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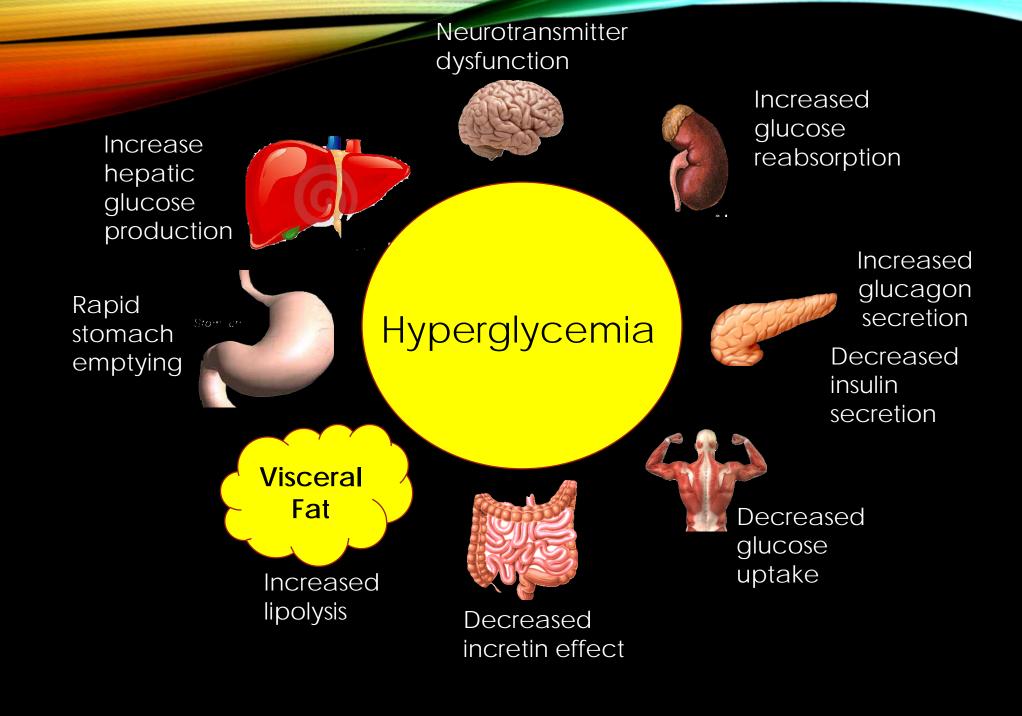
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OBJECTIVES

• Discuss diabetes medications on the US Market

• Prescribe a medication regimen to meet target blood glucose



CONSIDERATIONS FOR CHOOSING MEDS

Feature	More strict	←	7% Aic	→	Less strict
Hypoglycemia	Low				High
Disease duration	LOVV				Long
	Short				20119
Life expectancy	Long				Short
Important comorbididites	Few				Many
Established vascular complications					Many
	Few				wany
Patient motivation	High				Low
Resources and support	Many				Few

Medication Class	Route	Year	HbA1c % reduced
Alpha-glucosidase inhibitor	РО	1995	0.5-0.8
Amylin analog	SC	2005	0.6
Biguanide	РО	1995	1.5
Bile acid sequestrin	РО	2008	0.5 with metformin
Dopamine agonist	РО	2009	0.5-0.9
DPP-4 inhibitors	РО	2006	0.5-0.8
GLP-1 Receptor Antagonist	SC	2005	0.6
Insulin	SC	1921	> 2.5
Meglitinides	PO	1997	1-1.5
SGLT2 inhibitor	РО	2013	0.91-1.16
Sulfonylurea	РО	1946	1.5
Thiazolidinedione	РО	1999	0.8-1.0

BIGUANIDE: METFORMIN

 Metformin, Metformin ER, Glucophage, Glucophage ER, Glumetza, Fortamet, Riomet

- Activates AMP-kinase
- Improves insulin resistance indirectly
- Reduces hepatic glucose production



METFORMIN

Advantages

- Extensive experience
- Low cost
- No hypoglycemia
- Weight neutral
- Can be combined w other DM meds
- • Microvascular risk (UKPDS)

- Gastrointestinal side effects
- Lactic acidosis risk (rare)
- Vitamin B12 deficiency
- Contraindications
 - Acidosis, Dehydration
 - Severe liver, heart, kidney dz
 - Dye procedures, surgery
 - Heavy alcohol use



TITRATING METFORMIN

- Week 1: 500 mg PO q pm
- Week 2: 500 mg PO q am & pm
- Week 3: 500 mg PO q am & 1 g q pm
- Week 4: 1 g PO q am & pm
- Reduce dose if excessive N & / or diarrhea

