DM Fundamentals – Class 4
Meds for Type 2

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President, Diabetes Education Services
2017

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.

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
Poll Question 1

1. Which factors are most important to consider matching meds to patients?
   a. Their insurance coverage
   b. Their ability to self manage
   c. Their willingness to take meds
   d. Their glucose history
   e. all of the above

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.
- Shared decision making – final decisions re: lifestyle choices ultimately lie with the patient.


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

Patient Centered Approach
Poll Question 2

59 yrs, type 2, overwt woman, A1c 8.4. Lifestyle not working. GFR 62. What 1st class of med would you suggest?
- a. Sulfonylureas
- b. Metformin
- c. DPP-IV Inhibitors
- d. Insulin
- e. TZD (Actos or Avandia)

Antihyperglycemic Therapy – 1st Step

- Lifestyle Changes
  - Weight control
  - Healthy eating
  - Activity
  + Metformin

ADA Step Wise Approach to Hyperglycemia 2017

- Start lifestyle coaching and metformin therapy
- Metformin is effective, safe, affordable, lowers CV Risk
- If A1c target not achieved after 3 mos, start 2nd med/ins
- If A1c target not achieved after 3 mos, add 3rd agent
- If A1c target not achieved after 3 mos, add basal insulin
- If A1c target not achieved after 3 mos, keep metformin, consider adding bolus insulin, or switching to GLP-1 RA + Basal, or premixed insulin
- A1c ≥ 9% consider initiating dual therapy or insulin if
- A1c ≥ 10% consider initiating combo insulin therapy
Poll Question 3

2. What are qualities of an ideal diabetes medication? (multiple)
   a. No weight gain or some weight loss
   b. Affordable
   c. Only cause hypoglycemia once a week
   d. They cause a slight increase in LDL
   e. Lower cardiovascular risk

Ideal Diabetes Med -

- No hypoglycemia
- No weight gain
- Affordable
- Lowers CV risk
- Most people can tolerate / use?
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 – long term use
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 2016 suggests GFR may be a more appropriate measure

Metformin – New GFR Guidelines

<table>
<thead>
<tr>
<th>Class/Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin (Glucophage)</td>
<td>500 - 7500 mg (usually 800 mg)</td>
<td>Side effects: nausea, bloating, diarrhea, GI distress. For monotherapy (≤ 80 g/day), metformin can be given with or without meals. The GFR should be &lt;60 mL/min/1.73 m².</td>
</tr>
<tr>
<td></td>
<td>Oral (metformin)</td>
<td>500 - 1500 mg 500 mg/500 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-release (Glucofort, Metformin)</td>
<td>1000 - 1500 mg</td>
<td>For patients &gt;180 kg or with renal insufficiency (GFR &lt;60 mL/min/1.73 m²), switch to a once-weekly formulation.</td>
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Biguanide derived from: Goat’s Rue (Galega officinalis), French Lilac

Metformin – How does it rate?

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<td>Affordable?</td>
<td>Yes</td>
</tr>
<tr>
<td>Lowers CV risk?</td>
<td>Yes</td>
</tr>
<tr>
<td>Can most tolerate /use?</td>
<td>Yes/No (GI, creat)</td>
</tr>
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</table>
Life Study

- 69 year old slightly overweight woman with type 2 diabetes for past 3 years. Has been trying to control diabetes with diet and exercise. GFR 32.
- Most recent A1c 8.4%
- Limited income, pays cash for meds.
- What class are you considering?

Poll question 4

- Which of the following groups of meds for type 2 are cheapest? (multiple)
  a. Actos and Avandia
  b. Glipizide, Glyburide, Glimepiride
  c. Metformin and Metformin XR
  d. Januvia and Onglyza
  e. Bydureon and Victoza

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
  - More cost info – ADA Standards 2017
Sulfonylureas –

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

- 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

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

Sulfonylureas: 2nd Generation

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Diabeta, Micronase,</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td></td>
<td>most likely to cause hypo – last choice</td>
<td></td>
</tr>
<tr>
<td>Glipizide*</td>
<td>Glucotrol, Glucotrol Xi</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>16-24 hrs</td>
</tr>
</tbody>
</table>
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

Squirters – How does they rate?

