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Threading the Needle: Practical Considerations in the Modern, Evidence-based Management of Type 2 Diabetes

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1

Conflict Disclosure

- Ron Ackermann has research funding from NIH, CDC, and UnitedHealth Group to evaluate the health and economic effects of different treatment approaches and policies relating to diabetes care and prevention
- Ron Ackermann declares no financial conflicts of interest related to the topic of this presentation

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2

After the presentation, you should be able to…

- Describe causes of type 2 diabetes and the physiologic changes that occur during development & progression of the disease
- Identify behaviors that impact diabetes development & progression
- Recognize how the actions, benefits, harms, and costs of different diabetes medications should factor into appropriate prescribing decisions
- Discuss practical strategies for assisting patients to achieve meaningful behavior change
- Describe policy & system changes that could help integrate evidence into practice for how to maximize health in people with type 2 diabetes

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How Common is Diabetes in America?

- **Diabetes Prevalence:** 30.3 million (9.4% of the US population)[1]
  - **Diagnosed:** 23.1 million (between 91% and 93% are type 2 diabetes)[2,3]
  - **Undiagnosed:** 7.2 million (23.8% of people with T2D)
  - **Prevalence varies** by race/ethn (NHW 7.4%; NHB 12.7%; H 12.1%; AS 8%; NA 15.1%)
- **About 1.7 to 1.9 million Americans develop T2D annually**[1]

[1] CDC National Diabetes Statistical Report (2017) www.cdc.gov/diabetes/data/statistics-report/index.html
[2] Menke A, et al. Epidemiology 2013;24(5):773-4
[3] Bullard KM, et al. MMWR 2018; 67(12);359–361

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What is Diabetes?

Origin of the word….
Diabetes (Greek; to pass through or siphon) + mellitus (sweet)

Immediate upstream physiologic defect….
Insufficient quantity or action of the hormone insulin

But what causes these insulin problems?

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"CliffsNotes" of physiology

6

A slight reminder…

- Glycogen – multi-branch polysaccharide of glucose used to store energy within cells
- Glycogenolysis – phosphorylation of glycogen stores into glucose monomers
- Gluconeogenesis – synthesis of glucose from amino acids
- Glycolysis – oxidation of glucose to acetyl-CoA to enter Kreb's cycle (energy production within mitochondria)

- Lipogenesis – synthesis of TG's from acetyl-CoA for storage as lipid droplets in adipose
- Lipolysis – hydrolysis of lipids to release fatty acids
- Lipid oxidation – breakdown of fatty acids to acetyl-CoA to enter Kreb's cycle

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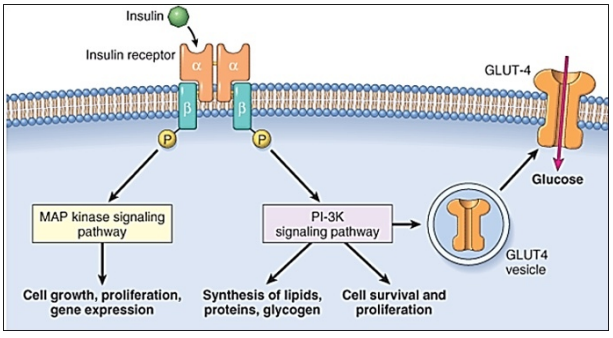
Cellular "Sensing" of Insulin



Bekele S, et al. J Mol Pathophysiol. 2019; 8(1): 1 - 13

- Insulin is a peptide hormone
- Binding of insulin to its cell membrane receptor activates tyrosine kinase on the intracellular side
- Tyrosine kinase is an enzyme that phosphorylates target proteins (Insulin Receptor Substrates) in the cytosol
- IRS pathways stimulate cell growth & proliferation, as well as synthesis of lipids, proteins, and glycogen (i.e., anabolic effects)

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Normal Effects of Insulin Action

Insulin's effects are generally anabolic – storing of energy by tissues

- Liver
  - ↑ transport of glucose into cells
  - Activation of glycogen synthase
  - ↓ gluconeogenic enzymes
  - ↑ fatty acid (FA) synthesis
- Muscle
  - ↑ transport of glucose into cells
  - Activation of glycogen synthase
  - ↑ fatty acid synthesis
- Adipose
  - Inhibition of lipolysis, leading to net synthesis of triglycerides from FAs

