - Takes up to 5 days to see effect, so dosing adjustments cannot happen daily
- Dosage Form:
  - Solostar pen with 1.5ml lasting about 28 days approximately \$420

# Levemir<sup>®</sup> (insulin detemir)

- Indication:
  - Type 1 or 2 diabetes
- Dose
  - Type 1 insulin-naïve start 30-50% of total dose based on 0.2-0.4u/kg
  - Type 2 use 10 units/day or 0.1-0.2u/kg and titrate to 50-75% of TDD
  - Converting from Lantus is a 1:1 equivalent
- Efficacy:
  - No difference between insulins
- Adverse effects:
  - Hypoglycemia and weight gain

• Cost:	<b>Vial</b>	<b>FlexTouch</b>
	\$323 (10 mL)	\$485 (1 box, 15 mL)

# Insulin Degludec (Tresiba)

- Most physiologic replacement for absent or insufficient basal insulin secretion
- Indication:
  - Type 1 and Type 2 Diabetes
- Dosing
  - Type 1 insulin naïve start 30-50% of total dose based on 0.2-0.4u/kg
  - Type 2 insulin start 10 units/day or 0.1-0.2u/kg
  - Already on insulin it is a 1:1 conversion of daily doses
- Efficacy
  - True once a day insulin that can be given at any time of the day with titration every 3-4 days
  - Non-inferior to other insulins – efficacy is the same but more convenient for dosing
  - Appears to have less hypoglycemia than other “long-acting” insulins
- Dosage forms:
  - 300u (110u/ml) pens with 5 pens per pack
  - 600u (200u/ml) pens with 3 pens per pack
  - \$535-629 per pack

# Long-acting Insulin Comparison

Generic	Brand	Onset	Peak	Duration	Cost	Comments
Insulin glargine	Lantus	3-4 hr	None  (Levemir possibly)	~24 hr	\$307-\$460	Split dose when $\geq 70$ -80 units
	Basaglar	3-4 hr		~24 hr	\$380	Split dose when $\geq 60$ units
	Toujeo	6 hr		16-36 hr	\$420	Takes up to 5 days to see an effect
Insulin detemir	Levemir	3-4 hr		6-23 hr	\$323-\$485	Duration is dose-dependent; Split dose when $< 0.6$ units/kg or $\geq 60$ units
Insulin degludec	Tresiba	1 hr		$\geq 42$ hr	\$535-\$629	True once daily insulin; apparent less hypoglycemia

# AES Question



# AES Question 2

50yom presents to office with complaints of polyuria and polydipsia. Patient is otherwise healthy and no comorbid conditions. A1c is 12.8%. Ht 6'0" Wt 80 kg. Patient is diagnosed with new onset Type 2 DM. Which medication regimen would you initiate today?

- A. Metformin 1000 mg daily + glimepiride 2 mg AM
- B. Metformin 500 mg daily + Lantus 10 units HS
- C. Metformin 1000 mg daily + Lantus 20 units HS
- D. Metformin 500 mg daily + Lantus 10 units HS + Humalog 2 units TID



# Intermediate-acting Insulin



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# Humulin N, Novolin N (insulin NPH)

- Strength: 100 units/mL
- Availability: vials and pens, available OTC
- Onset: 1-2 hr
- Peak: 4-12 hr
- Duration: 14-24 hr
- Dosing: once or twice daily

• Cost:

Humulin N	Humulin N Kwikpen	Novolin N/ReliOn
\$54 (3 mL) \$100* (10 mL)	\$566 (1 box, 15 mL) \$288*	\$165 (10 mL) \$24*





# Short-acting Insulin



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# Humulin R, Novolin R (insulin regular)

- Strength: 100 units/mL
- Availability: vials, available OTC
- Dosing: with meals
- Onset: 15-30 min
- Peak: 2.5-5 hr
- Duration: 4-12 hr (may increase with dose)

• Cost:

