

Diabetes Medication Management A to Z (ish)

What, Why, When and How Much?

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Learning Objectives

- Describe what is meant by "pattern management" when treating patients with uncontrolled diabetes.
- Describe the usual blood glucose pattern of patients with diabetes and GFR <40, lean elderly patients and patients on morning oral steroids.
- Describe a Multiple Dose Insulin (MDI) Regimen.
- Describe basic insulin pump and CGMS (continuous glucose monitoring system) principles.

**GLYCEMIC TARGETS
ADA 2017**

A1C <7.0 – mean plasma glucose 155

- Preprandial capillary glucose 80-130
- Postprandial peak capillary glucose <180

A1C <6.5 – mean plasma glucose 126

- Long life expectancy
- No significant CVD/vascular complications
- Rx with lifestyle or metformin only

GLYCEMIC TARGETS

A1C <8.0- mean plasma glucose 183

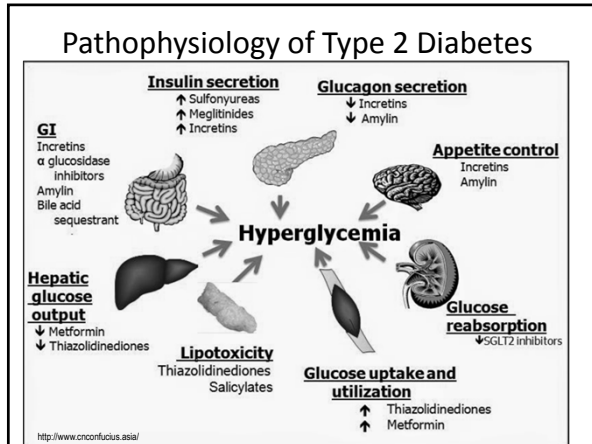
- Severe hypoglycemia history
- Limited life expectancy
- Advanced micro/macrovascular complications
- Extensive comorbidities
- Long term diabetes where general A1C targets are difficult to obtain

MORE OR LESS STRINGENT TARGETS MAY BE APPROPRIATE FOR INDIVIDUAL PATIENTS IF ACHIEVED WITHOUT SIGNIFICANT HYPOGLYCEMIA OR ADVERSE EVENTS

GLYCEMIC TARGETS

- Treat blood glucose not a1c
- Blood glucose targets and must be individualized
- Not everyone benefits from aggressive glucose management (Accord Study ~2011)
- Decisions about an individual patient's glycemic targets must be made in conjunction with the patient
- **More than one way to get to targets**

Type 2 Diabetes Oral Medications					
Drug class	Mechanism of Action (MOA)	A1c Reduction	Examples	Dosage Range/Day & Frequency	
Biguanide	Reduce hepatic glucose production Insulin sensitizer	1.0-2.0%	Metformin	IR: 500-2550mg XR: 500-2000mg	BID Daily w/ food
Sulfonylurea	Insulin secretion	1.0-1.5%	Glimepiride Glipizide Glyburide Tolbutamide	1-8mg 5-40mg 5-20mg 1-2g	Daily BID BID Daily/BID
Meglitinides	Insulin secretion, rapid onset	0.5-1.5%	Nateglinide (NF) Repaglinide (NF)	60-360mg 0.5-16mg	AC meal
Thiazolidinediones	Insulin sensitizer	1.0-1.5%	Pioglitazone Rosiglitazone (NF)	15-45mg 4-8mg	Daily QD-BID
Alpha-glucosidase inhibitors	Delays CHO absorption in the intestine	0.5-0.8%	Acarbose Miglitol (NF)	25-300mg	AC meal
DPP - IV inhibitors	Glucose dependent insulin secretion & glucagon suppression	0.4-0.7%	Alogliptin (NF) Linagliptin Saxagliptin (NF) Sitagliptin (NF)	6.25 - 25mg 5mg 2.5-5mg 50-100mg	Daily w/ or w/o food
SGLT2 Inhibitor	Reduces plasma glucose concentrations by reducing filtered glucose reabsorption	0.4-0.6%	Canagliflozin(NF) Dapagliflozin (NF) Empagliflozin	100-300mg 5-10mg 10-25mg	Daily



Preferred Therapies for Adults with Type 2 Diabetes

Line	Therapy	Efficacy	% Δ in HbA1c	Hypoglycemia risk	Weight	Side effects	Cost (\$)	Annual % Δ in A1c
1 st Line	Metformin or Metformin ER (Biguanide)	High	1 to 2%	Low risk	Neutral/Loss	GI, Lactic Acidosis	\$	5
2 nd Line	Glipizide, Glimepiride, or Glyburide (SU)	High	1 to 1.5%	Moderate risk	Gain	Hypoglycemia	\$	5
3 rd Line Preferred	NPH (Insulin)	Highest	2.0%	High risk	Gain	Hypoglycemia	\$	5
	Pioglitazone (TZDs)	High	1 to 1.5%	Low risk	Gain	Edema, HF, Bone FX, TBC	\$	5
Non-Preferred Therapies	Insulin (IPII-A)	High	1 to 1.5%	Low risk	Gain	Edema, HF, Bone FX, TBC	\$	5
	Insulin (IPII-B)	High	1 to 1.5%	Low risk	Gain	Edema, HF, Bone FX, TBC	\$	5
	Insulin (IPII-C)	High	1 to 1.5%	Low risk	Gain	Edema, HF, Bone FX, TBC	\$	5

MRAR >80% (CMSS)
Max dose unless CKD (GFR30-44 max 1000mg)
Treat To Target

Effective for A1c gap >1%
Use Actos early

A1c gap <1%, reassess @ 3 & 6m

- ### BIGUANIDES-metformin, glucophage
- Efficacy – decreases A1c 1-2%
 - Decrease hepatic glucose production and increases insulin sensitivity
 - First line agent for type 2 dm
 - Does not cause hypoglycemia
 - Side effects: n/v, diarrhea (better with XR formulation) metallic taste
 - DOES NOT CAUSE NEPHROTOXICITY

BIGUANIDES-metformin, glucophage

CONTRAINDICATIONS:

- Decompensated heart failure -> increased risk for lactic acidosis due to hypo perfusion
- Renal disease – GFR <45, no more than 1000mg /day and don't start metformin
- Contraindicated if GFR <30 as risk for lactic acidosis
- Iodinated studies- stop before procedure for approximately 48 hrs

Quick Think #1

- Metformin should not be initiated in pts with:

- A) Heart Failure
- B) History of pancreatitis
- C) GFR <60
- D) GFR <45

Case Study # 1

- Doug is a 48 y/o male accountant with new onset Type 2 diabetes. A1c 8.2.