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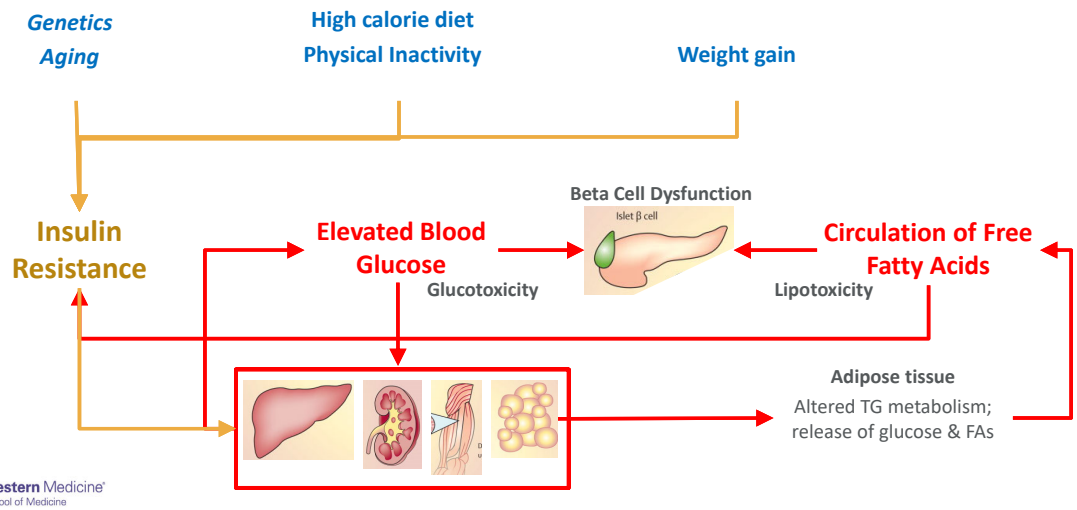
Type 2 Diabetes begins with Resistance to Insulin

T2D is an impairment in insulin sensitivity that is generally identified by blood glucose elevation



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Type 2 Diabetes & Energy Balance

- T2D is a catabolic state; normal signaling of the anabolic hormone insulin is impaired
- Failure of normal nutrient storage causes…
  - Impairment of normal cell growth and differentiation in many tissues
  - Elevation of blood glucose and fatty acids to toxic / inflammatory levels
  - Exceeding renal threshold for glucose resorption → glycosuria → weight loss
  - Compensatory increases in insulin secretion → hyperinsulinemia
- Hyperinsulinemia slows catabolism of T2D; unlikely that it (alone) causes weight gain
  - Catabolism & weight loss stops when ↑ insulin is sufficient to inhibit lipolysis, gluconeogenesis, & glycosuria
  - Weight gain occurs when ↑ insulin is combined with a sustained energy dense diet (positive calorie balance)

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In the Setting of Insulin Resistance, Any Form of Positive Calorie Balance can be Bad…

- All carbohydrates are digested to glucose, fructose, & galactose (converted to glucose by the liver)
- In the absence of inhibition by insulin
  - Glucose absorbed/produced after a meal is not stored as glycogen or used to synthesize tri-acyl-glycerides (for transport to and storage by adipose tissues)
  - Fatty acids absorbed after a meal are not taken up normally and stored in adipose tissues via lipogenesis
  - The liver converts dietary peptides/amino acids to glucose (gluconeogenesis)
- Any source of positive energy balance can lead to weight gain
  - Insufficient energy expenditure
  - Excess calories from carbohydrate or fat

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Insulin Resistance

- Type 2 Diabetes is a disease of insulin resistance – resulting in high blood glucose, abnormal lipid metabolism, pro-inflammation, and accelerated atherosclerosis
- Weight gain, loss of lean body mass, & physical inactivity worsen insulin resistance
- Insulin resistance is present before and during diabetes, and should be targeted for treatment as an underlying cause
- But HOW?

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Improving Insulin Sensitivity

- Lowering blood glucose reduces microvascular and macrovascular complications of diabetes, but does not improve insulin sensitivity
- Multiple forms of physical activity improve insulin sensitivity for 24-72 hours
- Weight loss (loss of abdominal fat) & increasing skeletal muscle mass improves insulin sensitivity

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Common T2D Medications & How They Work

	Insulin	Metformin	Sulfonylurea	GLP1	DPP4 Inhibitor	SGLT2 Inhibitor	TZD
Route	Injection	Oral	Oral	Injection; Oral	Oral	Oral	Oral
↑Insulin Supply?	Yes	No	Yes	Yes; glucose-dependent	Yes; glucose-dependent	No	No
Improves Insulin Sensitivity?	No	Possibly	No	Possibly	Possibly	No	Yes
Other Actions	↑ tissue glucose uptake; ↑ lipid storage	↓ liver glucose production	↑ pancreatic insulin release	↓ appetite; Glucose-dependent pancreatic insulin release	Prolongs action of gut hormones that ↑ glucose-dependent pancreatic insulin release	↑ glucose excretion by kidney (in urine)	↑ sensitivity of muscle & adipose to actions of insulin
Mean A1c ↓	No limit	1.0 - 1.5%	1.0 - 1.5%	0.8 – 1.5%	0.25 - 1.0%	0.5 – 1.0%	0.5 – 1.5%
Body Weight	Gain	Loss	Gain	Loss	Neutral	Loss	Gain (fluid)

If you needed to take a medication for T2D, which medication would you choose first? Why?