Humulin R	Novolin R/ReliOn
\$54 (3 mL) \$100* (10 mL)	\$165 (10 mL vial) \$24*

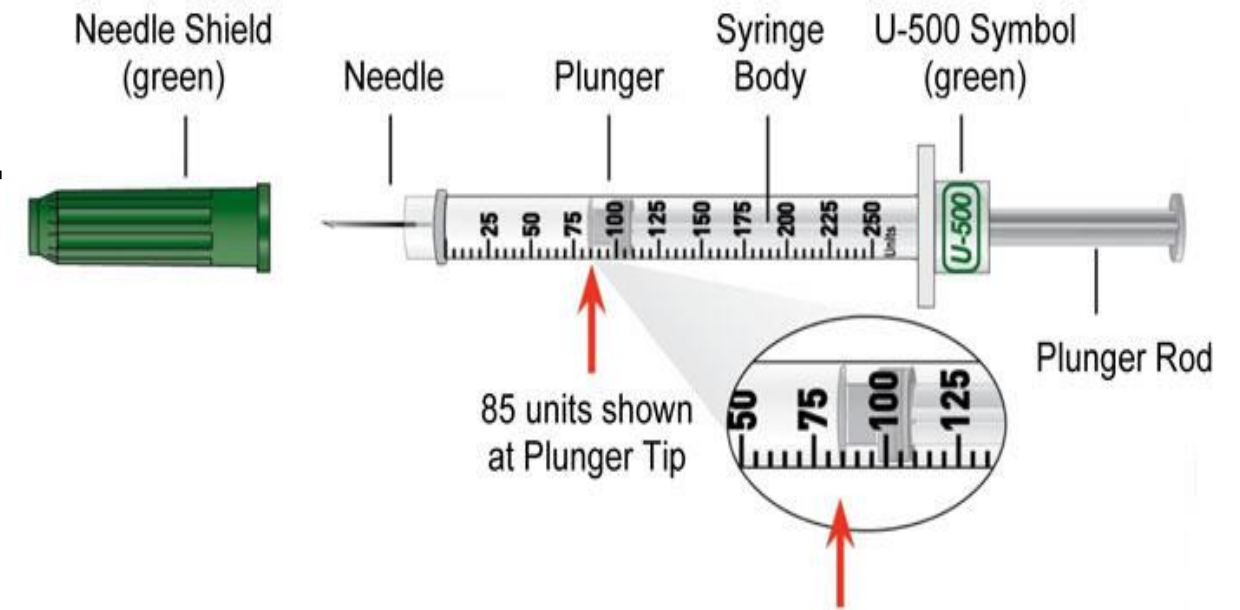
# Humulin R U-500 (insulin regular)

- Strength: 500 units/mL
- Availability: vials and pens
- Onset: 15-30 min
- Peak: 4-8 hr
- Duration: 13-24 hr

• <u>Cost</u> :	Vial	KwikPen
	\$1,784 (20 mL)	\$690 (1 box, 6 mL)

# Humulin<sup>®</sup> R U-500

- Use U-500 insulin syringes for dosing and prescribe in units of insulin



- Why?
  - 80 units of regular 100 units/mL = 0.8 mL
  - 80 units of regular 500 units/mL = 0.16 mL
    - 0.8 mL using U-100 syringe = 400 units

<https://www.drugs.com/pro/images/b60e8dd0-1d48-4dc9-87fd-e14675255e8c/humulin-r500-syr-ifu-v1.jpg>





# Rapid-acting Insulin



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# Novolog (insulin aspart)

- Strength: 100 units/mL
- Availability: vials and pens
- Dosing: with meals
- Onset: 15 min
- Peak: 1-3 hr
- Duration: 3-5 hr

• Cost:	Vials	FlexPen
	\$331 (10 mL)	\$639 (1 box, 15 mL)

# Insulin Aspart (Fiasp)

- Second aspart insulin but not generic Novolog
  - addition of vitamin B3 to help increase speed of absorption
- Dose:
  - Can inject up to 2 min before starting the meal or up to 20 min after the meal
  - Type 1: initiate 0.2-0.6units/kg/day in divided doses then maintenance 0.5-1 units/kg/day in divided doses
  - Type 2: initiate at 4u or 10% of basal dose and titrate
  - Should be approximately 25-50% of daily insulin requirement in the end
- Efficacy:
  - May see faster presence in blood but does not translate increased efficacy
  - May lower PP glucose faster to achieve 1h and 2h goals
- Safety:
  - Hypoglycemia, weight gain and if stored at room temperature good for 28 days
- Cost:
  - 3ml pen x 5 pens in a pack = \$650
  - Must write specifically for this insulin, not a therapeutic interchange