	<u>morning</u>	<u>dinner</u>	<u>bed</u>
	180	135	
	175		225
	200	165	
	155		240

SULFONYLUREAS – glipizide, glyburide, glimepiride

- Efficacy- decreases A1c 1.0-1.5%
- Stimulates secretion of insulin from pancreas regardless of meals and glucose level
- Can cause hypoglycemia, weight gain
- Caution with renal disease and the elderly- use glipizide as shorter acting and less hypoglycemia- give 20-30 minutes before meals

Quick Think #2

Which Sulfonylurea is the Drug of Choice for a pt with renal disease?

- A) Glimepiride
- B) Glipizide
- C) Glyburide
- D) Tolbutamide

MEGLINTINIDES

Prandin (repaglinide) Starlix (nateglinide)

- Efficacy- decrease A1c 0.5-1.5
- Increase insulin production by the pancreas
- Shorter acting and used for post meal rise in glucose
- Can use if allergic to sulfa drugs
- Side Effects: weight gain, mild hypoglycemia

CASE STUDY # 2- ORAL AGENTS

- 52 y/o female on Metformin 1000mg bid with a1c 8.3.
- She is checking her blood sugar 4 times a day.

Morning	lunch	dinner	bed
124	245	170	200
150	205	145	199
135	180	164	240

CASE STUDY # 3- ORAL AGENTS

- 60y/o male with BMI 30 on metformin 1000mg bid and glipizide 10mg before breakfast and dinner with a1c 8.5.

Preferred Therapies for Adults with Type 2 Diabetes

1st Line Efficacy: High % ↓ in A1c: 1 to 2% Hypoglycemia risk: Low risk Weight: Neutral/Loss Side effects: GI, Lactic Acidosis Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Metformin or Metformin ER (Biguanide)	MRAR >80% (CMSS) Max dose unless CKD (GFR30-44 max 1000mg) Treat To Target
2nd Line Efficacy: High % ↓ in HbA1c: 1 to 1.5% Hypoglycemia risk: Moderate risk Weight: Gain Side effects: Hypoglycemia Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Glipizide, Glimepiride, or Glyburide (SU)	
3rd Line Preferred Efficacy: High % ↓ in HbA1c: 2.2% Hypoglycemia risk: High risk Weight: Gain Side effects: Hypoglycemia Cost (\$) per year: \$ Annual %/↓ in A1c: \$	NPH (Insulin)	Effective for A1c gap >1% Use Actos early
Non-Insulin Therapies Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: None Side effects: Gastrointestinal upset, Pain, Rash Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Insulin (DPP-4) Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: None Side effects: GI, Headache, Rash Cost (\$) per year: \$ Annual %/↓ in A1c: \$	
Non-Insulin Therapies Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: None Side effects: GI, Headache, Rash Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Insulin (TZD) Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: Gain Side effects: Edema, HF, Bone FX, TPC Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Effective for A1c gap <1%, reassess @ 3 & 6m
Non-Insulin Therapies Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: None Side effects: GI, Headache, Rash Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Sulfonylurea (SU) Efficacy: High % ↓ in HbA1c: 0.5 to 0.7% Hypoglycemia risk: Low risk Weight: Gain Side effects: Hypoglycemia Cost (\$) per year: \$ Annual %/↓ in A1c: \$	Effective for A1c gap <1%, reassess @ 3 & 6m

THIAZOLIDINEDIONES (TZDs)
Actos (pioglitazone and rosiglitazone)

- Efficacy – decreases A1c 1.0-1.5%
- Increases insulin sensitivity in muscle and adipose tissue, decreases hepatic glucose production
- Start at 15mg a day and increase dose by 15 mg every 4 wks up to 45mg/day
- Cons: fluid retention so careful with CHF, weight gain, linked to fractures in women.

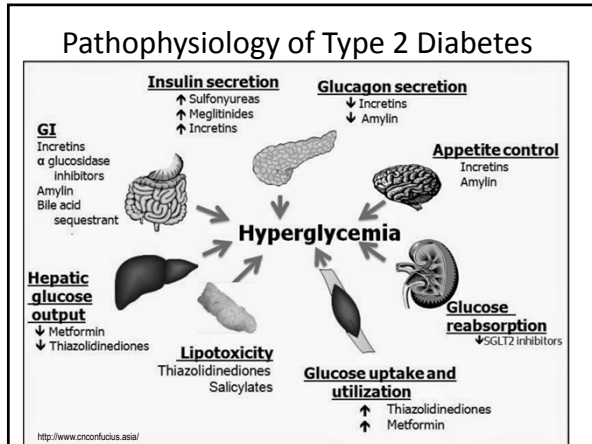
Quick Think #3

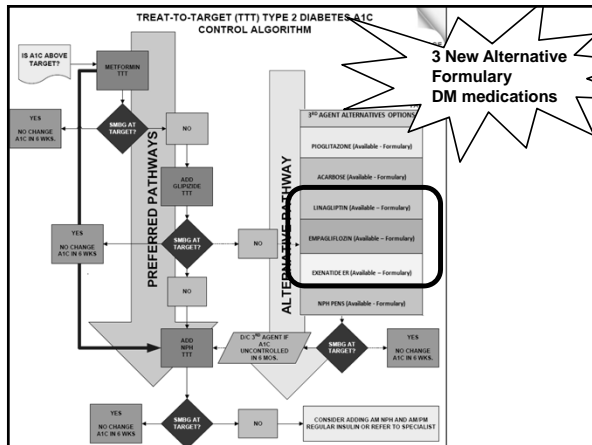
- Actos can be titrated in increments of 15 mg to a max of 45mg daily every:

- a) Weekly
- b) 2 weeks
- c) 4 weeks
- d) 6 weeks

Alpha-Glucosidase Inhibitors
Precose, Acarbose

- Efficacy- decreases A1c 0.5-0.8%
- It delays absorption of glucose
- Dosing 25mg with first bite of food tid, can increase to up to 4 tabs tid.
- Side effects: flatulence (74%) diarrhea, abd pain
- Don't give with inflammatory bowel disease, cirrhosis, hx intestinal obstruction
- Hypoglycemia rx with dextrose not sucrose (table sugar)