If on 500 mg PO q pm and has excessive N &/or diarrhea, discontinue metformin

TITRATING METFORMIN ER

- Week 1: 500 mg tablet: 1 tablet PO qd
- Week 2: 500 mg tablet: 2 tablets PO qd
- Week 3: 500 mg tablet: 3 tablets PO qd
- Week 4: 500 mg tablet: 4 tablets PO qd
- Reduce dose if excessive N & / or diarrhea



If on 500 mg PO q pm and has excessive N &/or diarrhea, discontinue metformin

SULFONYLUREA: 2ND GENERATION

- Glipizide (Glucotrol), Glipizide XR (Glucotrol XL),
- Glyburide (Micronase), Micronized Glyburide (Glynase Prestab),
- Glimepiride (Amaryl)
 - Closes KATP channels on β-cell plasma membranes
 - Insulin secretion



SULFONYLUREAS

Advantages

- Highly effective in those with good beta cell function
- Low cost
- Long acting

- Hypoglycemia
- **•** weight



MEGLITINIDES

Repaglinide (Prandin); Nateglinide (Starlix)

- Closes KATP channels on β-cell plasma membranes
- Insulin secretion



MEGLITINIDES

Advantages

- May replace SU if sulfa allergy
- Prandin may be better if CKD
- Lower risk for hypoglycemia compared to SU
- Shorter acting than SU
- Dosed with meals

- Hypoglycemia
- **n** weight
- Frequency of dosing



THIAZOLIDINEDIONES

- Pioglitazone (Actos); Rosiglitazone (Avandia)
 - Peroxisome proliferator-activated receptor Y modulator
 - Activates the nuclear transcription factor PPAR-Y
 - Insulin sensitivity



THIAZOLIDINEDIONES

Advantages

- No hypoglycemia
- THDL-C
- ◆ Triglycerides

- **\(\Pi \)** Weight
- Edema / heart failure
- Bone fracture
- LDL-C (rosiglitazone)
- ? MI (rosiglitazone)



DIPEPTIDYL PEPTIDASE-4 INHIBITOR

- Sitagliptin (Januvia); Saxagliptin (Onglyza); Linagliptin (Tradjenta); Alogliptin (Nesina)
 - Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations
 - Glucose dependent insulin secretion
 - ◆ Glucose dependent glucagon secretion



DIPEPTIDYL PEPTIDASE-4 INHIBITOR

Advantages

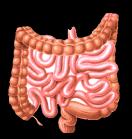
- Angioedema / urticaria and other immune-mediated dermatological effects
- ? Acute pancreatitis
- ? Heart failure hospitalizations

- No hypoglycemia
- Well tolerated



ALPHA-GLUCOSIDASE INHIBITOR

- Acarbose (Precose), Miglitol (Glyset)
 - Inhibits intestinal α-glucosidase
 - Slows intestinal carbohydrate digestion / absorption



ALPHA-GLUCOSIDASE INHIBITOR

Advantages

- No hypoglycemia
- ◆ Postprandial glucose excursions
- Nonsystemic
- Generally modest A1c efficacy

- Gastrointestinal side effects
 - Flatulence
 - Diarrhea
- Frequent dosing schedule



SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITOR

- Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)
 - Inhibits SGLT2 in the proximal nephron
 - Blocks glucose reabsorption by the kidney, increasing glycosuria
 - The lower the eGFR is, the less effective the medication. Do not use if eGFR < 45





SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITOR

Advantages

- No hypoglycemia
- Weight
- ◆ Blood pressure
- Effective at all stages of T2DM

- Polyuria
- † risk for UTI, & yeast infections
- † risk for DKA
- Volume depletion / hypotension / dizziness
- 1 LDL-C
- Transient creatinine increase



DOPAMINE AGONIST

- Bromocriptine (Cycloset)
 - Activates dopaminergic receptors
 - Moderates hypothalamic regulation of metabolism
 - Insulin sensitivity
 - Used as adjunct with other diabetes medication



DOPAMINE AGONIST

Advantages

- No hypoglycemia

- Generally modest A1c efficacy
- Dizziness / syncope
- Gl upset, Headache,
- Hypotension, Syncope
- Somnolence
- Nausea
- Fatigue
- Rhinitis



BILE ACID SEQUESTRANT

- Colesevelan (Welchol)
 - Binds bile acids in intestinal tract, increasing hepatic bile acid production