# Humalog, Admelog (insulin lispro)

- Strength: 100 units/mL, 200 units/mL
- Availability: vials and pens
- Dosing: with meals
- Onset: 15-30 min
- Peak: 0.5-2.5 hr
- Duration: <5 hr

- Cost:

Vials	Kwikpen 100 units/mL	Kwikpen 200 units/mL
\$99 (3 mL) \$98 (3ml)	\$636 (1 box, 15 mL) \$540 (1 box, 15ml)	\$1,275 (1 box, 15 mL)



# Apidra (insulin glulisine)

- Strength: 100 units/mL
- Availability: vials and pens
- Dosing: with meals
- Onset: 15-30 min
- Peak: 1.6-2.8 hr
- Duration: 3-4 hr

• Cost:











Vials	Solostar
\$306 (10 mL)	\$590 (1 box, 15 mL)

# Afrezza (insulin inhalation)



<https://www.thediabetescouncil.com/wp-content/uploads/2016/11/afrezza.jpg>

- Ultra-rapid acting
- Strength: 4, 8, 12 units
- Availability: cartridge combinations of 4 units, 8 units, and 12 units
- Dosing: with meals
- Onset: 12 min
- Peak: 35-55 min
- Duration: 1.5-4.5 hr (proportional to dose)
- Cost: \$328-\$1312

Injected Mealtime Insulin Dose 	AFREZZA Dose	# of cartridges needed			
		4 unit (blue)	8 unit (green)	12 unit (yellow)	
up to 4 units	4 units				
5-8 units	8 units				
9-12 units	12 units		+	 or/ 	
13-16 units	16 units				
17-20 units	20 units			+	
21-24 units	24 units				

[https://www.afrezza.com/wp-content/uploads/2016/08/how\\_to\\_start\\_chart-1.png](https://www.afrezza.com/wp-content/uploads/2016/08/how_to_start_chart-1.png)

# Short-acting Insulin Comparison

Generic	Brand	Onset	Peak	Duration	Cost	Comments
Insulin aspart	Novolog	15 min	1-3 hr	3-5 hr	\$331-639	
	Fiasp	2-5 min	1.5-2 hr	5-7 hr	\$650	Newest product, fast acting aspart
Insulin lispro	Humalog	15-30 min	0.5-2.5 hr	<5 hr	\$99-\$636	
Insulin glulisine	Apidra	15-30 min	1.6-2.8 hr	3-4 hr	\$306-590	
Insulin inhalation	Afrezza	12 min	35-55 min	1.5-4.5 hr	\$328-\$1312	Oral inhalation

# AES Question



# AES Question 3

Current regimen: 20 units NPH and 8 units regular before breakfast  
8 units regular before lunch and dinner with 10 units NPH at bedtime

Current blood glucose levels:

Before Breakfast	Before Lunch	Before Dinner	Bedtime
103	122	198	200
107	134	210	135
110	116	200	112
117	127	233	140
98	120	250	180

How would you adjust this patient's insulin?

- A. Increase morning insulin dose
- B. Increase dinnertime insulin dose
- C. Increase lunchtime insulin dose
- D. Continue with current regimen



# Insulin Combinations



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# Humulin 70/30, Novolin 70/30 (insulin NPH and insulin regular)

- 70% intermediate-acting, 30% short-acting
- Strength: 100 units/mL
- Availability: vials and pens, available OTC
- Onset: 30 min
- Peak: 1-2 hr (regular), 6-10 hr (NPH)
- Duration: 18-24 hr
- Dosing: BID

• Cost:	Humulin 70/30	Humulin 70/30 KwikPen	Novolin 70/30 /ReliOn
	\$54 (3 mL vial) \$100* (10 mL)	\$566 (1 box, 15 mL) \$288*	\$165 (10 mL vial) \$24*

Insulin NPH and Insulin Regular. Lexi-Drugs. Lexicomp Online.