Incretin Mimetics

- Two major incretin hormones
 - GLP-1 - glucagon-like peptide 1
 - GIP - glucose-dependent insulinotropic polypeptide
- Actions of incretins
 - Enhances insulin secretion after eating
 - Suppresses post prandial glucagon secretion
 - Delays gastric emptying
 - Centrally suppresses appetite
- Two classes of drugs are Incretin Mimetics
 - Dipeptidyl Peptidase IV (DPP-IV) inhibitors
 - GLP-1 receptor analog

Adapted from USPharmacist.com

DPP-IV Inhibitors Tradjenta (linagliptin)

- MOA: Increase insulin secretion and decrease glucagon secretion after eating
- Dosing: 5 mg once daily with or without food
 - No renal dose adjustments
- Efficacy: Decreases A1c 0.4-0.7%,
- SMBG effects seen in about 1 week
- Well tolerated

Source: Lexicomp. NF - Commercial/Non-Formulary

DPP-IV Inhibitors-Clinical Pearls Tradjenta (linagliptin)

- Does not cause hypoglycemia
- Weight neutral
- Pancreatitis: Avoid use with history of pancreatitis
 - Cases of acute pancreatitis, including fatalities, have been reported
- Cost: Average cost per year per patient = \$1,400

Source: Lexicomp. NF - Commercial/Non-Formulary - Spring 2017

Quick Think #4

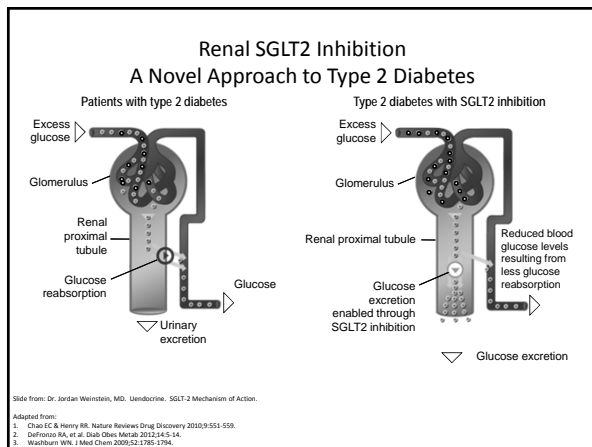
- True or False: A patient who uses Tradjenta (Linagliptin) should expect to lose about 5lbs.

False: Tradjenta is weight neutral

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SGLT2 Inhibitor Jardiance (Empagliflozin)

- MOA: ↓ reabsorption of glucose resulting in ↑ urinary excretion of glucose
- Efficacy: A1c reduction 0.7 – 1.0%, SMBG effects seen in about a week
- Side effects:
 - Genital mycotic infections, polyuria, UTI, volume depletion/hypotension/ dizziness, increased LDL, DKA
- Monitoring: Check baseline GFR and while on therapy
- Drug interactions: Diuretic increase risk of volume depletion
- Renal Dosing: Do not use in GFR <45

Source: Lexicomp. Inivikana. Empagliflozin Package Insert.

SGLT2 Inhibitor- Clinical Pearls

Jardiance (Empagliflozin)

- Diabetic ketoacidosis (DKA): Increased risk with SGLT2 inhibitors
 - BS levels not remarkably high
 - Possible triggers: Major illness, reduced food & fluid intake & reduced insulin dose
- Weight loss: Average weight loss on max dose 25mg/day ~5lbs

Source: Lexicomp. Invokana. Farigra. Jardiance Package Insert.
Zemke S, Warner G, Lachin JL, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015 Sep 17; doi: 10.1056/NEJMoa1504720.

Quick Think #5

- True or False: There is only a 0.1% difference in A1c reduction for Empagliflozin 10mg vs 25mg
- True: A1c reduction with 10mg is 0.7 vs 0.8 with 25mg

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Injectables (Non-Insulin) for Type 2 Diabetes

Drug class	Mechanism	A1c Reduction	Example	Dosage Range/Day & Frequency	
Incretin Mimetic GLP-1 Agonist	Glucose dependent insulin secretion, glucagon suppression & ↑ satiety	0.7-1.5%	Byetta (Exenatide)NF Bydureon (Exenatide ER) Victoza (Liraglutide)NF Tanzeum (Alogliptide) NF Trulicity (Dulaglutide) NF	5-20mcg 2mg 0.6-1.8mg 30-50mg 0.75-1.5mg	SQ BID SQ Q week SQ Daily SQ Q week SQ Q week

Source: Endocrinol Metab Clin North Am. 2009;34:77-98. Lexicomp. NF-Commercial Non-Formulary

GLP-1 receptor Agonist
Bydureon (exenatide ER)

- MOA: ↑ insulin secretion, ↓ glucagon secretion, delays gastric emptying & ↑ satiety
- Dosing: 2mg SQ once weekly, Any time of day with or without food
- Efficacy: Decreases A1c ~1.5% monotherapy, reduces post prandial BS
 - Triphasic effect: Phase 1: 2-5 hours; Phase 2: ~2 weeks; Phase 3: ~7 weeks

Source: Lexicomp. MF Commercial Non-formulary, Bydureon Package Insert

GLP-1 receptor Agonist
Bydureon (exenatide ER)

- Adverse Effects:
 - GI – nausea/vomiting/diarrhea
 - Nodules: small, raised bump at injection site
 - Occur in the first month
 - Body reacting to the microspheres that contain and slowly release exenatide
- Drug Interactions:
 - Warfarin – increase INR
 - May slow absorption of other drugs due to slowing GI motility

GLP-1 receptor Agonist - Clinical Pearls
Bydureon (exenatide ER)

- Weight loss: ~2kg (<5lbs)
- Risk of thyroid C-cell tumors (per rat studies)
 - Contraindicated in pts with:
 - Personal or family history of medullary thyroid carcinoma
 - Multiple Endocrine Neoplasia syndrome type 2
- Pancreatitis: Avoid if history of pancreatitis
 - fatal and non-fatal hemorrhagic/necrotizing pancreatitis
- GI/Renal:
 - Avoid using in patients with gastroparesis or severe gastrointestinal disease
 - Do not use if GFR <30

Source: Lexicomp. MF Commercial Non-formulary

GLP-1 receptor Agonist Bydureon (exenatide ER) Clinical Pearls

- Weight loss: ~2kg (<5lbs)
- Risk of thyroid C-cell tumors - observed in rat studies
 - Contraindicated in pts with:
 - Personal or family history of medullary thyroid carcinoma
 - Multiple Endocrine Neoplasia syndrome type 2
- Pancreatitis: Consider other therapies if history of pancreatitis
 - Case reports included fatal and non-fatal hemorrhagic/necrotizing pancreatitis
- Gastrointestinal disease:
 - Not recommended in patients with gastroparesis or severe gastrointestinal disease