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Intensive Glucose-Lowering Trials: Cautionary Tale?

↓ Microvascular Outcomes but Mixed CVD & Mortality Outcomes

Long-term follow-up[1,4,5]

Study	Baseline A1c; ↓ Control vs Intensive	Mean duration T2D at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓↔*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

Table adapted from 1. Bergenstal et al. Am J Med 2010;123:374.e9–e18

2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8; 3. Ismail-Beigi et al. Lancet 2010;376:419–30;

4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT); 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

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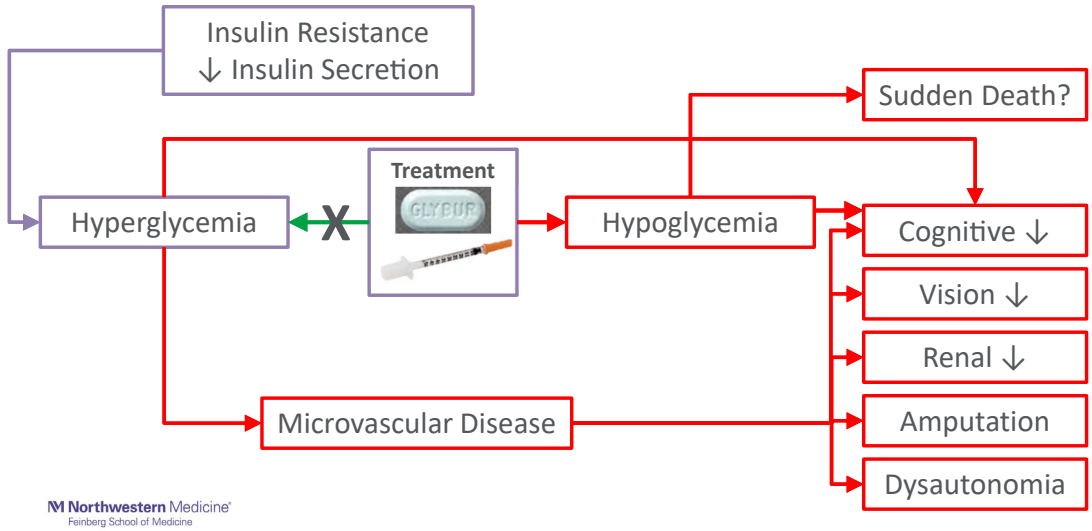
16

Harms of High & Low Blood Glucose



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Weight Change with Different Glucose Lowering Meds

Medication Class	Weight Changes	Hypoglycemia	Notes
Metformin	**- 1.0 to -2.9 kg (net loss)**	Rare	Losses in first 3 to 6 months
Insulin	+0.4 to +4.8 kg (net gain)	Common	
Sulfonylureas	-0.9 to +4.2 kg (variable/ net gain)	Common	Gain more likely if monotherapy
Meglitinides	-0.2 to +1.8 kg (neutral)	Common	
DPP4 Inhibitors	-0.9 to +2.6 kg (neutral)	Uncommon	
GLP1 Receptor Agonists	**-1.2 to -4.0 kg (loss)**	Uncommon	Greater loss with SC semaglutide
SGLT2 Inhibitors	**-1.0 to -4.5 kg (loss)**	Uncommon	
TZDs	+2.0 to +3.9 kg (net gain)	Uncommon	75% of gain believed from volume

Wharton S, et al. Diabetes Metab Syndr Obes. 2018 Aug 21;11:427-438.

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CV Outcome Trials

Relative Benefits of SGLT2i's and GLP1ra's

	Relative Odds/Hazard		
	SGLT2i's	GLP1ra's	Annual Event Probability
All Cause Mortality	**HR 0.85 (0.78-0.93)**	**OR 0.88 (0.83-0.95)**	Prior CVD: 2.6%; No Prior CVD: 1.3%
Any MACE Event	**HR 0.89 (0.83-0.96)**	**OR 0.88 (0.82-0.94)**	Prior CVD: 4.4%; No Prior CVD: 1.4%
Acute Myocardial Infarction	HR 0.89 (0.80-0.98)	OR 0.91 (0.84-1.00)	Prior CVD: 2.1%; No Prior CVD: 0.6%
Hospitalization for Heart Failure	**HR 0.69 (0.61-0.79)**	OR 0.91 (0.83-0.99)	Prior CVD: 1.4%; No Prior CVD: 0.5%
Stroke	HR 0.97 (0.86-1.10)	**OR 0.84 (0.76-0.93)**	Prior CVD: 1.1%; No Prior CVD: 0.5%
Decline in Renal Function	**HR 0.63 (0.56-0.70)**	OR 0.87 (0.79-1.03)	Prior CVD: 1.0%; No Prior CVD: 0.6%

For GLP1 RA: Kristensen SL, et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785.
For SGLT2i: Zelniker TA, et al. Lancet. 2019 Jan 5;393(10166):31-39.; Qiu M, et al. Medicine. 2021 Mar 12; 100(10): e25121.

