DM Fundamentals – Class 4 Meds for Type 2

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Diabetes Meds for Type 2: Class 4

1. Describe the main action of the different categories of type 2 diabetes medications.
2. Discuss strategies to determine the right medication for the right patient.
3. List the side effects and clinical considerations of each category of medication.

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Diabetes Agents Considerations

- Diabetes medications can be used as monotherapy, in combo or with insulin
- Combining agents from different classes has additive effect
- Most reduce A1c 0.5 – 2.0%
- Not to be used during preconception, pregnancy or when breastfeeding

Patient Centered Approach

"...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

- **Gauge patient's preferred level of involvement.**
- **Explore, where possible, therapeutic choices.**
- **Utilize decision aids.**
- **<u>Shared</u> decision making – final decisions re: lifestyle choices ultimately lie with the patient.**

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

Diabetes Care **2012;35:1364–1379**
Diabetologia **2012;55:1577–1596**

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Approach to the management of hyperglycemia

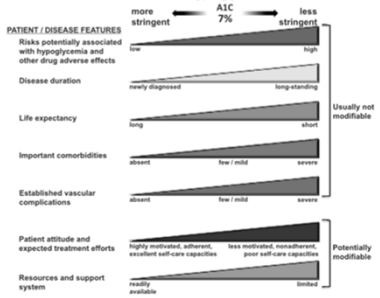

Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (45).

ADA Standards of Care 2015

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Antihyperglycemic Therapy – 1st Step

- Lifestyle Changes
  - Weight control
  - Healthy eating
  - Activity

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

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Action/Classes of Type 2 Meds

1. Suppressor	Biguanide – Metformin
2. Squirter	Sulfonylureas Meglitinides
3. Satiators	AmylinoMimetics Incretin Mimetics DPP-4 Inhibitors
4. Sensitizer	Thiazolidinediones (TZD)
5. Glucoretics	SGLT2 Inhibitors
6.Circadian Switchers	Dopamine Receptor Agonists
7. Slower	Alpha-glucosidase inhibitors

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Ideal Diabetes Med -

- No hypoglycemia
- No weight gain
- Affordable
- Lowers CV risk
- Most people can tolerate /use?

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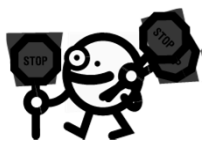
Biguanides – Suppressor Metformin (Glucophage®)

- Action: suppresses release of glycogen from the liver
- Who?
  - Fasting hyperglycemia
  - Dysmetabolic Syndrome
  - For pediatrics starting age 10
    - (XR age 17)



Glycogen Stopper and **GLP Enhancer?**

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Biguanides - Metformin

- **Action:** decrease hepatic glucose (glycogen)
- **Names:**
  - Metformin (Glucophage)
    - Starting dose: 500 BID, max 2500mg daily
  - Metformin extended release (3 different versions)
    - Starting dose 500mg at dinner, max dose 2000 to 2500 mg daily
  - **Efficacy:**
    - Decrease fasting plasma glucose 60-70 mg/dl
    - Reduce A1C 1.0-2.0%

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Biguanides - Metformin

- Benefits
  - Decrease LDL cholesterol and triglycerides
  - No weight gain, possible modest weight loss
  - Cancer protective?
- Concerns
  - Diarrhea and abdominal discomfort – Use XR
  - Lactic acidosis if improperly prescribed
  - Watch for B12 deficiency
  - Hold prior to IV contrast dye studies and use caution during acute illness. Resume when kidney function adequate