 - ? Incretin levels
 - Use as adjunct if maxed out on everything else



BILE ACID SEQUESTRANT

Advantages

- No hypoglycemia
- **↓** LDL-C

- Generally modest A1c efficacy
- Constipation
- **↑** Triglycerides



GLP-1 RECEPTOR AGONISTS

- Exenatide (Byetta), Exenatide ext-rel, (Bydureon, Bydureon Pen); Liraglutide (Victoza), Albiglutide (Tanzeum), Dulaglutide (Trulicity)
- Activates GLP-1 Receptors
- • Glucose dependent insulin secretion
- ◆ Glucose dependent glucagon secretion
- Slows gastric emptying



GLP-1 RECEPTOR AGONISTS

Advantages

- No hypoglycemia
- Weight
- Postprandial glucose excursions
- ◆ Some CV risk factors

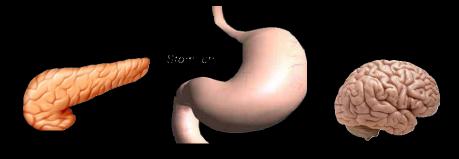
- Nausea, vomiting, diarrhea
- Heart rate
- ? **^** Acute pancreatitis
- C-cell hyperplasia / medullary thyroid tumors in animals
- Injectable
- Training required





AMYLIN ANALOG

- Pramlintide (Symlin)
 - Activates amylin receptors
 - ◆ Glucagon secretion
 - Slows gastric emptying
 - Satiety



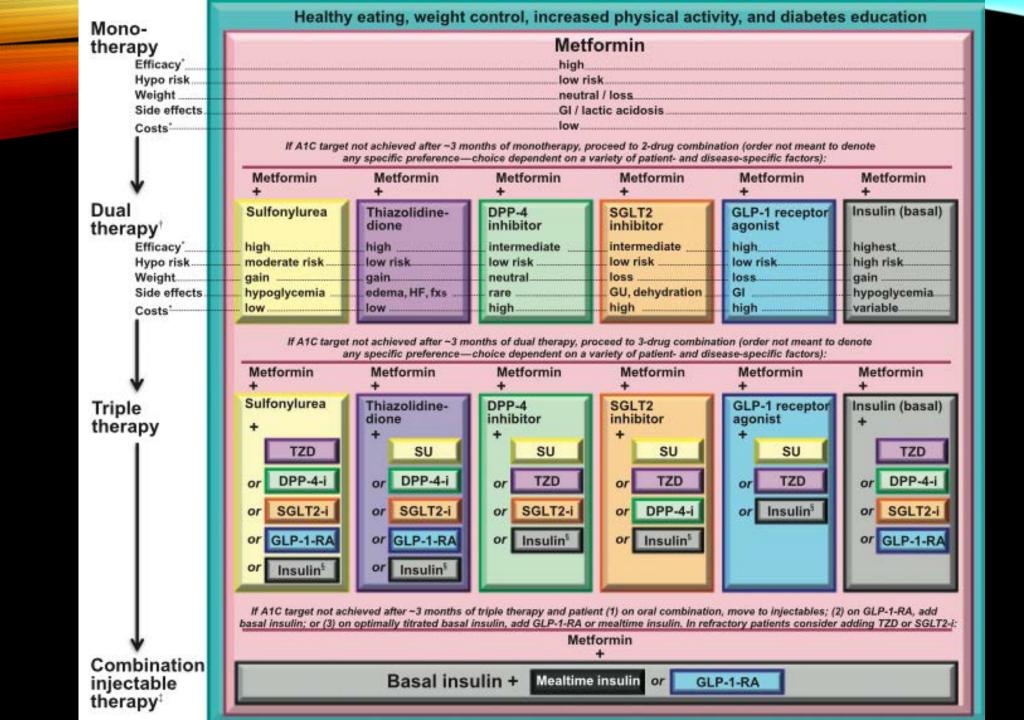
AMYLIN ANALOG

Advantages

- ▶ PP BG excursions
- Used for T1 and T2DM

- Nausea, vomiting
- May need to adjust prandial insulin dose to avoid \(\) BG
- Injectable
- Frequent dosing schedule
- Training requirements





ADA RECOMMENDATIONS

Start with metformin unless contraindicated

If A1c target is not met after ~ 3 months, proceed to 2-drug combination

If A1c target is not met after ~ 3 months, proceed to 3-drug combination

 If A1c target is not met after ~ 3 months on oral combination, consider basal insulin + mealtime insulin or GLP-1 RA