Source: Lexicomp. NF -Commercial Non-formulary

GLP-1 receptor Agonist Bydureon (exenatide ER) Clinical Pearls

- Renal Dose Adjustment: Avoid in Crcl <30ml/min
 - Cases of acute renal failure and chronic renal failure exacerbation, including severe cases requiring hemodialysis have been reported
 - Occurred predominately in patients with nausea/vomiting/diarrhea or dehydration;
 - renal dysfunction was usually reversible
 - Has not been found to be directly nephrotoxic
- Cost: Average cost per year per patient \$4,900

Source: Lexicomp. NF -Commercial Non-formulary

Quik Think #6

- Which of the following is False regarding Bydureon?
 - A. A common side effect is N/V/D
 - B. Increased risk for hemorrhagic and necrotizing pancreatitis
 - C. There is a black box warning for Thyroid C-cell tumor risk
 - D. It is very inexpensive, all DM2 Kaiser patients should be prescribed to help with weight loss

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Kaiser Criteria

DPP4V Inhibitors (Tadjenta), SGLT2 Inhibitors (Jardiance) and GLP-1 Agonists (Bydureon)

Criteria required for adding one of these new drugs:

1. A1c within 1% of target due to modest glucose lowering
 - Ex: Target is 7%, A1C has to be <8% at start
2. Patient on max dose of 2 oral hypoglycemic agents
3. Assess medication adherence
 - MRAR>80%
4. 6 month trial of agent
 - If A1C not at goal within 6 months, stop new agent and start insulin

ALL 4 CRITERIA MUST BE MET

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Diabetes and CVD

- Metformin, Jardiance and Victoza have shown CV risk reduction in pts with DM2 (ADA 2017 guidelines)
 - Actos was reported by ADA to have questionable decrease in CVD events (PROactive study did not have a strong association)
 - Actos did show strong association with reduced risk of recurrent stroke (PROactive)
 - Ongoing trials for: Tadjenta vs Glimepiride (CAROLINA Trial) and Exenatide (EXSCEL Trial)
- Statins and aspirin are recommended for CVD reduction
 - Recommend statin
 - dose based on A Risk
 - ASA if aged 50-59 with A-risk >10%

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Diabetes and CKD

- Patients with eGFR levels <60 are more prone to hypoglycemia
 - Primarily due to prolonged action of hypoglycemic agents (ie: sulfonylureas and insulin)
 - Dose adjustments are required for many hypoglycemic agents in patients with CKD
 - Insulin clearance decreases in parallel with a decline in eGFR

42 | October 31, 2017 | © 2011 Kaiser Foundation Health Plan, Inc. For internal use only. "Diabetes Care 2014 Oct 31;1(10):2864-2883. <https://doi.org/10.2337/14-2706> Diabetic Kidney Disease: A Report From an ADA Consensus Conference.

Diabetes and Liver disease

- **Metformin: does NOT cause liver disease**
 - Beneficial in patients with nonalcoholic fatty liver disease
 - Not recommended in decompensated cirrhosis or alcohol binge drinkers
 - Lactic acidosis – usually in pts with cirrhosis also drinking alcohol
- **Sulfonylurea: Glipizide safest. Caution:**
 - Hypoglycemia may be prolonged
 - Patients with decompensated cirrhosis → reduced ability to counteract hypoglycemia

* Diabetes Care 2007 Mar; 30(3): 734-743. <https://doi.org/10.2337/dc06-1539> Spectrum of Liver Disease in Type 2 Diabetes and Management of Patients With Diabetes and Liver Disease. Foundation Health Plan, Inc. For internal use only. October 31, 2017

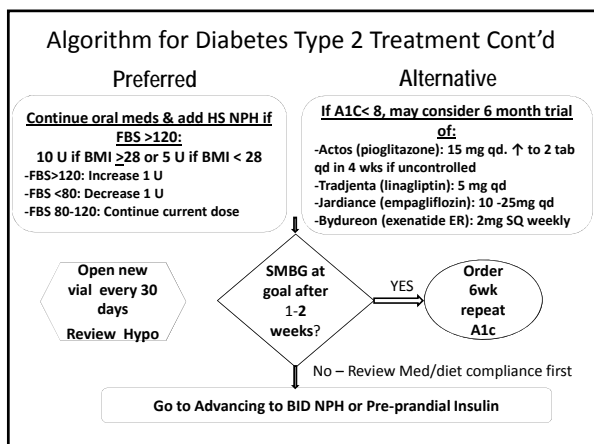
Diabetes and Liver disease

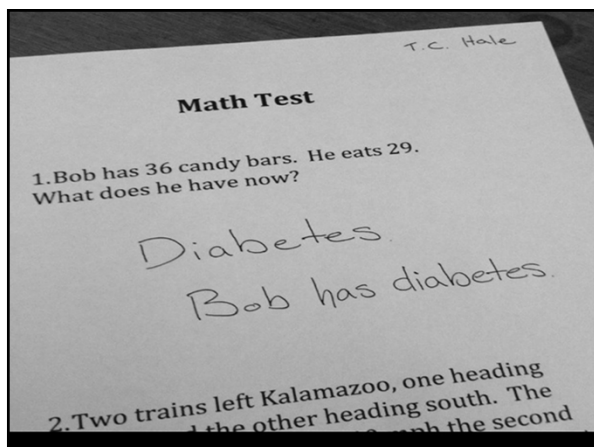
- **Actos: Hepatotoxicity is rare**
 - Check ALT at baseline, at 3-12 months and annually
 - Hold if ALT >3 times the ULN and recheck in six weeks.
 - Usually reversible
- **Tradjenta, Bydureon and Jardiance**
 - No known hepatotoxicity
 - No dose adjustment in liver disease

44 October 31, 2017 © 2011 Kaiser Foundation Health Plan, Inc. For internal use only. * Diabetes Care 2007 Mar; 30(3): 734-743. <https://doi.org/10.2337/dc06-1539> Spectrum of Liver Disease in Type 2 Diabetes and Management of Patients With Diabetes and Liver Disease. <https://www.nhlbi.nih.gov/fgl/actos.htm>

Considerations for Selecting a 3rd Line Agent

- How much lower does the A1C need to be?
- What part of the day is the glucose high?
- Co-existing conditions
- Cost to patient
- Patient preference for route of administration (oral, injection)?





