UPDATE ON THE NEW DIABETES MEDICATIONS AND HOW TO INCORPORATE INTO YOUR PRACTICE

Amy DeGueme, MD, ECNU
Madison Medical Affiliates
3/15/19

WITH SO MANY NEW CLASSES OF MEDICATIONS OUT THERE...

Which ones to choose?
Disclosures:

• Speaker’s Bureau: Novo Nordisk, Medtronic, Janssen

• Consultant: Medtronic

OBJECTIVES

• To review and contrast the latest and greatest diabetes medications available

• To understand the significance of the cardiovascular outcomes studies

• To realize the cost to patients, insurers, and our health systems of these new medications
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.

Adult (nonpregnant) A1c Goals

• A1c < 7% - a reasonable goal for adults.

• A1c < 6.5% - may be appropriate for those without significant risk of hypoglycemia or other adverse effects of treatment.

• A1c < 8% - may be appropriate for patients with history of hypoglycemia, limited life expectancy, or those with longstanding diabetes and vascular complications.
**Metformin**

- Start 500mg once daily with biggest meal x 7 days, then 500mg BID with meals x 7 days, then 1000mg BID with meals.
- Needs to be with meals to help prevent GI side effects.
- GFR < 30 - contraindicated.
- Not recommended to start with GFR 30-45.
- If GFR falls below 45 on metformin, assess risks vs benefits.
- Continue if start on insulin.
- Could try extended release if GI side effects bothersome.

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**Glycemic Control Algorithm**

**Individualize Goals**

- **A1C ≤ 6.5%**
  - For patients without concurrent serious illness and at low hypoglycemic risk.

- **A1C > 6.5%**
  - For patients with concurrent serious illness and at risk for hypoglycemia.

**Lifestyle Therapy**

- **Entry A1C < 7.5%**
  - Monotherapy:
    - Metformin
    - GLP-1 RA
    - SGLT2i
    - DPP4i
    - TZD
    - AGi
    - SU/SGLN

- **Entry A1C ≥ 7.5%**
  - Dual Therapy:
    - Metformin
    - GLP-1 RA
    - SGLT2i
    - DPP4i
    - TZD
    - Basal Insulin
    - Colesevelam
    - Bromocriptine QR
    - AGi
    - SU/SGLN

- **Entry A1C ≥ 9.0%**
  - Triple Therapy:
    - Metformin
    - GLP-1 RA
    - SGLT2i
    - DPP4i
    - TZD
    - Basal Insulin
    - Colesevelam
    - Bromocriptine QR
    - AGi
    - SU/SGLN

**Symptoms**

- **No**
  - Dual Therapy
  - Insulin OR Other Agents

- **Yes**
  - Triple Therapy

**Progression of Disease**

1. Order of medications represents a suggested frequency of usage, length of use, and frequency of therapy maintenance.
2. Type 2 diabetes and type 1 diabetes both benefit from metformin in patients with these complications.
3. Includes one of these medications if T2D patient.
GLP-1 receptor agonists

• Multifactorial effects

• Weight loss

• Ease in dosing (once a week)

• Side effects - mainly GI - background nausea, diarrhea, rarely emesis

• Don’t give if pt has hx of pancreatitis or MTC (self or family)
Current options

- Semaglutide - FDA approved 2017
- Dulaglutide - FDA approved 2014
- Exenatide - FDA approved 2012
- Liraglutide - FDA approved 2010, cardiovascular indication 2017
- Exenatide daily and Lixisenatide

How do I start a GLP-1 medication

- Get the patient on board
- Review how to use pen; give first injection in office?
- Reduce portions to avoid nausea
- Nausea should go away; if it doesn’t or causes emesis, then stop
- Put a reminder on phone (or 2) for weekly dosing
- Stop DPP4 inhibitors
- Reduce SU and insulin depending on starting A1c
<table>
<thead>
<tr>
<th>Name</th>
<th>Dosing and Schedule</th>
<th>Smallest Needle Size</th>
<th>Renal dosing</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide - extended release</td>
<td>2mg once weekly</td>
<td>23-gauge 8mm</td>
<td>GFR &lt; 30: not recommended; GFR 30-59: use with caution</td>
<td>Mean change in A1c from baseline -1.1 to -1.4% Mean change in body weight from baseline -3.1lbs</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75mg or 1.5mg once weekly</td>
<td>29-gauge, 5mm</td>
<td>no dosing adjustments needed</td>
<td>Mean change in A1c from baseline -0.7% to -1.6% for the 0.75 mg dose and -0.8% to -1.6% for the 1.5 mg dose Mean change in body weight from baseline -3.0 to -5.0lbs</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>0.5mg or 1.0mg once weekly</td>
<td>31-gauge, 4mm</td>
<td>no dosing adjustments needed</td>
<td>Mean change in A1c from baseline -1.4 to -1.6% Mean change in body weight from baseline -8.4 to -10.4lbs</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.2mg or 1.8mg once daily</td>
<td>use insulin pen needles, need separate rx</td>
<td>no dosing adjustments needed</td>
<td>Mean change in A1c from baseline -0.8 for the 1.2mg dose and -1.1 for the 1.8mg dose Mean change in the body weight from baseline -4.6 to -5.5lbs</td>
</tr>
</tbody>
</table>