2 DRUG COMBINATION

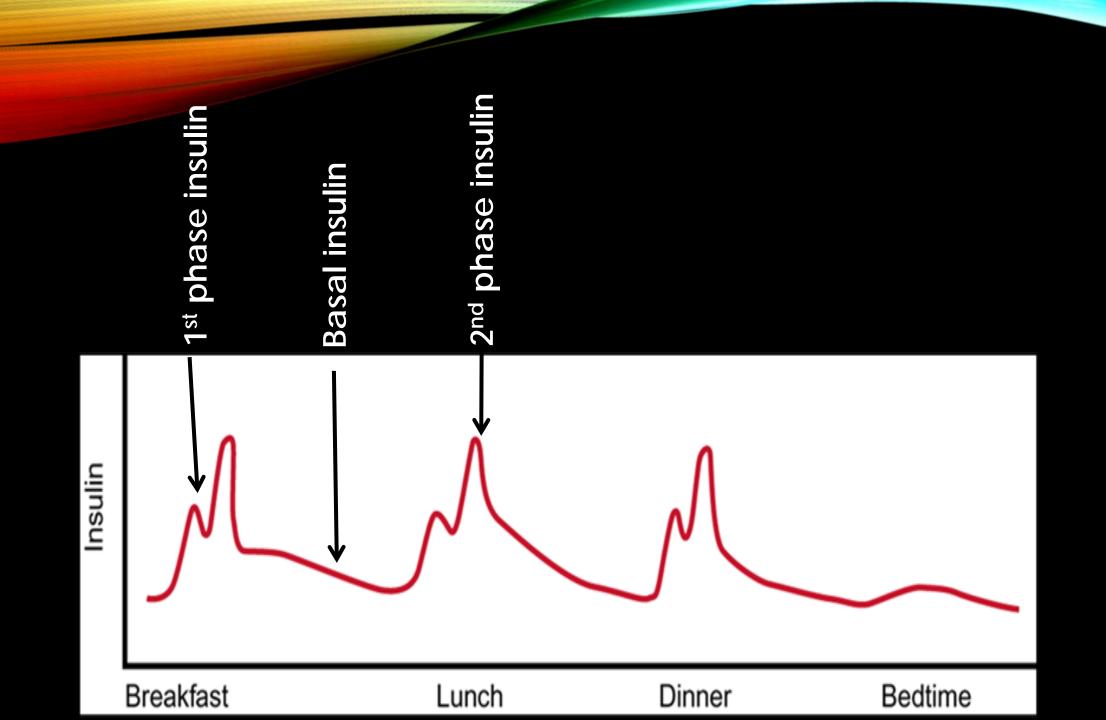
Metformin HbA1c↓ High Hypo: Low Weight: Neutral or loss Major SE: GI / lactic acidosis Cost: Low +						
	SU	TZD	DPP-4	GLP-1	SGLT2	Insulin
HbA1c↓	High	High	Medium	High	Medium	Highest
Нуро	High	Moderate	Low	Low	Low	Highest
Waiaht	Coin	Gain	Neutral	Loss	Loss	Coin
Weight	Gain	Gain	Neutrai	Loss	Loss	Gain
Major SE	Hypogly	Edema HF	Rare	GI	UTI Mycotic	Hypogly
Cost	Low	High	High	High	High	Variable

COMMON 3 DRUG COMBINATION

Met	Met	Met	Met	Met	Met
+	+	+	+	+	+
SU	TZD	DPP-4	GLP-1	SGLT2	Insulin
+	+	+	+	+	+
TZD	SU/meg	SU/meg	SU/meg	SU/meg	TZD
DPP-4	DPP-4	TZD	TZD	DPP-4	DPP-4
GLP-1	GLP-1	Insulin	Insulin	Insulin	GLP-1
Insulin	Insulin	SGLT2		TZD	SGLT2
SGLT2	SGLT2				

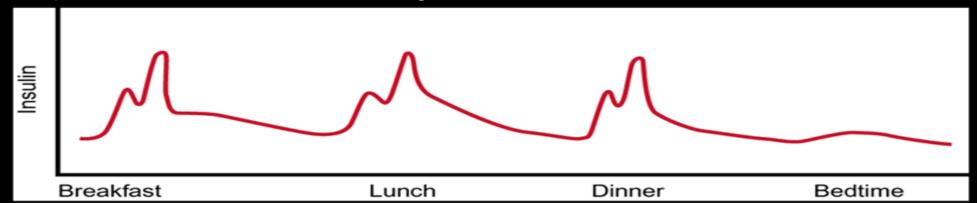
INSULIN





NORMAL INSULIN SECRETION

- Basal: continuous insulin to compensate for liver glucose
- Bolus: surge for food
 - 1st phase: rapid rise in serum insulin levels inhibits glucagon release and therefore liver glucose release
 - 2nd phase: to cover the food ingested