CASE STUDY # 1

- 64 y/o female with Type 2 dm, BMI 28 on metformin 1000mg bid and glipizide 10mg bid.
- Hx of heart disease on lasix 20mg a day and lisinopril 40mg a day.
- A1c 10.5
- GFR 50

Treat to Target (TTT) Algorithm ~ 2008

- Step 1: Start & titrate metformin
If SMBG not at goal →
- Step 2: Start & titrate glipizide
If SMBG not at goal →
- Step 3: Start another oral med if A1c goal is <1% if criteria met for 6 months
- Step 4: Start & titrate insulin at bedtime

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Pros and Cons of TTT Insulin Algorithm - single dose HS NPH

- Pro → covers nocturnal HGO (hepatic glucose output).
??What is nocturnal HGO?
- Con → does not cover daytime hyperglycemia.
- Does not consider blood glucose patterns
- Pattern management - another level

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PATTERN MANAGEMENT

- Looks for patterns and assess relationship between glucose values with medication and behaviors
- Need to know individual target blood sugars
- Pt must get blood sugar data
- Determine causes and make changes
- Blood glucose affected by medication, food, stress, physical activity and probably more than we know

Insulin Basics

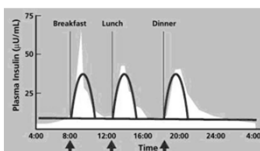
Mechanism of action: Stimulates carbohydrate metabolism, transfers glucose to muscles, convert glucose to glycogen
 Side effects: Weight gain, hypoglycemia

Basal

- Aka: "Background insulin"
- Long-acting - Lantus
- Intermediate-acting - NPH

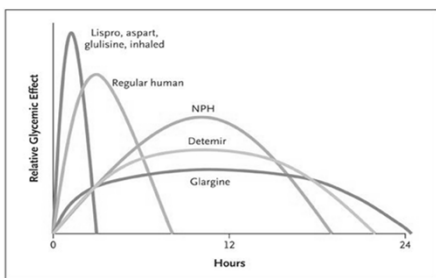
Bolus

- Meal time bolus
- Correction bolus
- Rapid-acting – Humalog
- Short-acting – Regular



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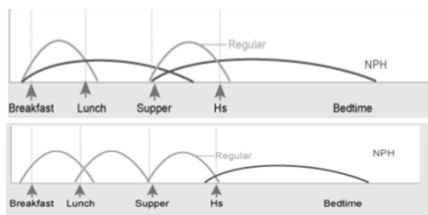
Insulin Actions



Basal Insulin

- Purpose: suppress glucose and ketone production
- Required in ALL patients with type 1 diabetes (Usually Glargine insulin)
- 1. Long acting- intermediate insulin such as NPH insulin (peaks 6-10 hrs) OR
- 2. Long acting insulin analogs (Glargine, Detemir) – little or no peak
- 3. Continuous Subcutaneous Insulin Infusion (insulin pumps) which use short acting analogs

Common Basal Bolus Regimens NPH/Regular



NPH Insulin

- Has a peak (6-10 hrs) so action is not consistent during the day
- Dosed once to twice a day, am and bed
- Can work up to 18 hrs
- Can mix with short acting insulin
- Starts working in 2 hrs so can avoid a lunch shot
- The patient should have a regular schedule, need to eat on time

Pharmacodynamics/kinetics of Humulin N

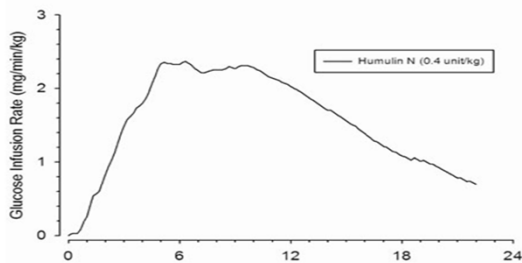


Figure 1: Mean Insulin Activity Versus Time Profile After Subcutaneous Injection of HUMULIN N (0.4 unit/kg) in Healthy Subjects.

<http://uspl Lilly.com/humulin/humulin.html>

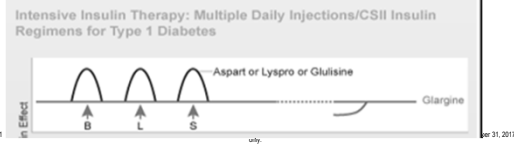
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Lantus

- Dosed usually 1 time daily, sometimes twice daily
- Peakless so don't need a particular schedule
- Unable to mix with short acting insulin
- If need prandial insulin, will need lunch shot



NPH VS LANTUS

- Type 1 vs Type 2 dm
- Nocturnal hypoglycemia on NPH?
- Is insulin needed for post prandial glucose rise?
- How many shots is patient willing to take a day?
- What are the patients blood sugar patterns?
- Cost
- Once a day Lantus idea is very seductive.....

Case for Basal Insulin

<u>MORNING</u>	<u>LUNCH</u>	<u>DINNER</u>	<u>BED</u>
156	185	203	286
175			
200		277	
164	196	194	188

**Oral Medications with Insulin
ADA 2017**

Basal insulin only- when starting basal insulin only (NPH/Lantus)
 -continue metformin or actos for insulin sensivity (unless contraindicated)
 -can continue sulfonylurea, trajenta or GLP-1 (Bydureon) for postprandial coverage

Basal/Bolus insulin- stop sulfonylurea, tradjenta and Bydureon

Case for Basal Insulin and Oral Meds

<u>MORNING</u>	<u>LUNCH</u>	<u>DINNER</u>	<u>BED</u>
156		203	286
175	210		
200		277	230
164	196	194	242

IMPACT OF LOW GFR ON GLUCOSE PATTERN

- Pts with GFR <60 are more prone to hypoglycemia- decreased insulin clearance
- Have a typical pattern of rising glucose during the day with bed to morning drop
- If GFR <40 they generally need for little or no basal insulin during the night
- So what would be the best basal insulin to use?