# Novolog Mix 70/30

(insulin aspart protamine and insulin aspart)

- 70% intermediate-acting, 30% short-acting
- Strength: 100 units/mL
- Availability: vials and pens
- Onset: 10-20 min
- Peak: 1-4 hr
- Duration: 18-24 hr
- Dosing: BID

• Cost:	Vial	FlexPen
	\$343 (10 mL)	\$639 (1 box, 15 mL)



# Humalog Mix 50/50, 75/25 (insulin lispro protamine and insulin lispro)

- 75%/25% or 50%/50% intermediate-acting/short-acting
- Strength: 100 units/mL
- Availability: vials and pens
- Onset: 15-30 min
- Peak: 1-5 hr (50/50), 1-6.5 hr (75/25)
- Duration: 14-24 hr
- Dosing: BID but can use TID if 50/50

• <u>Cost</u> :	Humalog Mix 50/50 vial	Humalog Mix 75/25 vial	Humalog Mix 50/50 KwikPen	Humalog Mix 75/25 KwikPen
	\$342 (10 mL)		\$637 (1 box, 15 mL)	

	Component(s)	Concentration	Onset	Peak	Duration	Cost/Comments
<b>Long-acting</b>	Lantus, Basaglar	U-100	3-4 hr	None*  *Levemir possibly	22-24 hr	Split higher doses
	Toujeo	U-300	6 hr		16-36 hr	Up to 5 days to see an effect
	Levemir	U-100	3-4 hr		6-24 hr (dose-dependent)	Split dose when <0.6 units/kg or ≥60 units
	Tresiba	U-100, U-200	30-90 min		≥42 hr	Truly once daily, most expensive long-acting
<b>Intermediate-acting</b>	NPH	U-100	1-2 hr	4-12 hr	14-24 hr	Dose once-twice daily
<b>Short-acting</b>	Regular	U-100	30-60 min	2-5 hr	4-6 hr	OTC, \$
<b>Rapid-acting</b>	Humalog	U-100, U-200	15-30 min	1-2 hr	3-4 hr	Similar kinetics and price
	Novolog	U-100				
	Apidra		15 min	1.5-2 hr	5-7 hr	Faster acting aspart
	Fiasp					
<b>Ultra-rapid acting</b>	Afrezza	Dry powder	12-15 min		3 hr	Oral inhalation, \$\$\$
<b>Pre-mixed</b>	Humulin/Novolin 70/30	U-100	30-60 min	Variable	14-24 hr	Dose BID, OTC, \$
	Novolog 70/30		15-30 min			Dose BID
	Humalog 75/25					Dose BID-TID
	Humalog 50/50					
<b>Concentrated</b>	Humulin R U-500	U-500	30-60 min	2-5 hr	18-24 hr	Use U-500 syringes



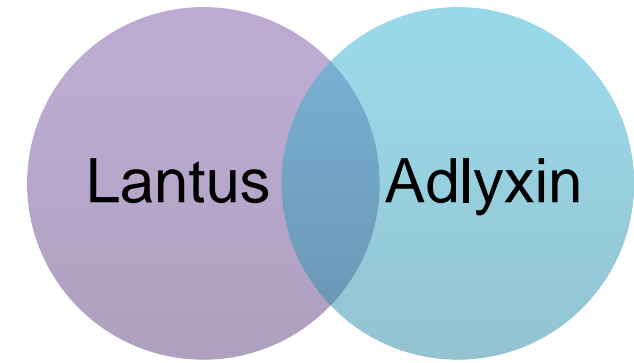
# Insulin + GLP-1 Agonists



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# Soliqua

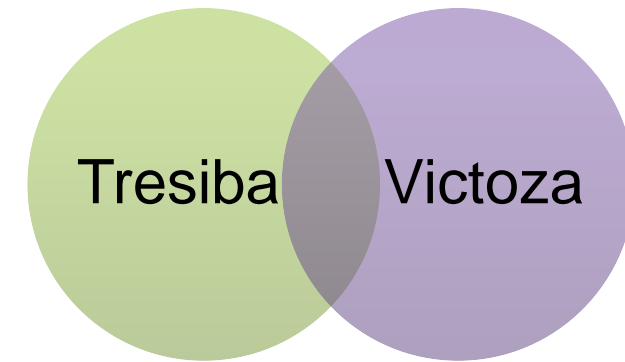
(insulin glargine and lixisenatide)



- Strength: 100 units-33 mcg/mL
- Use: Type 2 DM; adjunct to diet & exercise when inadequately controlled on <60 units daily of basal insulin or on lixisenatide
- Initial dose:
  - Controlled on <30 units: 15 units once daily
  - Controlled on 30-60 units: 30 units once daily
  - Dose between 15-60 units insulin glargine once daily
- MAX daily dose: 60 units insulin glargine-20 mcg lixisenatide
- Adverse effects: hypoglycemia, nausea, diarrhea, nasopharyngitis, headache
- Monitoring: A1c, weight, electrolytes
- Cost: \$762 (1 box, 15 mL)