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Number Needed to Treat

	NNT for 10 Years to Prevent 1 More Event if CVD Risk is ~20%			
	SGLT2i's	GLP1ra's	Statins	ACE/ARB
All Cause Mortality	NNT 46 (32-100)	NNT 63 (44-152)	NNT 59 (43-93)	NS
Any MACE Event	NNT 50 (32-139)	NNT 51 (33-103)	NNT 14 (9-167)	NA
Acute MI	NNT 108 (59-598)	NNT 138 (77-4172)	NNT 32 (20-381)	NNT 52 (36-104)
Hospitalization for HF	NNT 47 (32-113)	NNT 194 (102-1750)	NS	NNT 75 (53-137)
Stroke	NS	NNT 110 (73-252)	NS	NS
Decline in Renal Function	NNT 6 (5-8)	NS	NS	NNT 17 (11-39)

For CVD Outcomes, estimates assume 20% mean risk for composite CVD event (MACE)
Data for Relative Risk/Odds/Hazard from meta-analyses:
For GLP1 RA: Kristensen SL, et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785.
For SGLT2i: Zelniker TA, et al. Lancet. 2019 Jan 5;393(10166):31-39.; Salah HM, et al. Am Heart J. 2021 Feb;232:10-22.

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Prevalence of CVD Related Risks in Diabetes

National Health and Nutrition Examination Survey, 1999-2006

Comorbidity	Diagnosed Diabetes (% ± SEM)
Hypertension	71.9 ± 1.9
Hypercholesterolemia	59.6 ± 2.1
Chronic kidney disease	40.0 ± 2.3
Coronary heart disease	29.9 ± 1.9
PAD	21.1 ± 3.2
Congestive heart failure	15.6 ± 1.3
Stroke	14.0 ± 1.3

Kalyani RR, et al. Diabetes Care 2010 May; 33(5): 1055-1060.

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Additional Harms of Diabetes Medications

	Harm: NNH	Notes
GLP1 receptor agonists (3.1 yrs)	Pancreas cancer: ? Thyroid medullary cancer: ?	Lab & animal studies suggest risk for thyroid & pancreas cancer; trials & epi evidence show NA & pancreatitis is not likely drug-related
SGLT2 inhibitors (2.9 yrs)	DKA: 665 Genital mycotic: 52	Several large population studies show UTI, Fractures, & amputation are likely not drug related
DPP4 inhibitors	URI: NS	Lab & animal studies suggest thyroid & pancreas CA risk; RCT & epi evidence show NA Meta analyses show no risk for URI: OR 0.98 (0.91-1.05)
Pioglitazone (2.4 yrs)	Bladder cancer: ? Hosp CHF: 44* Fractures in Women: ?	Risk of bladder seen in observational studies could be related to confounding Bladder cancer risk in trials is mixed; recent meta-analysis no added risk
Statins (10 yrs)	Diabetes: NS Myopathy: NNH 80 Hepatotox:: NNH 132	Only one trial to date showed increased T2D risk with statins; many show no risk

Thyroid CA: Overbeek JA, et al. Diabetes Metab Res Rev. 2018 Jul;34(5):e3004
Bladder CA: Sinha B, et al. Sci Rep. 2020; 10: 15781. (note, most patients in trials reporting increased HF events had a history of LV dysfunction at baseline)
URI: Yang W, et al. Diabetes Metab Res Rev. 2016 May;32(4):391-404
SGLT2 Risks: Salah HM, et al. Am Heart J. 2021 Feb;232:10-22
GLP1 RA Risks: Kristensen SL, et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785

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How we should think about treating T2D

- Reverse the physiologic changes causing insulin resistance (prevent and reverse weight gain; increase physical activity; optimize diet composition)
- Keep blood glucose as close to physiologic levels as is possible without causing harm (hypoglycemia & other medication related AEs)
- Identify and manage other reversible risk factors that increase cardiometabolic risk (Dyslipidemia; Hypertension; Unstable atherosclerotic plaque)
- Identify complications/risk early, when progression can be slowed
  - Foot care if neuropathy or deformity
  - RAAS & SGLT2i if albuminuria or reduced of eGFR
  - Early detection/management of retinopathy
  - GLP1ra &/or SGLT2i if elevated CV risk

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- If cost were not an issue, how would <u>you</u> treat your patients with type 2 diabetes?
- How does medication cost change your prescribing decisions?