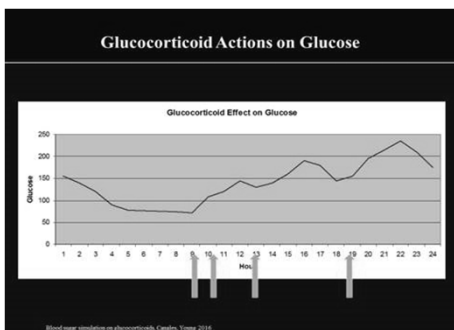
Typical Glucose Pattern with GFR <40

<u>MORNING</u>	<u>LUNCH</u>	<u>DINNER</u>	<u>BED</u>
101		203	286
86	210		
120		277	230
97	196	194	

IMPACT OF STEROIDS ON GLUCOSE

- Steroids increase insulin resistance
- Most steroids given outpatient are given in the morning such as once a day prednisone
- Typical steroid pattern is rising glucose during the day with bed to morning drop
- What would be the best basal insulin to use?
- Insulin needs to be adjusted as steroid doses change

Glucocorticoid Actions on Glucose



GFR <40 and am Steroid Insulin

- So look at the glucose pattern and consider stopping or decreasing the Bed NPH
- Lantus may not be a good choice if they need little or no insulin during the night
- Usual regimen is am NPH/Regular and dinner regular
- No bedtime insulin

Case Study # 3 Insulin

Nutritional/Prandial Insulin Regular OR Humalog

- If A1c above goal on basal insulin and trends of post prandial highs, consider starting prandial insulin
- Given to patients who are eating meals
- Purpose: cover ingested carbohydrates
- Must be matched to the patient's nutrition pattern-as set dose or carb counting
- Carbohydrate counting given as a ratio –example 1 unit for 15 grams of cho

Blood Sugar Pattern for Prandial Insulin

- 52 y/o female on NPH insulin 20 units am and 10 units at Bed and metformin 1000mg bid and glipizide 10mg bid with an a1c 8.3.
- She is checking her blood sugar 4 times a day.

<u>Morning</u>	<u>lunch</u>	<u>dinner</u>	<u>bed</u>
124	136	170	200
150		145	199
135	114	164	240

Correction Insulin

- Formally known as “sliding scale”
- Used to correct high blood sugar, expressed as a ratio example - 1 unit for 50 points
- Is not associated with meals
- Used with short acting insulin (regular or Humalog)
- Rule of 1500, 1700, 1800 to determine ratio

Quick Think

A patient is going to have a colonoscopy and is on lantus at night and 4 regular in the morning and correction scale of 1 unit for 50 points.

150-200 1 unit of insulin

201-250 2 units of insulin

He is not to eat the morning of the test.

His blood sugar is 249

How much regular insulin does he take?

Bolus (regular/humalog) Calculations

Rule of 1500 – correction calculation (1800 if humalog)

- 1500 / total daily dose of insulin
- Example: 1500 / 44 units = 34- round up to 40
- 1 unit will lower the blood glucose 40 points
- Start at target (ie 120) – correction would start at 160

Rule of 450 for carbohydrate calculation (500 if humalog)

- 450/total daily dose of insulin
- Example: 450/44 =
- 1 unit will cover grams of carbohydrate

76

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October 31, 2017

Prandial + Correction Case

Pt with blood sugar of 250 before breakfast. Insulin doses are 20N/10r + correction. He is eating.

Correction is 1 unit for 30 points:

150-180 = 1 unit

181-210 = 2 units

211- 240 = 3 units

240-271 = 4 units

How many total units of regular does he get?

Pathophysiology DM 2

- It is hard to predict someone’s insulin response!
- Younger, more obese – insulin resistant
- Older, more lean – insulin deficient



CASE STUDY # 1 Again

- 64 y/o female on metformin 1000mg bid and glipizide 10mg bid.
- Hx of heart disease on lasix 20mg a day and lisinopril 40mg a day.
- A1c 10.5
- GFR 50
- Weight is 100 kg
- What do you do?

Case Study #4

<u>MORNING</u>	<u>LUNCH</u>	<u>DINNER</u>	<u>BED</u>
236	280	180	340
286	304	263	267
300	364	277	197
200		301	245

Weight Based Calculation for Insulin

Total Daily Dose of Insulin = weight in kg x 0.3-.06

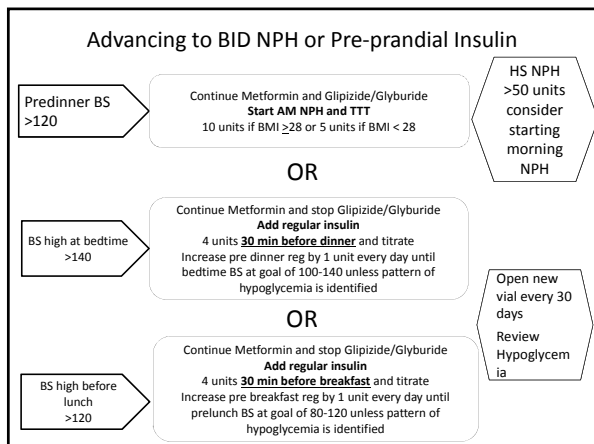
Example : 88 kg x 0.3-0.6 = 26-52 total units/day

Type 2 pts -> 2/3 am (20) and 1/3 pm (10)

(2/3 N, 1/3 R) (1/2 N, 1/2 R)

14N/6r 5r dinner, 5N bed

Lantus insulin 1/2 basal and 1/2 bolus-> 13 lantus and 4 Humalog before meals



Same Case blood sugars 2 weeks later

Insulin Actions and Adjustments

Type	Time Injected	Peak	Time of Effect
NPH	Breakfast	4 – 10 hours	Dinner
NPH	Dinner/Bedtime		Bedtime/Breakfast
Regular	Breakfast	2 – 4 hours	Lunch
	Lunch		Dinner
	Dinner		Bedtime
Lantus	Bedtime	Flat/Peakless	Breakfast
Lispro	Breakfast	1 – 2 hours	Between Breakfast/Lunch
	Lunch		Between Lunch/Dinner
	Dinner		Between Dinner/Bedtime

Approach to Pattern Management

- Check the blood sugar pattern and adjust the insulin accordingly.
- See when the blood glucose is not in target and adjust the correct insulin
- Slow titration to avoid hypoglycemia
- Treat the low blood sugars first!