# Xultophy

(insulin degludec and liraglutide)



- Strength: 100 units-3.6 mg/mL
- Use: Type 2 DM; adjunct to diet and exercise when inadequately controlled on <50 units daily of basal insulin or  $\leq 1.8$  mg daily of liraglutide
- Initial dose: 16 units (0.58mg) once daily
  - Range of 16-50 units once daily
  - If  $\geq 3$  days elapse since last dose, must reinitiate initial dose
- MAX daily dose: 50 units insulin degludec-1.8 mg liraglutide
- Adverse effects: headache, nausea, diarrhea, nasopharyngitis
- Monitoring: A1c, weight, electrolytes
- Cost: \$1,144 (15 mL, 100 units-3.6 mg/mL)



# Bonus Section: Insulin Dosing



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# AES Question



# AES Question 4

SA is a 12yof who presents to the office with complaints of polydipsia and polyuria. A1c is checked and comes back at 14%. Wt 35kg. What is the best option?

- A. Start metformin 500 mg daily + Lantus 10 units daily
- B. Start metformin 500 mg daily + Lantus 30 units daily
- C. Start Lantus 10 units daily
- D. Start Lantus 20 units daily



# Initial Basal Insulin Dosing

- Type 1 DM: 0.5-0.6 units/kg/day (0.4-1.0 units/kg/day)
- Type 2 DM: 10 units/day or 0.1-0.2 units/kg/day
- Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target
- Long-acting or intermediate-acting insulin

# Initial Bolus Dosing

- Initial: 4 units, 0.1 unit/kg, or 10% of basal dose
- Adjust: increase by 1-2 units or 10-15% once or twice weekly to reach SMBG target
- Rapid-acting or short-acting insulin

# AES Question



# AES Question 5

What is considered the optimal dosing ratio of long-acting insulin to rapid-acting?

- A. 90:10 LA to RA
- B. 70:30 LA to RA
- C. 50:50 LA to RA
- D. 60:40 RA to LA

# Initial Basal-Bolus Regimen

1. Calculate TDD
  2. Divide TDD into 50% basal and 50% bolus
  3. Divide bolus among 3 meals
- If using NPH and regular insulin:
    - 2/3 of TDD as NPH and 1/3 as regular

# Sliding Scale

- 1800 Rule
  - $1800/\text{TDD} = \text{the drop in BG for 1 unit of insulin}$
- Example:  $\text{TDD}=80$ 
  - $1800/80 = 22.5 \rightarrow 1 \text{ unit of insulin would drop BG by } \sim 23 \text{ mg/dL}$ 
    - Sliding scale as follows:

BG	Insulin
151-175	1 unit
176-200	2 units
201-225	3 units
226-250	4 units
251-275	5 units

# Sliding Scale

- 1800 Rule using correction factor
  - $1800/\text{TDD} = \text{the correction factor for 1 unit of insulin}$
  - $\text{Correction dose} = \text{BG now} - \text{BG target} / \text{correction factor}$
- Example: 22.5 (correction factor) & BG target of 150  
2 hr postprandial
  - BG is 230
    - $230 - 150 = 80$
    - $80/22.5 = 3.55 = 4$

BG	Insulin
151-175	1 unit
176-200	2 units
201-225	3 units
226-250	4 units
251-275	5 units

# Barriers



Barriers  
to  
Practice

- You cannot live with your patient
- Even the most physiologic insulin is not a Superhero
- Newest agents are expensive
- Numerous dosage forms now based on pharmacokinetics
- No dosage ceiling for insulin but sensitivity can be maxed
- Weight gain is a major side effect
- Lowering BG makes the patient feel horrible (not even hypoglycemia levels)
- Limited interactions in the office secondary to time



# Best Practice Recommendations

- Nonpharmacologic management is crucial
- Set your goal and then determine which insulin will work
- Counsel patients regarding expectations
- Dosing titration should be aggressive but with consideration for patient
- Realize that not all patients are candidates for insulin therapy
- Proactively outline the next steps
  - Consider adding GLP-1
  - Readjusting insulin type based on readings and/or finances
- Read, Read, Read.....post marketing streams data endlessly

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# Answers

1. A
2. B
3. B
4. D
5. C



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