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Weighing Benefits, Harms, & Treatment Costs

- Considerations when weighing treatment indications
  - Average Probability the Patient Benefits: NNT
    - 1/ ((Absolute Risk for Event without treatment * (1 – RRR with treatment))
  - Average Probability the Patient is Harmed: NNH
    - 1/ ((Absolute Risk for Harm without treatment * (RRI with treatment - 1))
  - The relative *severity* of the event prevented by treatment (e.g. heart attack) relative to the *severity* of the potential harm caused by treatment (e.g. myalgia), from the patient's perspective
- If 2 treatments have a comparable benefit-to-harm profile, it is reasonable to choose the treatment with the lowest cost

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Tradeoffs of Common T2D Medications

	Insulin	Metformin	Sulfonylurea	GLP1	DPP4 Inhibitor	SGLT2 Inhibitor	TZD
Route	Injection	Oral	Oral	Injection; Oral	Oral	Oral	Oral
Improves Insulin Sensitivity?	No	Possibly	No	Possibly	Possibly	No	Yes
Mean A1c ↓	No limit	1.0 - 1.5%	1.0 - 1.5%	0.8 – 1.5%	0.25 - 1.0%	0.5 – 1.0%	0.5 – 1.5%
Body Weight	Gain	Loss	Gain	Loss	Neutral	Loss	Gain (fluid)
Hypoglycemia	Yes	No	Yes	No	Usually No	No	No
Body Weight	Gain	Loss	Gain	Loss	Neutral	Loss	Gain
ARP/month	$390 - $580	$50-$120	$50 - $94	$670 - $1226	$255 - $540	$319 - $592	$349 - $355

Do Average Retail Costs of T2D Medications Change Your Prescribing Decisions?

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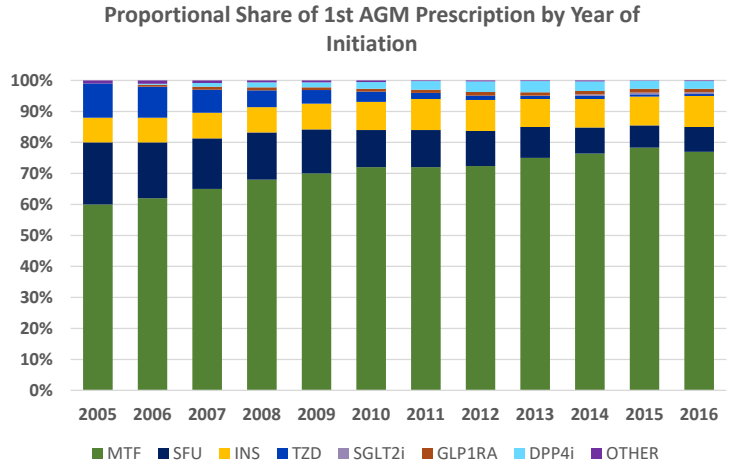
1st Line Antiglycemic Medication (AGM) Therapy



Metformin

- Preferred 1st line T2D Rx
- Approved in U.S. 1995
- $50-$120 monthly
- Reduces hepatic gluconeogenesis
- No weight gain
- Hypoglycemia rare
- GI intolerance; vitamin B12 deficiency; lactic acidosis rare

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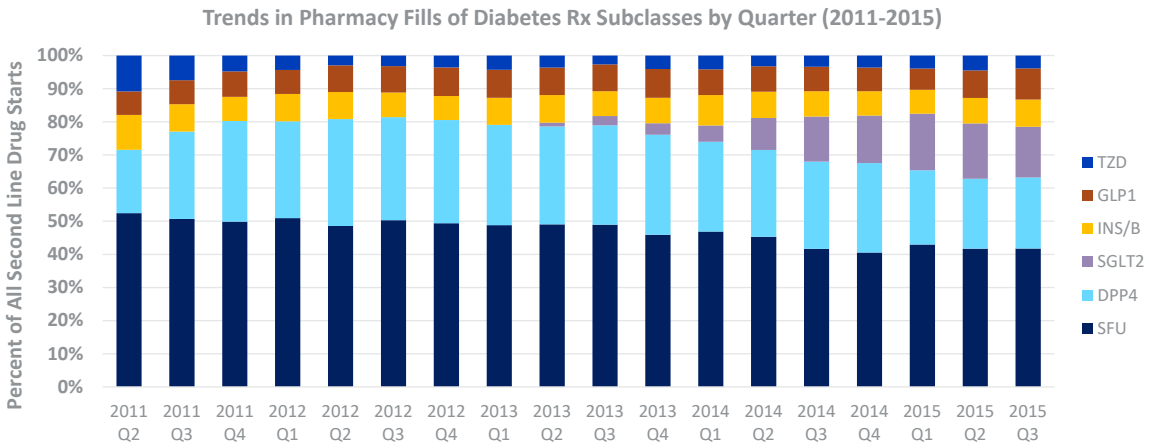
Olga Montvida et al. Dia Care 2018;41:69-78

27

2nd Line Antiglycemic Medications (AGM)



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Ackermann RT, et al. BMJ Open Diabetes Res Care. 2017 Sep 1;5(1):e000421.