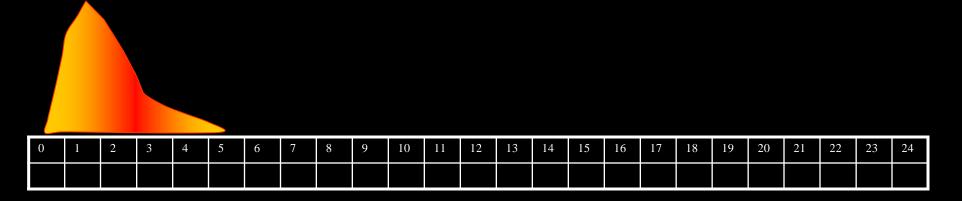
RAPID ACTING INSULIN

Lispro/Humalog U-100 and U-200 Glulisine/Apidra Aspart/Novolog

Onset: 15 minutes

Peak: 30-90 minutes

Duration 3-5 hours



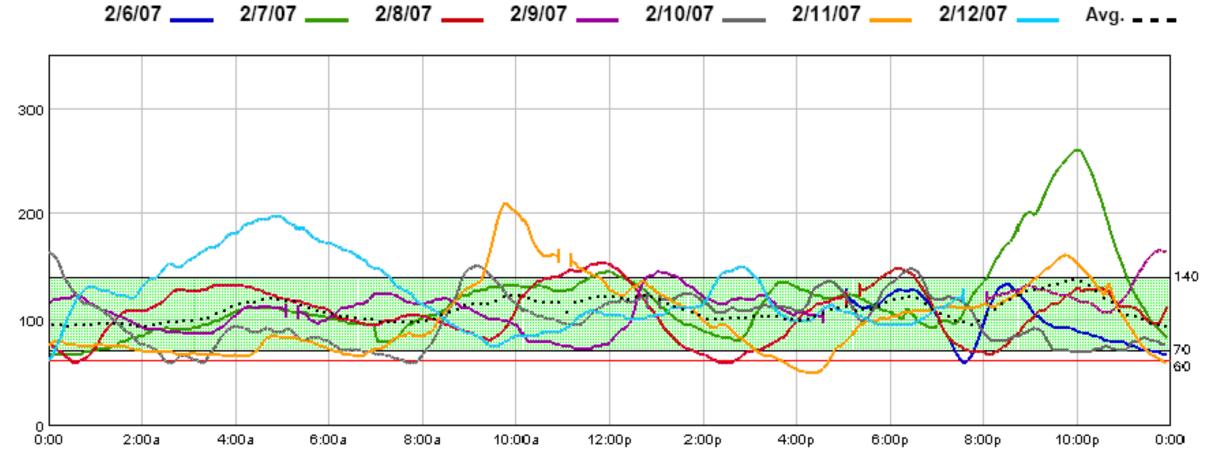


TIMING OF PREMEAL RAPID-ACTING INSULIN IN T1DM

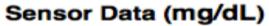
 Administration of rapid-acting inslin analogs 15 min before mealtime results in lower postprandial glucose excursions and more time spent in target range without increased risk of hypoglycemia

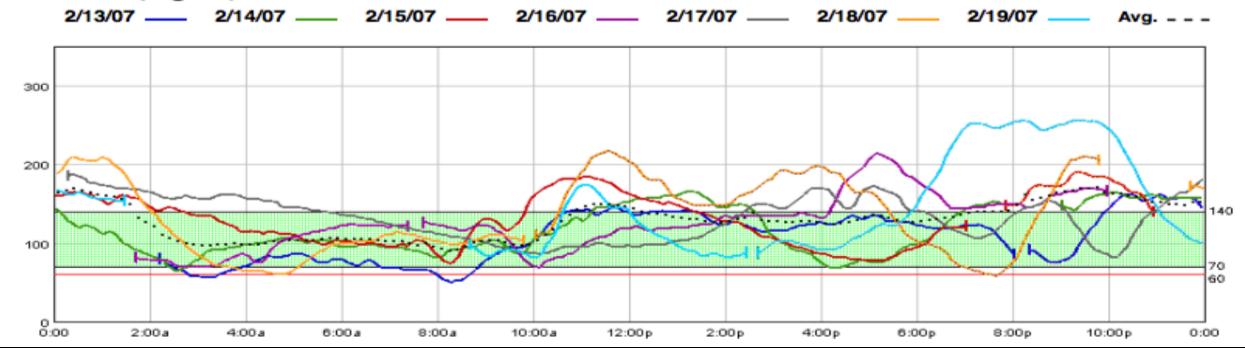
Luijf, et al. Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. Diabetes Care 2010; 33: 2152-55.