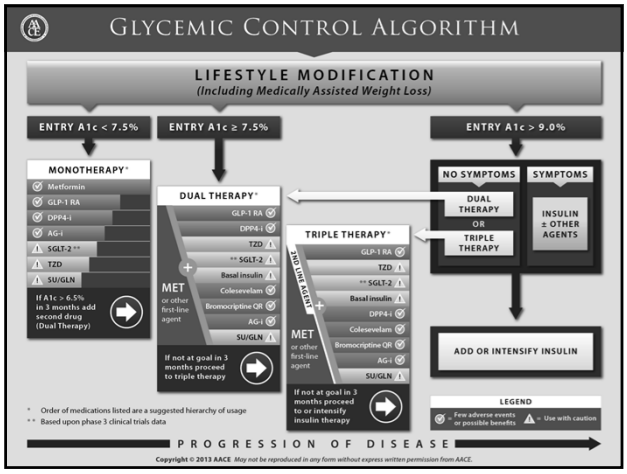
Considerations
Biguanide - Metformin (Glucophage®)

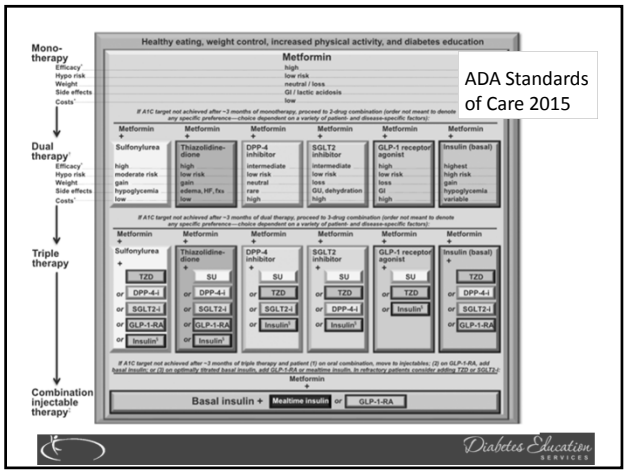
- Contraindications due to risk of lactic acidosis:
  - creatinine >1.4 females, >1.5 males
  - liver disease
  - alcohol abuse
  - over 80 years old
  - risk of acidosis
  - during IV dye study
  - CHF requiring meds

ADA Stds 2015 suggests GFR may be a more appropriate measure. If GFR <45, max dose is 1000mg a day. If GFR <30, stop metformin.

Metformin – How does it rate?

Question	Answer
Cause hypoglycemia?	No
Cause weight gain?	No
Affordable?	Yes
Lowers CV risk?	Yes
Can most tolerate /use?	Yes/No (GI, creat)





ADA Standards of Care 2015

Life Study

- 59 year old overweight woman with type 2 diabetes for past 3 years. Has been trying to control diabetes with diet and exercise.
- Most recent A1c 8.4%
- What medication would you consider? Labs?

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Sulfonylureas –

- Action: tells pancreas to squirt insulin all day
- Who?
  - Lean type 2

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Sulfonylureas - Squirts

- Action: Increase endogenous insulin secretion
- Efficacy:
  - Decrease FPG 60-70 mg/dl
  - Reduce A1C by 1.0-2.0%
- Secondary failures: 5-10% shortly after initial response, many more later
  - Usually after 5 or more years of therapy due to natural history of DM 2

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Sulfonylureas: 2nd Generation

Generic	Trade	Duration
Glyburide	Diabeta, Micronase, most likely to cause hypo – last choice	12-24 hrs
Glipizide*	Glucotrol, Glucotrol Xl	12-24 hrs
Glimepiride	Amaryl	16-24 hrs

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Sulfonylureas

- Other Effects
  - Hypoglycemia
  - Weight gain
  - Cleared by kidney, use caution for pts with kidney problems
  - Generally the least expensive class of medication
  - Amaryl safest for those with CV Disease

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Indication for "Fast Acting" Insulin Secretagogues- Meglitinides

- Action: tells pancreas to squirt insulin with meals
- Who?
  - Targets post-prandial hyperglycemia

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When goal is to minimize cost

- Go generic. Metformin and Sulfonylureas
- Walmart offers 3 month supply of following meds for ~ $10
  - Metformin and Metformin XR
  - Glipizide, Glyburide, Glimepiride