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If on Metformin and Sulfonylurea – A1c 8.4 - Pt struggling with weight
Poll Question 5

5. 44 year old on Metformin and Sulfonylurea, A1c 8.4. Struggling with wt. Best options? (multiple)
   a. Refer to RD
   b. Suggest GLP-1 Agonist (exenatide, liraglutide, etc)
   c. Increase dose of sulfonylurea
   d. Suggest add on of SGLT-2 Inhibitor (Invokana etc)
   e. Suggest starting insulin
SGLT2 Inhibitors - “Glucoretics”

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

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>Main Action</th>
<th>Name(s)</th>
<th>Daily Dose Range</th>
<th>Considerations</th>
</tr>
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<tbody>
<tr>
<td><em>Glucoretic</em></td>
<td></td>
<td>Canagliflozin</td>
<td>100 mg x 1x daily</td>
<td>Side effects: Hypotension, UTI, increased urination, genital infections, ketones/lost.</td>
</tr>
<tr>
<td><em>Glucoretic</em></td>
<td></td>
<td>Dapagliflozin</td>
<td>5 - 10 mg x 1x daily</td>
<td></td>
</tr>
<tr>
<td><em>Glucoretic</em></td>
<td></td>
<td>Empagliflozin</td>
<td>10 - 25 mg x 1x daily</td>
<td>May temporarily lower GFR, Monitor BP, K+ &amp; renal function.</td>
</tr>
</tbody>
</table>

**EMPA-REG OUTCOME**: Summary

- 
  Empagliflozin, as used in this trial, for 3 years in 1,000 patients with type 2 diabetes at high CV risk:
  - Empagliflozin reduced hospitalisation for heart failure by 35%
    - 14 fewer hospitalisations for heart failure (42 vs 28)
  - Empagliflozin reduced CV death by 38%
    - 25 lives saved (82 vs 57 deaths)
      - 22 fewer CV deaths (59 vs 37)
  - Empagliflozin improved survival by reducing all-cause mortality by 32%
    - 53 additional genital infections (22 vs 75)

**Considerations**

- May temporarily lower GFR
- Monitor BP, 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.
**SGLT2 Inhibitors- How do they rate?**

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**What questions?**


**Poll Question 6**

- Best actions? 72 yr old, thin, lives alone, A1c 7.3. History MI Stroke. Diet controlled, limited income. Creat 1.4. (multiple)
  - a. Start Metformin
  - b. Encourage her to lose 5% of her body wt
  - c. Start low dose glipizide
  - d. Continue current strategy and ongoing monitoring
  - e. Consider DPP-IV Inhibitor (Januvia, Onglyza, etc)
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-IV Inhibitor Updates
- Can cause severe, disabling join pain.
  - Contact Provider, Stop Medication
- Saxagliptin (Onglyza) and Alogliptin (Nesina) can increase risk of heart failure.
  - Notify provider for shortness of breath, edema, weakness, etc.
- Side effects: headache and flu-like symptoms
- Report signs of pancreatitis
- No wt gain or hypoglycemia
- Lowers A1c 0.6% - 0.8%

DPP-IV Inhibitors – How do they rate?