28

Interpreting Prescribing Patterns

- Most patients do begin with Metformin as the 1st line treatment
  - Beneficial; low harms; familiar to prescribers; low $
- 50-65% of patients receive SFU, DPP4, or Insulin as 2nd line
  - SFU: potent glucose lowering; familiar to prescribers; low $; no Δ IR; hypoglycemia
  - DPP4: not potent; newer; not cheap; no Δ IR; no compelling benefits
  - Insulin: potent glucose lowering; familiar; not cheap; no Δ IR; hypoglycemia
- GLP1ra & SGLT2i are increasing but still <⅓ of patients
  - Compelling CV / renal / mortality benefits
  - Weight loss; at least indirect effects from GLP 1ra on insulin sensitivity
  - new to some prescribers; high cost

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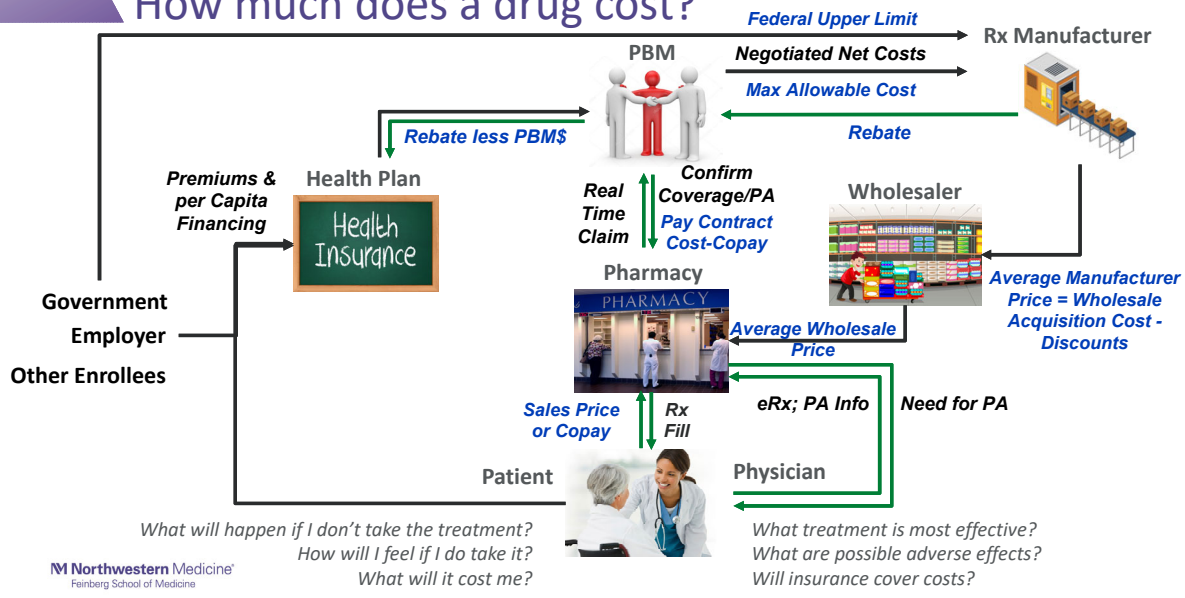
How much does a drug cost?



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Important Caveats for Clinicians

- PDL, Prior Authorization, and Step Therapy
  - Health payer tools to control utilization of select medications if they are more costly and do not have compelling additional benefits
  - Not ideal for drugs that are more costly but have unique benefits > harms
  - Create incentives for pharma to lower the net drug acquisition costs for health payers (and PBMs), often via vouchers – these data are typically not published
- Patients may or may not experience lower out of pocket costs but generally have an easier time receiving a new Rx if the health plan / PBM negotiate a lower cost

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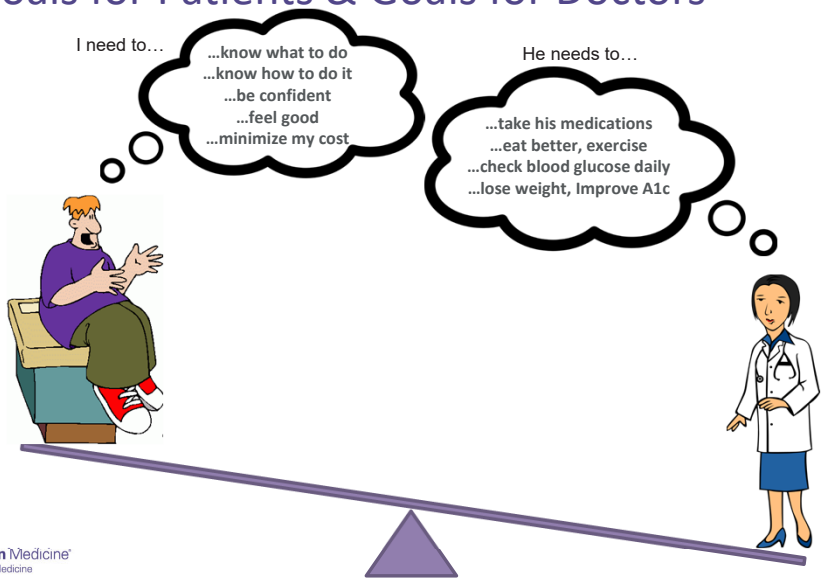
Threading the Needle: Helping Patients Adopt an Effective Treatment Plan