**Cardiovascular Studies**

- Cardiovascular safety studies are required of all new diabetes medications
- Goal of study is to show non-inferiority to standard of care or no increased incidence of cardiovascular outcomes
- Surprising results are now being seen
<table>
<thead>
<tr>
<th>Name</th>
<th>CV Study</th>
<th>Population</th>
<th>Duration</th>
<th>Primary end-point</th>
<th>Outcomes</th>
<th>Label Indication</th>
<th>Other results?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide - extended release</td>
<td>EXSCEL 2017</td>
<td>14,752 patients</td>
<td>3.2 years</td>
<td>3-point MACE</td>
<td>11.4% vs 12.2% = noninferior to placebo</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide (1.5mg dose)</td>
<td>REWIND</td>
<td>9,901 patients</td>
<td></td>
<td>3-point MACE</td>
<td>superior - results to be released this summer</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN-6</td>
<td>3,297 patients</td>
<td>2.1 years</td>
<td>3-point MACE</td>
<td>0.6% vs 8.9% = 26% relative risk reduction, noninferior</td>
<td>NO</td>
<td>increase retinopathy complications</td>
</tr>
<tr>
<td>Liraglutide (1.8mg dose)</td>
<td>LEADER</td>
<td>9,340 patients</td>
<td>3.8 years</td>
<td>3-point MACE</td>
<td>13% vs 14.9% = 13% relative risk reduction</td>
<td>YES - to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease</td>
<td>Reduction in all-cause mortality (8.2% vs 9.6%)</td>
</tr>
</tbody>
</table>

• 3-point MACE - death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
How do I use these results

• Patient with established CV disease = preferentially use liraglutide; if not on insurance formulary I will write an appeal letter quoting the LEADER study and the current ADA guidelines

• Patient without established CV disease = I chose whichever GLP1 receptor agonist is on the formulary and patient preference

• I’m not certain if this is a class effect or not, but appears to be that way

Question #1

• GLP-1 receptor agonists increase insulin release in response to food intake, suppress glucagon secretion, suppress appetite, and slow gastric emptying.

• TRUE

• FALSE
Question #2

• What class of medications does the American Academy of Clinical Endocrinologists (AACE) diabetes guidelines recommend after metformin failure?
  • 1. sulfonylurea
  • 2. pioglitazone (TZD)
  • 3. GLP-1 receptor agonist
  • 4. basal insulin
  • 5. SGLT2 inhibitors

WHAT IF A PATIENT REFUSES ANY INJECTABLE MEDICATION?
Patients with type 2 diabetes

Excess glucose → Glomerulus → Renal proximal tubule → Glucose reabsorption
Urinary excretion

Type 2 diabetes with SGLT2 inhibition

Excess glucose → Glomerulus → Renal proximal tubule → Glucose excretion enabled through SGLT2 inhibition → Reduced blood glucose levels resulting from less glucose reabsorption

SGLT2 inhibitors

Adapted from:

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosing</th>
<th>Renal dosing</th>
<th>Efficacy</th>
<th>COMBOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>canagliflozin</td>
<td>100mg and 300mg daily (post-prandial glycemic control)</td>
<td>GFR &gt; 60 - 300mg ok</td>
<td>Mean change in A1c from baseline -0.77% to 1.03%</td>
<td>metformin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GFR 45-60 - 100mg ok</td>
<td>Mean change in body weight from baseline -4.8 to -7.3lbs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GFR &lt; 45 - NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>1mg and 10mg daily</td>
<td>GFR &lt; 60 - NO</td>
<td>Mean change in A1c from baseline -0.8% to -0.9%</td>
<td>metformin XR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change in body weight from baseline -3.0 to -4.4lbs</td>
<td></td>
</tr>
<tr>
<td>empagliflozin</td>
<td>10mg and 25mg daily</td>
<td>GFR &lt; 45 - NO</td>
<td>Mean change in A1c from baseline -0.7 to -0.8%</td>
<td>metformin metformin XR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change in body weight from baseline -5.5 to -6.2lbs</td>
<td></td>
</tr>
<tr>
<td>ertugliflozin</td>
<td>1mg and 15mg daily</td>
<td>GFR &lt; 60 - NO</td>
<td>Mean change in A1c from baseline -0.7 to -0.8%</td>
<td>metformin sitagliptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change in the body weight from baseline -4.4 to -4.6lbs</td>
<td></td>
</tr>
</tbody>
</table>
How do I start/monitor SGLT2s