Sensor Data (mg/dL)



	Tue Feb 6	Wed Feb 7	Thu Feb 8	Fri Feb 9	Sat Feb 10	Sun Feb 11	Mon Feb 12	Average / Total
# Sensor Values	83	288	286	245	286	286	236	1,710
High SG (mg/dL)	134	260	154	166	164	210	196	260
Low SG (mg/dL)	58	66	58	72	58	48	60	48
Average SG (mg/dL)	98	119	106	110	99	100	123	109
Standard Dev.	22	40	25	19	25	35	33	31
MAD %	12.1	17.8	1.7	N/A	6.7	14.7	3.9	10.2
# Valid Calibrations	2	2	2	2	3	2	1	14



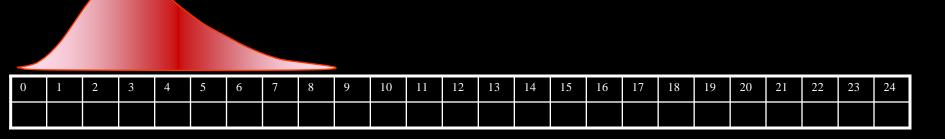


REGULAR SHORT ACTING INSULIN

• Onset: 60 min

• Peak: 2-4 hours

• Duration: 6-8 h





NPH INTERMEDIATE ACTING INSULIN

• Onset: 1-3 hrs

• Peak: 6-12 hours

• Duration: 12-24 h



0	1	2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

LONG ACTING INSULIN

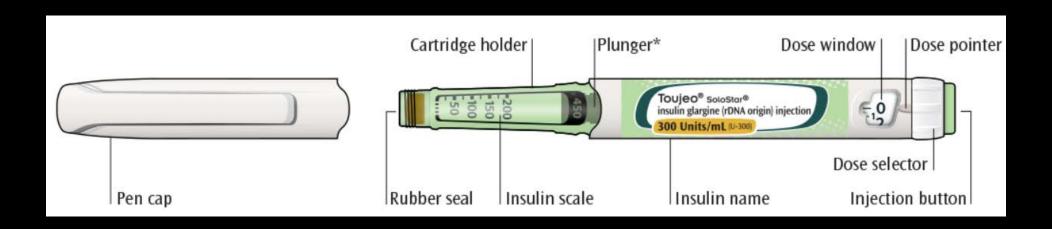
Name	Onset	Peak	Duration
Detemir Levemir	0.8-2 hrs	3.2-9.3	Up to 24 hrs
Glargine Lantus	1-2 hrs	Peakless	Up to 24 hrs
Degludec Tresiba	30-90 min	Peakless	Over 24 hrs

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24



GLARGINE U-300 (TOUJEO)

- May be used in patients with type 1 or type 2 diabetes
- Contains 300 units per milliliter
- Comes in a Solostar pen containing 450 units per pen, dial to the desired units



HUMULIN R U-500

May be use in patients with type 1 or type 2 diabetes requiring more than 200 units of insulin per day

Contains 500 units per milliliter



 The vial is marked with a band of diagonal brown strips to distinguish it from the U-100 vial which has no stripes and has "U-500 highlighted in red



HUMULIN R U-500

Requires special training: mistakes in drawing up can easily be made

 The Lilly company provides patient education literature helping patients to know how to correctly draw up U-500 Regular insulin

 The prescribed dose is expressed in actual units along with corresponding milliliters if using a tuberculin syringe, or corresponding markings if using an insulin syringe



HUMULIN R U-500

Units of U-500	Markings on TB syringe	Markings on U-100 syringe
20	0.04 ml	4 units
30	0.06 ml	6 units
40	0.08 ml	8 units
50	0.1 ml	10 units
60	0.12 ml	12 units
70	0.14 ml	14 units