32

Goals for Patients & Goals for Doctors



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How is Diabetes Managed?

T2D requires daily attention to multiple behaviors & coordinated follow up with health care providers

- Daily Actions by Patients
  - Test blood 1-5 times per day
  - Take 0 to 5 medications daily; eventually transitioning to insulin
  - Navigate physician advice & costs of meds and supplies, determined by insurance
  - Daily physical activity, diet restriction; tobacco cessation/avoidance
  - Check feet / shoes daily
- Healthcare checks 2 to 4 times per year
  - Blood and urine tests
  - Medication monitoring & adjustments (glucose; cholesterol; blood pressure)
  - Education, coaching, and other forms of support
  - Foot examination
  - Dilated eye exams every 1-2 yrs

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Standards of Medical Care in Diabetes. Diabetes Care 2019 Jan; 42(Supplement 1):S1-S164.

34

Patient Perceived Health Related Quality of Life

Utility range: 0 (death) to 1 (perfect health)

Perceived HrQoL with Complications

Complication	Mean (SD) Utility
Angina	0.64 (0.31)
Mild Stroke	0.70 (0.31)
Major Stroke	0.31 (0.31)
Neuropathy	0.66 (0.34)
Amputation	0.55 (0.36)
Retinopathy	0.53 (0.36)
Blindness	0.38 (0.35)
Nephropathy	0.64 (0.35)
ESRD	0.35 (0.33)

Perceived HrQoL with Diabetes Treatments

Treatment	Mean (SD) Utility
Standard Glucose Management	0.76 (0.31)
Intensive Glucose Management	0.67 (0.34)
Standard BP Management	0.77 (0.30)
Intensive BP Management	0.73 (0.32)
Daily ASA	0.80 (0.29)
Daily Cholesterol Rx	0.78 (0.29)
Comprehensive Diabetes Care	0.64 (0.34)
Diet Restriction	0.88 (0.24)
Daily Physical Activity	0.89 (0.23)

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Huang ES, et al. Diabetes Care 2007 Oct; 30(10): 2478-2483.

35

Relevance of Diabetes Treatment Burden

Patients perceive the effort needed to intensively self-manage their diabetes as equivalent to having angina, neuropathy, or a mild stroke

- Management features perceived by patients as more favorable…
  - Fewer finger stick blood glucose tests per day
  - Avoidance of insulin shots; if insulin needed – fewer shots daily
  - Fewer pills / doses of pills daily
  - Avoidance of hypoglycemia and other side effects
  - Avoidance of weight gain
  - Lower treatment expense

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Notes on T2D Prescribing

- Metformin should remain 1st line therapy unless GI intolerant or eGFR<30
- SGLT2i
  - Consider if HF, ASCVD Risk>15-20%, microalbuminuria; eGFR 45-60
  - Consider if obesity / weight gain is a big concern; also patients taking TZD
  - Genital yeast infections ↑ if poor glucose control in ♀, or uncircumcised ♂
- GLP1ra
  - Consider if ASCVD Risk>15-20%; obesity; weight gain concern
  - Titrate slowly; nausea is main dose-limiting side effect
  - Can help "deprescribe" insulin, particularly basal only at dose 20U or less
- It makes little sense to prescribe SFU, MEG, GLP1ra, and/or DPP4i together
- Patients with β cell failure will not respond normally to SFU, DPP4, GLP1ra

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Additional notes…

- Talk to patients about out of pocket costs
  - Source of financial stress that might be avoidable
  - Common reason for treatment non-adherence, particularly as time passes
- If costs are comparable…
  - Consider once daily (or weekly) formulations (e.g., Metformin ER)
  - Consider whether costs are actually lower with a combination tablet (e.g. SGLT2i+MTF; DPP4+MTF) rather than separate tablets
  - Meglitanides rarely have advantages and likely add burden for patients
  - Sometimes a single PM basal insulin dose reduces complexity of a treatment plan
  - It is sometimes possible to deprescribe lower dose insulin by introducing a GLP1ra

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Sometimes more data can help…