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<td>Can most tolerate /use?</td>
<td>Yes</td>
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</table>
Indication for “Fast Acting” Insulin Secretagogues- Meglitinides

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

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%
**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

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**TZDs – How do they rate?**

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<td>Cause weight gain?</td>
<td>Yes</td>
</tr>
<tr>
<td>Affordable?</td>
<td>Generic</td>
</tr>
<tr>
<td>Lowers CV risk?</td>
<td>??</td>
</tr>
<tr>
<td>Can most tolerate /use?</td>
<td>Watch CHF</td>
</tr>
</tbody>
</table>

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**Combination Oral Medications PocketCard**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Amount Doses in mg</th>
<th>Medications</th>
<th>Amount Doses in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actos + Xiglu*</td>
<td>30 / 1500</td>
<td>Avandia + Xiglu*</td>
<td>2.5 / 5000</td>
</tr>
<tr>
<td>Actos + Xiglu*</td>
<td>30 / 1000</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
<tr>
<td>Actos + Xiglu*</td>
<td>30 / 500</td>
<td>Glimepiride</td>
<td>12.5 / 250</td>
</tr>
<tr>
<td>Avandia + Xiglu*</td>
<td>2.5 / 500</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
<tr>
<td>Avandia + Xiglu*</td>
<td>2.5 / 1000</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>15 / 500</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>25 / 500</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>30 / 500</td>
<td>Glimepiride</td>
<td>12.5 / 500</td>
</tr>
</tbody>
</table>

*Available in generics. Always consult pharmacist of each combined drug. The information listed here are not guidelines. Please consult provider/patient information before use.
Incretin Mimetics –
“Gut Hormone Imitators”
GLP-1 Agonists

How do they work?

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

GLP-1 secreted upon
the ingestion of food

Promotes satiety and
reduces appetite

† Beta-cell
response

Alpha cells:
↓ Postprandial
glucagon secretion

Liver:
↓ Hepatic glucose output

Stomach:
Helps regulate
gastric emptying

GLP-1 degraded by
DPP-4 w/in minutes

Stomach: Helps regulate gastric emptying
Promotes satiety and reduces appetite

Liver: ↓ Hepatic glucose output

Beta cells:
Enhances glucagon-dependent insulin secretion

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

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Stomach:
Helps regulate
gastric emptying

GLP-1 degraded by
DPP-4 w/in minutes
### 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

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### 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

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### 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
dulaglutide (Trulicity)

**Dulaglutide Dosing**: 0.75/1.5 mg weekly
- **Efficacy**: lowers; A1c by ~1%, body wt by ~2.5kg
- **Indication**: Type 2 Monotherapy or in combo.
- **Other**: it comes in a single-dose pen and does not require mixing, measuring or needle attachment. And the needle is hidden from the user and retracts after use.
- **Black box** - thyroid tumor warning (avoid if family hx, notify MD of hoarseness, lump).

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. Reduces risk of CV events
- **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).

Liraglutide Approved for Weight Loss

- Saxenda and Victoza contain the same active ingredient (liraglutide) at different doses
  - Saxenda 3 mg and Victoza 1.8 mg
- Saxenda – as a treatment option for chronic weight management in addition to a reduced calorie diet and physical activity.
- Saxenda is approved for use in adults with a
  - BMI of ≥ 30 or
  - BMI of ≥ 27 or greater who have hypertension, type 2 diabetes, or dyslipidemia.
Poll Question 7

7. Patient is taking Victoza once daily for 3 months. Which side effect should they report immediately?
   a. sneezing fits
   b. constipation
   c. headaches
   d. sudden abdominal pain

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?

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   (GI)
What questions?

- 65 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

Poll Question 8

  - Refer to RD and DSME
  - Start basal insulin
  - Consider adding SGLT-2 Inhibitor (Invokana etc)
  - Start bolus insulin
  - Stop orals, go to basal bolus.
Basal Insulin + GLP-1 RA

Benefits
- Improved glycemic control
- Low risk of hypoglycemia
- Less weight gain
- Less treatment burden (one shot a day)
- Safe and effective alternative to basal/bolus

Side Effects
- Hypoglycemia, weight gain (insulin)
- Nausea, vomiting, pancreatitis (GLP-1 RA)

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.
Thank You

- Questions?
- Email
  bev@diabetesed.net
- Web
  DiabetesEdUniversity.net