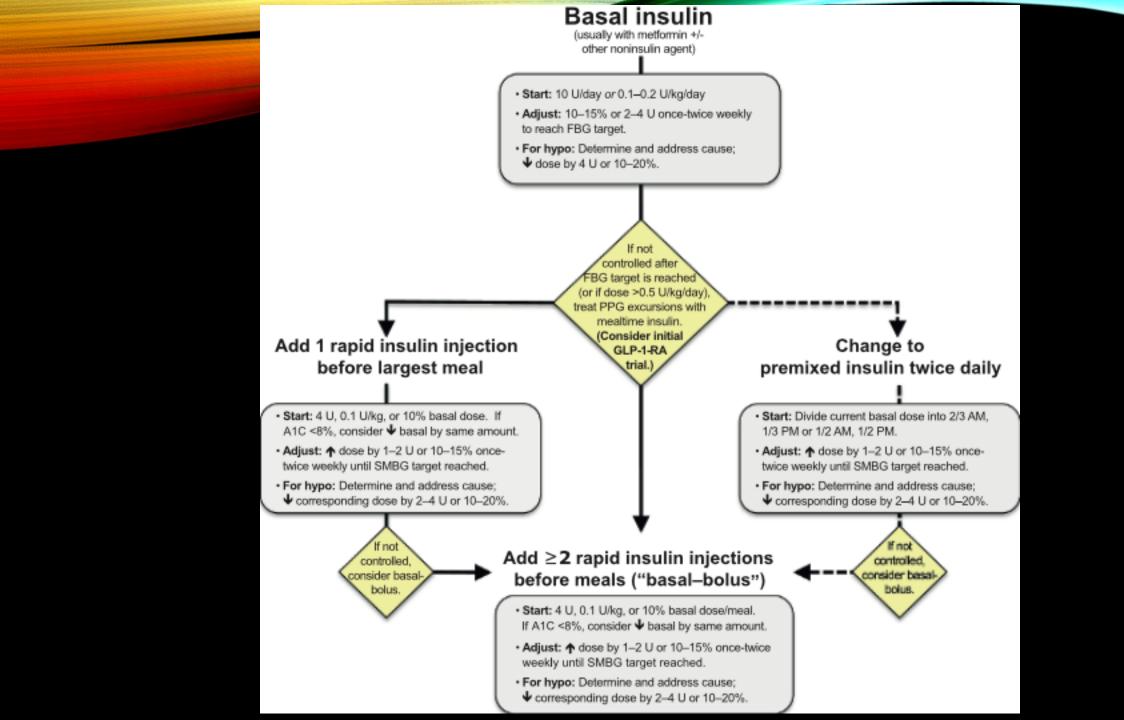


AFREZZA

- Inhaled insulin
- Peak 53 min, duration 160 min
- Prandial insulin
- Forms: 4 units, 8 units cartridges
- Contraindications: smokers, lung disease, DKA hynersensitivity







INITIATING INSULIN IN T2DM: ADA RECOMMENDATIONS

• Start: 10 units per day or 0.1-0.2 units / kilogram / day

 Adjust by increasing 10-15% or 2-4 units once or twice weekly to reach target fasting blood glucose

• For hypoglycemia: determine and address the cause. Decrease dose by 4 units or 10-20%

INITIATING PRANDIAL INSULIN IN T2DM

- Add 1 rapid acting insulin injection before the largest meal
- Start: 4 units or 0.1 units / kilogram or 10% basal dose if A1c < 8%. Consider decreasing the basal dose by the same amount.
- Adjust by increasing dose by 1-2 units or 10-15% once or twice weekly until blood glucose target is reached
- For hypoglycemia: determine and address the cause. Decrease dose by 2-4 units or 10-20%

ADDING ≥ 2 PRANDIAL INSULIN DOSES IN T2DM

• Start: 4 units or 0.1 units/kg or 10% basal dose if A1c < 8%.

Consider decreasing the basal dose by the same amount.

 Adjust by increasing dose by 1-2 units or 10-15% once or twice weekly until blood glucose target is reached

 For hypoglycemia: determine and address the cause. Decrease dose by 2-4 units or 10-20%

ALTERNATIVE TO BASAL / BOLUS DOSING: USE PREMIXED INSULIN TWICE DAILY

• Start: Divide current basal dose into 2/3 in am and 1/3 in pm, or ½ in am and ½ in pm

Adjust by increasing the dose by 1-2 units or 10-15% once or twice weekly until
the blood glucose is at target

• For hypoglycemia: Determine and address cause. Decrease corresponding dose by 2-4 units or 10-20%

TOTAL DAILY DOSE IN T1DM

Units / Kg / Day	Patient
0.5	Conditioned athlete, honeymoon phase
0.6	Motivated exerciser, woman in 1st phase follicular cycle
0.7	Women in luteal phase or 1 st trimester preg, adult with mildly ill with virus, child starting puberty
0.8	Women in 2 nd trimester preg, adult with severe infection
0.9	Women in 3 rd trimester preg, adult with bacterial infection
1.0	Women at term preg, adult with severe bacterial infection or illness, child at peak puberty
1.5-2.0	Child at peak puberty who is ill