- Insulin resistance can be estimated from fasting insulin and glucose
  - HOMA1-IR[1] = (Fasting Plasma Insulin Concentration (µIU/mL) × Fasting Plasma Glucose Concentration (mg/dL)) ÷ 405
  - HOMA-IR ≤1: Normal
  - HOMA-IR>1.9: Insulin Resistant
- C-peptide levels can help identify the need for insulin
  - In the setting of elevated blood glucose, an undetectable C-peptide level suggests…
    - Pancreas β cell failure
    - Insulin is needed
    - Secretagogues will be less effective for glucose control (SFU, MEG, DPP4, GLP1)

1. Wallace TM, et al. Diabetes Care 2004 Jun; 27(6): 1487-1495

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Consider weight gain effects of other therapies…

Medication Class	Weight Changes	More Weight Neutral Alternatives
Citalopram	- 0.1 to +7.1 kg	Consider alt SSRI/SNRI or Bupropion
Amitriptyline & Nortriptyline	+0.4 to +7.3 kg	Imipramine & doxepin; trazodone
Other SSRIs and SNRI's	+/- 2.0 kg (**variable**)	Monitor response; consider Bupropion
Bupropion	-0.4 to -2.4 kg	*Weight neutral or very slight weight* loss
Ziprasidone	-1.1 to +0.1 kg	
Aripiprazole	-1.4 to +0.2 kg	
Valproic acid	+0.7 to +6.9 kg	
Lamotrigine	-4.2 to +0.6 kg	
Carbamazepine	-2.1 to +0.4 kg	
Topiramate	Variable	Typically no weight gain; insulin sensitizing effects

Wharton S, et al. Diabetes Metab Syndr Obes. 2018 Aug 21;11:427-438.

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Coaching Towards Lifestyle Changes for Weight Loss

- Recommend a goal for 5-10% (10-25 lbs) of weight loss
  - Cuts by half the rate of progression from prediabetes to T2D
  - Improves glucose control in T2D & lowers the need for diabetes & HBP medications
- Advise aiming for weight loss at pace of ½ to 1 lb per week
- Patients who self-weigh daily are ~5x more likely to reach weight goal
- Patients who engage in a high-contact lifestyle coaching program are ~5x more likely
  - Source of supportive accountability
  - Action plan & coaching support for both PA and healthful diet goals
  - Recurring contact to build self-regulation, self-efficacy, and problem solving skills
  - Longitudinal support while people remain in the same homes, jobs, neighborhoods

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Doc, what's the best exercise?

- Uncommon to lose weight by exercise alone, without dietary change
  - Generally requires ~daily & higher volume – 60+ minutes moderate; 40+ min vigorous
  - Must avoid compensatory increase in dietary calories
- Many forms of PA can improve insulin sensitivity for 24-72 hours
  - 170+ min/week of moderate to vigorous PA
  - Briefer, high intensity bouts of activity
    - 4 to 10 bouts of 30- to 60-second high intensity cycling bursts
    - 3 min bursts of speed walking (80-95% PMHR) separated by 1-4 min of active rest
  - Resistance training >60 min/week
- Advise a specific goal; self-monitoring (Fitbit; iWatch); accountability (meeting friend)

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Doc, what's the best diet?

- It's the diet you will be able to adopt and maintain over time
- Generally good to…
  - Avoid all trans-fats
  - Avoid all sweetened beverages
  - Minimize refined CHOs (desserts, candy, bread, pasta, white rice)
  - Minimize animal fats (frying, non-lean meats, full fat dairy, dressings/sauces)
  - Increase fresh f/v
- Some fad diets have benefits but are costly or difficult to maintain

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Time Restricted Eating (Intermittent Fasting)

- Some forms of time restricted eating (eating most calories before 2pm and all calories before 5pm) may improve insulin sensitivity and glucose control and may help some patients achieve weight goals
  - Aligns food intake with circadian rhythms in metabolism
  - Avoids late snacking
  - Requires people to plan meals rather than eating ad hoc

https://www.sciencedirect.com/science/article/pii/S0026049517303293?via%3Dihub
https://www.sciencedirect.com/science/article/pii/S1550413118302535#bib62

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Clinician's Role in Advocacy & Policy

- Marketing is a large cost for Pharma that increases drug prices; avoid engaging in pharma marketing events; office visits; and free samples
- The average daily retail price for insulin has increased many-fold, even for older insulins
- Pharma rebates negotiated by PBMs or pharmacy wholesalers often lower costs for payers but not patients; advocate that out of pocket costs be based on net costs to payers rather than average wholesale costs (pre-rebate list price)
- Prior authorization strategies should not limit access to drugs for which there is not a less costly alternative; advocate for SGLT2i and GLP1ra coverage for patients with high ASCVD risk, similar to statins
- Intensive lifestyle programs are the most proven strategy to address insulin resistance but are not available in many markets or are too costly for patients – advocate that these programs be expanded and covered by health payers, beginning with Medicare

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Questions?

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46