- Other generics include
  - Actos and Avandia
  - Acarbose
  - Can still cost up to $100 a month
- Meds on a Budget Article

Meglitinides - Squirts

- **Action**: stimulate insulin secretion (rapid and short duration) when glucose present
- **Names**:
  - repaglinide (Prandin)
    - **Dosing**: 0.5 to 4 mg a.c. Max dose 16mg
    - Metabolized by liver and mostly excreted in feces (some renally).
  - nateglinide (Starlix)
    - **Dosing**: 120 mg tid with meals
    - Metabolized by liver, excreted by kidney
- Efficacy:
  - Decreases peak postprandial glucose
  - Decreases plasma glucose 60-70 mg/dl
  - Reduce A1C 1.0-2.0%

Meglitinides

- Other Effects
  - Hypoglycemia (less than with sulfonylureas if patient has a variable eating schedule)
  - Minimal weight gain
  - No significant effect on plasma lipid levels
  - Safe at higher levels of serum Cr than sulfonylureas

Squirters – How does they rate?

Question	Answer
Cause hypoglycemia?	Yes
Cause weight gain?	Yes
Affordable?	Yes
Lowers CV risk?	No
Can most tolerate /use?	Yes/No

What questions?

- 72 yr old, thin, lives alone, A1c 7.3%. History of MI, stroke. DM for 12 yrs, "diet controlled". Limited income. Creat 1.4.

DPP-4 Inhibitors – "Incretin Enhancers"

Januvia (sitagliptin) – Tradjenta (linagliptin)
Onglyza (saxagliptin) Nesina (alogliptin)

- **Action:**
  - Increase insulin release w/ meals
  - Suppress glucagon
- **Dosing**: Januvia – 100mg a day
  Onglyza – up to 5mg a day
  Tradjenta – 5mg a day
  Nesina – up to 25 mg a day
- **Efficacy:** Decreases A1c by 0.6 -0.8%
- **Indication**: For type 2s

DPP-4 Inhibitors – "Incretin Enhancers"

Januvia (sitagliptin) – Tradjenta (linagliptin)
Onglyza (saxagliptin) Nesina (alogliptin)

- Januvia, Onglyza eliminated via kidney, lower dose needed
- Do not cause wt gain or hypoglycemia
- Side effects – headache, runny nose, sore throat - watch for pancreatitis
- Cost $100 - $150 mo

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DPP-IV Inhibitors – How do they rate?

Question	Answer
Cause hypoglycemia?	No
Cause weight gain?	No
Affordable?	No
Lowers CV risk?	No
Can most tolerate /use?	Yes

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If on Metformin and Sulfonylurea – A1c 8.4 - Pt struggling with weight

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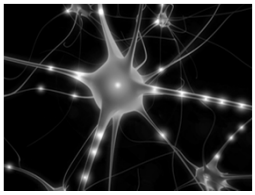
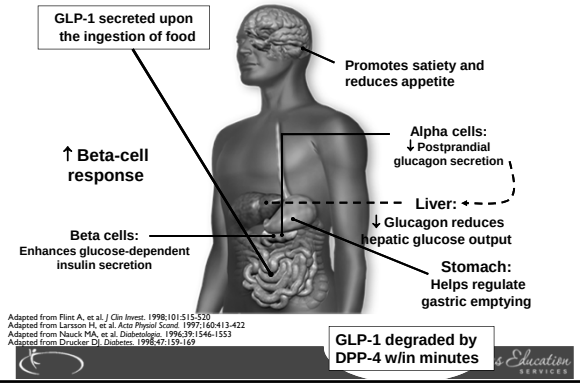
Incretin Mimetics – "Gut Hormone Imitators" GLP-1 Agonists

- How do they work?