PEARLS

- Look at HBA1C and see what the target is
- Look at GFR
- If A1c above goal on basal insulin and trends of post prandial highs, consider starting prandial insulin
- Continue Metformin/Actos if possible when starting/titrating insulin
- Adjust or discontinue (ie. glipizide) if necessary to prevent hypoglycemia or to simplify regimen especially when adding meal time insulin

True or False

- Provider wants to change NPH BID to Lantus once daily due to non-compliance. It is appropriate to change to lantus.
 - False, Lantus may not address compliance related to the number of injections

Insulin Pens



- Humalin N Kwik pen, Lantus Solostar
- Humalog Kwik pen
- Come in a box of 5, 300 units/pen
- Criteria include -> Type 1 dm, multiple daily injections, unable to draw up insulin accurately due to physical disabilities, visual impairment, pediatric patients
- Make sure you order pen needles
- Pens expire after 14 days

True or False?

- NPH insulin pen can be left at room temperature for 30 days
 - Answer: False, Humulin kwikpen expires after 14 days

True or False?

- You can put a new needle on the insulin pen after each use to prepare for the next injection
 - Answer: False, transfer of air and contamination can occur. Remove needle after each use

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METER DOWNLOAD

44 yo M DM 2, metformin, Glipizide, bydureon, NPH 35 units
 BID, A1c 9.8%, GFR 89

Date	Overnight 12 AM - 6 AM	Early Morning 6 AM - 9 AM	Late Morning 9 AM - 11 AM	Early Afternoon 11 AM - 2 PM	Late Afternoon 2 PM - 5 PM	Early Evening 5 PM - 7 PM	Late Evening 7 PM - 10 PM	Bedtime 10 PM - 12 AM
2/28/2017 Tuesday			388 9:14 AM					
2/27/2017 Monday			352 9:31 AM					
2/25/2017 Saturday	396 2:09 AM			315 11:36 AM				
2/24/2017 Friday	458 12:50 AM	250 8:40 AM						
2/23/2017 Thursday			511 9:25 AM					
2/22/2017 Wednesday			374 9:08 AM					
2/21/2017 Tuesday	440 12:26 AM							
2/20/2017 Monday	500 3:28 AM			273 11:44 AM				
2/19/2017 Sunday			437 10:37 AM					982 11:24 PM

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64y/o female, type 2 dm, end stage renal dz on dialysis on am 40N/5r, dinner 10r and sliding scale 1/30

Date	Overnight		Early Morning		Late Morning		Early Afternoon		Late Afternoon		Early Evening		Late Evening		Bedtime			
	12 AM - 6 AM	6 AM - 9 AM	9 AM - 9 AM	9 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 7 PM	7 PM - 10 PM	10 PM - 12 AM	Gluc	Meal	CHD	Gluc	Meal	CHD	Gluc	Meal	CHD
10/13/2017	917				294													
10/12/2017	445		214	6:21	19:22				450	15:20					338	22:56		
10/11/2017	261						275	11:49			263	18:52						
10/10/2017	615								232	15:25				269	19:40			
10/9/2017	226		454				234	11:45			378	18:35						
10/8/2017					153	10:21			373	15:23				470	21:14			
10/7/2017					293	19:46								441	23:32	372		
10/6/2017	186		450				235	12:40						394	19:09			
10/5/2017				321	8:36				235	16:47				481	20:25	318	22:39	

Blood sugar download from TAV 1 week ago:

Date	Overnight		Early Morning		Late Morning		Early Afternoon		Late Afternoon		Early Evening		Late Evening		Bedtime			
	12 AM - 6 AM	6 AM - 9 AM	9 AM - 9 AM	9 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 7 PM	7 PM - 10 PM	10 PM - 12 AM	Gluc	Meal	CHD	Gluc	Meal	CHD	Gluc	Meal	CHD
3/17/2017	396	5:44																
3/16/2017									480	13:25								
3/15/2017									76	15:12								
3/14/2017									155	11:29								
3/13/2017					477	9:51												
3/12/2017									135	11:25								
3/11/2017					96	10:11												
3/10/2017					96													
3/9/2017					135	7:41												
3/8/2017					136	9:39												
3/7/2017									124	13:21								
3/6/2017									160	12:45								
3/5/2017																		
3/4/2017					179	10:53										483	22:43	
3/3/2017					165	10:47												
3/2/2017					85	8:17												
3/1/2017					158	8:51												

Date	Overnight	Early Morning	Late Morning	Early Afternoon	Late Afternoon	Early Evening	Late Evening	Bedtime
	12 AM - 6 AM	6 AM - 9 AM	9 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 7 PM	7 PM - 10 PM	10 PM - 12 AM
3/16/2017 Thursday		145 7:33 AM						
3/15/2017 Wednesday		237				182 6:48 PM		
3/14/2017 Tuesday		110 6:56 AM				214 6:28 PM		
3/13/2017 Monday			168 9:03 AM					
3/12/2017 Sunday		149 6:32 AM				225 6:28 PM		
3/11/2017 Saturday		180 7:27 AM					141 7:18 PM	
3/10/2017 Friday		103 7:17 AM				162 6:33 PM		
3/9/2017 Thursday		262 8:34 AM						
3/8/2017 Wednesday		187 7:33 AM				184 6:31 PM		

* Post-meal Above/Below Target

INSULIN ACTIONS

Insulin Preparations	Onset of Action	Peak	Duration of Action
Aspart, glulisine, lispro	~15 minutes	1-2 hours	3-4 hours (Rapid)
Human regular	30-60 minutes	2-4 hours	6-8 hours (Short)
Human NPH	2-4 hours	4-10 hours	12-20 hours (Intermediate)
Detemir	2-3 hours	Flat	14 - 24 hours (Long)
Glargine	2-4 hours	Flat	~24 hours (Long)

For internal use only.

No pattern bs with low?