INITIATING INSULIN IN T1DM

- Start with approximately 50% basal / 50% bolus for food + add SF / CF
- Most will use an MDI or insulin pump regimen
- Must be willing to perform BG testing ac & hs for MDI or pump therapy
- Many will split their basal insulin am/pm
- CHO counting with insulin: carb ratio beneficial
- If not willing to use intensive insulin therapy then use split/mix insulin at breakfast and supper

INSULIN TO CHO RATIO

Divide 500 by the total daily dose

• Only accurate if the basal insulin and prandial insulin are in a 50% / 50% ratio

- Example:
 - 50 units per day
 - $500 \div 50 = 10$
 - Start with 1 unit per 10 grams of CHO

QUESTION

- Total daily insulin dose = 50
- What is the initial insulin to carbohydrate ratio?
- $500 \div 50 = 10$
- The initial insulin to carbohydrate ratio is 1 unit of rapid or short acting insulin per 10 grams of carbohydrate

SENSITIVITY FACTOR / CORRECTION FACTOR

 The mg/dl that 1 u rapid acting insulin will decrease BG Also called correction factor

- Math formula: 1700 rule
 - 1700 ÷ total daily dose = SF / CF

SENSITIVITY FACTOR

Total Daily Dose	Sensitivity
10	170
20	85
30	56
40	42
50	34
60	28
70	24
80	21
90	18
100	17

QUESTION

- SF = 50
- Target BG = 100 mg/dL
- Current BG = 250
- How units of rapid / short acting insulin should be given to correct the hyperglycemia?
- 250 100 = 150
- $150 \div 50 = 3$ units

INSULIN ADJUSTMENT

- If the overnight BG is high, raise the basal insulin
- If the lunch BG is above target: raise the breakfast fast/short acting
- If the supper BG is above target: raise the lunch fast/short acting
- If the bedtime BG is above target: raise the supper fast/short acting

INSULIN ADJUSTMENT

- If the overnight BG is low, lower the basal insulin
- If the lunch BG is below target: lower the breakfast fast/short acting
- If the supper BG is below target: lower the lunch fast/short acting
- If the bedtime BG is below target: lower the supper fast/short acting

- Ms. Washington is a 65 yo pt w newly dx T2DM
 - BMI 34, Ht 5' 4", 200 # / 90.9 kg
- HbA1c 8%, no symptoms of hyperglycemia
- Creatinine 1.0
- What therapy would you start first?
- What would you go to next if monotherapy is unsuccessful?

- Ms. Washington is a 65 yo pt w newly dx T2DM
 - BMI 34, Ht 5' 4", 200 # / 90.9 kg
- Start with metformin and titrate dose as tolerated
- Add second agent if needed
- If insulin: what would the initial regimen?

 Mr. Williams is a 25 yo pt w newly dx T1DM 6', 68.2 kg, BMI 20, he is a motivated exerciser

HbA1c 12%, with symptoms of hyperglycemia

• Creatinine 0.7

What therapy would you start first?

- Mr. Williams is a 25 yo pt w newly dx T1DM 6', 68.2 kg, BMI 20, he is a motivated exerciser
- Start MDI therapy: 50% basal, 50% bolus
- Total daily dose: 68.2 x 0.6 u/kg = 40.92
 - 50% Basal = approximately 20 units
 - 50% Bolus = approximately 20 units
- May need less basal than bolus because of exercise

 Mr. Williams is a 25 yo pt w newly dx T1DM 6', 68.2 kg, BMI 20, he is a motivated exerciser

- Basal insulin:
 - May use Detemir or Glargine in 1 or divided doses
 - May use Glargine U-300 once daily
 - May use NPH twice daily in am and bedtime, or just at bedtime if using Regular insulin during the day for 3 meals

 Mr. Williams is a 25 yo pt w newly dx T1DM 6', 68.2 kg, BMI 20, he is a motivated exerciser

- Bolus insulin:
 - Can start by dividing the total calculated bolus dose by 3
 - Can calculate an insulin to carb ratio
 - 500 ÷ TDD 40 = 12.5 can start with 1 unit per 12 or 13 grams of CHO

 Mr. Williams is a 25 yo pt w newly dx T1DM 6', 68.2 kg, BMI 20, he is a motivated exerciser

- Sensitivity / Correction factor
- $1700 \div TDD \ 40 = 42.5$
- Can round to 40 or 45