GLP-1 Effects in Humans
Understanding the Natural Role of Incretins



Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

Incretin Mimetics
Exenatide (Byetta), Exenatide XR (Bydureon)

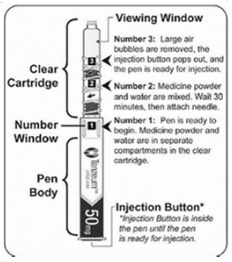
- **Action:**
  - Insulin release in response to meal
  - Slows gastric emptying
  - Causes Satiety
  - Protects Beta Cells
- **Exenatide Dosing**:
  - 5-10 mcg before break, dinner
  - Long acting version - 1x week (available in pens in 2015)
- **Efficacy:** Decreases A1c by 0.7%, wt by 3lbs
- **Indication**: For type 2s only - mono or in combo
- 

Incretin Mimetics – Exenatide XR - Bydureon

- **Once a Week Dosing:** 2mg
- **Efficacy:** Decreases A1c by 1.6%, wt by ~6lbs
- **Indication**: For type 2s only
- **Other**: – Available in pen
- **Caution**:
  - not indicated for pt's w/ history of medullary thyroid tumor
  - pancreatitis warning

Incretin Mimetics – Albiglutide - Tanzeum

- **Once a Week Dosing**: 30 – 50mg
- **Efficacy:** Decreases A1c by ~ 1%, wt by ~2lbs
- **Indication**: For type 2s only
- **Other**: Pen injector
- **Caution**: not indicated for those with history of medullary thyroid tumor - pancreatitis warning



Incretin Mimetics - GLP-1 Analog

Liraglutide (Victoza)

Liraglutide Dosing: 1x daily, time not critical

- 0.6 x 1 week – if tolerated (nausea), go to >
- 1.2 x 1 week – if tolerated go to >
- 1.8 mg daily

- **Efficacy:** lowers; A1c by 1%, body wt by ~ 2.5kg
- **Indication**: Monotherapy or in combo . Type 2 only
- **Other**: In pen 

Black box–thyroid tumor warning (avoid if family hx, notify MD of hoarseness, lump).

For all the Previous GLP-1 Agonists

- Pancreatitis Warning
  - Please tell all patients to report signs right away and discontinue meds
  - Signs include:
  - Sudden abdominal pain, nausea and vomiting
-

Incretin Mimetics – How do they rate?

Question	Answer
Cause hypoglycemia?	No
Cause weight gain?	No
Affordable?	No
Lowers CV risk?	No
Can most tolerate /use?	Yes/No (GI)

What questions?

- 69 year old male, BMI 25, on Metformin 1000mg BID and Exenatide 10mcg before breakfast and dinner.
- A1c 8.1%. Creat 1.2
- Pt is overweight, 11 yr history of diabetes

SGLT2 Inhibitors- "Glucoretics"

- **Action**: "Glucoretic" decreases renal reabsorption in the proximal tubule of the kidneys (reset renal threshold and increase glucosuria)

Name(s)	Daily Dose Range	Considerations
Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	100 – 300 mg 1x daily 5 – 10 mg 1x daily 10 – 25 mg 1x daily	For all, monitor B/P, K+ and renal function. If GFR<45, stop Invokana. If GFR<60, stop Farxiga. Do not start pts w/ GFR<45 on Jardiance. Side effects: hypotension, UTIs, increased urination, genital infections. Avoid Farxiga in pts. w/ bladder cancer. Lowers A1c 0.7% – 1.5%, lowers wt 1 – 3 lbs.

- **Efficacy:**
  - Weight loss of 1-3 lbs Reduce A1C ~0.7-1.5%

Decreases Glucose Reabsorption

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Considerations

- May temporarily lower GFR
- Monitor B/P, K+ & renal function.
- Side effects: hypotension, UTI, increased urination, genital yeast infections.
- Other benefits?
  - Reverses glucoses toxicity by increasing GLUT4 transport in muscle
  - Increase liver sensitivity to insulin and decreases gluconeogenesis.

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SGLT2 Inhibitors- How do they rate?

Question	Answer
Cause hypoglycemia?	No
Cause weight gain?	No
Affordable?	No
Lowers CV risk?	No
Can most tolerate /use?	Yes?