Food, Insulin and Blood Sugar



INSULIN PUMPS

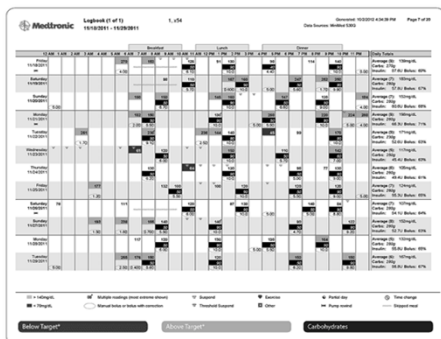


Minimed

Tandem Insulin Pump



Insulin Pump Reports



Insulin Pump Criteria


- Type 1 Diabetes
- Tests blood glucose ac, hs, sx of low BG, before driving
- Counts carbohydrates
- Using a Basal Bolus insulin regimen
- Has experienced low BG and treats appropriately
- Attends clinic appointments

Continuous Glucose Monitors (CGM)


- Rapidly evolving technology
- Minimally invasive glucose sampling of interstitial fluid
- Identifies BG excursions that may not be seen in BG testing
- Helpful in patients with hypoglycemia unawareness
- "Real time" vs "Blinded" data collection

Components of CGM Device


- **Sensor:** inserted under skin to measure glucose in interstitial fluid
- **Transmitter:** connects to sensor and relays data to receiver
- **Receiver:** displays and stores data, which can be downloaded to computer for report creation
- **Insulin pump:** integrated with CGM device in Medtronic MiniMed® Paradigm REAL-Time Revel™ and 530G with Enlite® systems



Dexcom G4 Platinum



Medtronic Guardian 3




Medtronic MiniMed® 530G

*Three of the RT-CGM devices available in December 2013 are shown.
 Neethercott. Diabetes Forecast. 2013
 Medtronic. Introducing MiniMed® 530G with Enlite®. 2013.

Real-Time vs Blinded CGM

<p>RT (Personal)</p> <ul style="list-style-type: none"> • Displays glucose data. Includes up & down trends. Alarms warn of high and low BG and rapid changes. • Intended to be worn daily 	<p>Blinded (Professional)</p> <ul style="list-style-type: none"> • Data not seen by the patient. • Placed at medical office. • 3-7 days of data are collected and are usually reviewed with a provider ("Dexcom Study")
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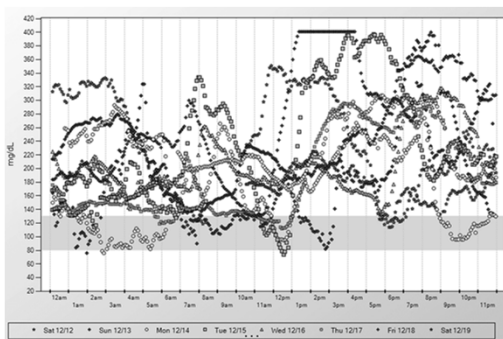
Dexcom (CGM)



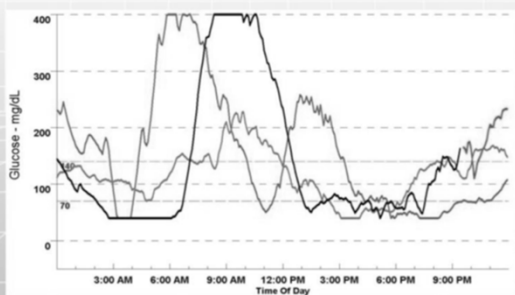
Dexcom CGM Alternate Receivers



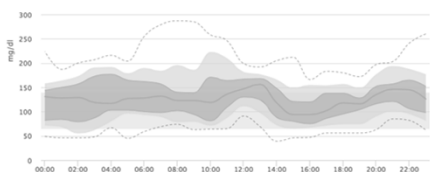
Sensor Report



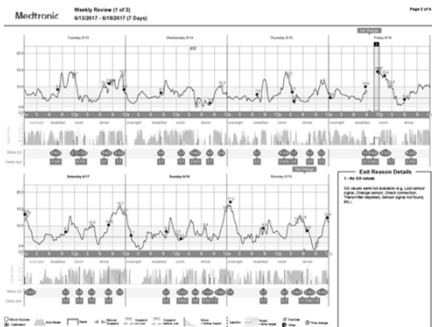
Using Blinded CGM for PM



Software Simplifies CGM in DM 1



CGM Daily Reports



CGM Pros and Cons

Per ADA re: DM 1

- May be a useful tool for lowering A1C
 - May be useful in preventing hypoglycemia
- Many patients use CGM inconsistently or stop using it because of:
- Inaccurate results
 - Skin irritation @ site (usually due to adhesive)

CGM in Type 2 Diabetes

- Blinded CGM in patients not taking insulin
 - Provides valuable information about effects of eating patterns and physical activity on BG values
 - Well tolerated
- Intermittent RT-CGM in patients not taking mealtime insulin
 - Associated with significantly greater mean reduction in A1C than SMBG alone
 - Benefit is durable
 - Some patients may benefit from long-term use, but others experience burnout

Allen et al. Diabetes Technol Ther 2009; Ehrhardt et al. J Diabetes Sci Technol 2012; Vigersky et al. Diabetes Care 2012; Fonda et al. Diabetes Care 2012

Flash CGM

Freestyle Libre Pro – new (2017) in the US

- “Blinded” CGM
- Sensor easier to insert
- Data only accessed per “Professional” electronic reader

(Personal Freestyle Libre recently approved by the FDA.

Launch date not yet announced)

Freestyle Libre Pro Sensor

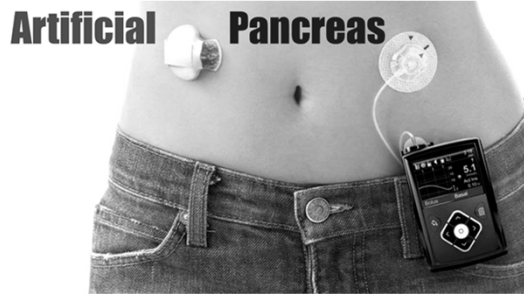


Artificial Pancreas

- Biostator (1977) – primarily used in research settings



Minimed 670g
(not quite ... Artificial Pancreas)



84 y/o male VS

GFR 50

Date	Overnight	Early Morning	Late Morning	Early Afternoon	Late Afternoon	Early Evening	Late Evening	Bedtime
	12 AM - 6 AM	6 AM - 9 AM	9 AM - 11 AM	11 AM - 2 PM	2 PM - 5 PM	5 PM - 7 PM	7 PM - 10 PM	10 PM - 12 AM
2/3/2017 Friday			108 10:05 AM					
2/2/2017 Thursday			89 9:57 AM					
2/1/2017 Wednesday			154 10:23 AM			317 6:02 PM		
1/31/2017 Tuesday		137 8:50 AM				473 6:03 PM		
1/30/2017 Monday			141 10:48 AM			141 6:23 PM		
1/29/2017 Sunday			138 10:05 AM					
1/28/2017 Saturday			132 10:23 AM			255 6:23 PM		
1/27/2017 Friday	116 12:15 AM		129 10:34 AM					81 11:59 PM
1/26/2017 Thursday			141 9:57 AM	332 12:58 PM	225 4:19 PM	163 6:19 PM		61 11:19 PM