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Indications for Insulin Sensitizers
Rosiglitazone (Avandia), Pioglitazone (Actos)

- **Action**: decrease insulin resistance by making muscle and adipose cells more sensitive to insulin. Decrease free fatty acids
- **Names**:
  - pioglitazone (Actos) – bladder cancer warning
    - Dosing: 15-45 mg daily
  - rosiglitazone (Avandia) – restriction relaxed
    - Dosing: 4-8 mg daily
- **Efficacy/ Considerations**
  - Reduce A1C ~0.5-1.0%
  - 6 weeks for maximum effect
  - $100 a month
  - Can cause fluid retention, not indicated w/ CHF

TZDs – How do they rate?

Question	Answer
Cause hypoglycemia?	No
Cause weight gain?	Yes
Affordable?	Generic
Lowers CV risk?	??
Can most tolerate /use?	Watch CHF

Indications for Glucosidase Inhibitors
Acarbose (Precose®), Miglitol (Glyset®)

Action: Slower

- Target post-prandial blood glucose
- Minimal systemic absorption

Alpha-glucosidase Inhibitors

- **Action**: blocks enzymes that digest starches in the small intestine
- **Name**: acarbose (Precose)
  - Dosing: 75-300mg based on weight
- Efficacy
  - Decrease postprandial glucose 40-50 mg/dl
  - Decrease A1C 0.5-1.0%
- Other Effects
  - Flatulence or abdominal discomfort
  - Contraindicated in patients with inflammatory bowel disease or cirrhosis
- Special Consideration
  - In case of hypoglycemia, treat with glucose tabs or milk
  - (other starches are blocked by medication))

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Amylin Mimetic Pramlintide (Symlin) 2005

- **Action:**
  - prevents post-meal rise in glucagon
  - slowing gastric emptying
  - Increases satiety
- **Efficacy:** Decreases A1c by 0.7%, wt by 3lbs
- **Dosing**:
  - Type 2 – max 120 mcg, BID before meals
  - Type 1 – max 60 mcg ac meals (meal = 30 gms carbs)
- **Other**: approved only as adjunct to insulin therapy – can't mix in same syringe with insulin

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Dopamine Agonists – Circadian Re-Setters

- **Action**: Increase am dopamine levels
- **Name**: bromocriptine mesylate QR (Cycloset)
  - **Dosing**: 1.6 to 4.8 mg per day
  - Each tab 0.8 mg, one tab a day, increase one tab a week
  - Give w/in 2 hrs of waking (before food)
- Efficacy:
  - Reduces A1C 0.6 – 0.9%
  - Reduces death from CV events
- Side Effects:
  - Nausea, vomiting, headaches, fatigue (watch for syncope)

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Critical Points

- Individualize Glycemic targets & BG-lowering
- Diet, exercise, & education: foundation T2DM therapy
- Metformin = optimal 1st-line drug.
- After metformin, data limited. Combo therapy reasonable
- Ultimately, many T2 patients will require insulin therapy
- All treatment decisions should be made in conjunction with the patient (focus on preferences, needs & values.)
- CV risk reduction - a major focus of therapy.

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

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Self Sudy - List the Treatment Options

- 35 yr old, BMI 28, creat 0.8, A1c 6.7%
  Sit 1: Wants to try lifestyle changes before meds
  Sit 2: Started on Januvia, can't afford it. What alt med?
- 72 yr old, thin, lives alone, A1c 7.3%. History of MI, stroke. On glyburide 10mg a day and beta blocker. Creat 1.4.
- 69 year old male, BMI 25, on Metformin 1000mg BID. AM glucose 120s, A1c 8.1%. Creat 1.3
- 64 yr old on daily; amaryl 4mg, Januvia 100mg, Avandia® 4 mg. A1c 9.2%. Pt c/o of 12 lb wt gain over past month. Creat 1.2, LDL 138
- Pt on Exenatide 10mcg BID, c/o of sudden abd pain.

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PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

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