- Check renal function
- Adjust HTN meds if needed
- Do not take if NPO or with GI bug causing emesis
- Discuss possible side effects
  
  A. stay hydrated (drink if thirsty, drink if urine dark yellow)
  
  B. good hygiene - baby wipes/barrier cream if needed

Other thoughts on SGLT2s

- Amputation signal in CANVAS - I try to avoid whole class in PVD/PAD, severe neuropathy, smokers, current DM ulcer
- Fournier’s gangrene - stress good hygiene
- DKA (euglycemic) - don’t use in T1DM or those you suspect have LADA
Question #3

- **What can you advise patients when starting an SGLT2 inhibitor to help prevent adverse events?**

- 1. Stay hydrated (if urine is dark yellow, you need to drink more)
- 2. Use good hygiene (especially for women or uncircumcised men)
- 3. Use baby wipes or a diaper/barrier cream to prevent irritation
- 4. Don’t take if NPO or with decreased PO intake due to GI bug, URI, etc
- 5. All of the above

<table>
<thead>
<tr>
<th>Name</th>
<th>CV Study</th>
<th>Population</th>
<th>Duration</th>
<th>Primary end-point</th>
<th>Outcomes</th>
<th>Label Indication</th>
<th>Other results?</th>
</tr>
</thead>
<tbody>
<tr>
<td>canagliflozin</td>
<td>CANVAS</td>
<td>10,142</td>
<td>3.6 years</td>
<td>3-point MACE</td>
<td>26.9 vs. 31.5 participants with an event per 1000 patient-years, 14% relative risk reduction, superior</td>
<td>YES - to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease</td>
<td>amputation signal</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>DECLARE-TIMI 58</td>
<td>17,160</td>
<td>4.2 years</td>
<td>3-point MACE</td>
<td>8.8 vs 9.4% = noninferior, + lower rate of heart failure hospitalization</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>empagliflozin</td>
<td>EMPA-REG</td>
<td>7,020</td>
<td>3.1 years</td>
<td>3-point MACE</td>
<td>10.5% vs 12.1% = 14% relative risk reduction, superior</td>
<td>YES - to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>ertugliflozin</td>
<td>VERTIS-CV</td>
<td>8,246</td>
<td>TBD</td>
<td>3-point MACE</td>
<td>TBD</td>
<td>TBD</td>
<td></td>
</tr>
</tbody>
</table>

• 3-point MACE - death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
Is there also a renal protective effect?

- We are seeing a positive signal for SGLT2 inhibitors and renal protection
- This effect is seen in patients with and without baseline renal impairment
ADA ASCVD recs

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for lixisenatide > exenatide > exenatide extended release. For SGLT2i evidence mostly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CVD progression in CVOTs.
4. Degludec or U100 glargine have demonstrated CVD safety.
5. Low dose may be better tolerated though less well studied for CVD effects.
DPP-4 inhibitors

- weight neutral
- pretty well tolerated overall - arthralgias?
- good option for elderly (although cost can be prohibitive)
- linagliptin - no renal adjustments; I like this + a basal insulin for ESRD (sitagliptin can also be used but needs dose adjustment)

Basal Insulin options

- NPH - dose BID (+ regular, or just 70/30, human insulin)
- Glargine (U100 and U300) - good for higher doses
- Detemir
- Degludec - U100 and U200 - great for those with varying schedules
- Regular U500 - I like to use as TID dosing to a smoother profile
WE HAVE ALL THESE FABULOUS NEW MEDICATIONS BUT...

Who is paying for them?

A Minnesota mother, Nicole Smith-Holt, said her son Alec died last year because he couldn't afford to refill his insulin medication. (Facebook)

He couldn't afford insurance or insulin meds, and he died. His mom is speaking out.
DURING THE PAST YEAR, HAVE YOU DONE ANY OF THE FOLLOWING?

- Skipped filling a prescription due to cost
- Skipped a scheduled dose NOT at your pharmacist or physician’s direction to save money
- Took an expired medication
- Cut pills in half NOT at your pharmacist or physician’s direction to save money
- Shared a prescription with someone else to save money

Experienced a price increase on their drugs in the last 12 months

Did not experience a price increase on their drugs

*Percentages won’t add up to 100 percent because people were able to report multiple actions taken.

Source: Consumer Reports Best Buy Drugs Tracking Part 6, conducted April 16-26, 2015

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What about costs?

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Company</th>
<th>Class</th>
<th>2017 sales</th>
<th>2012-17 growth ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia</td>
<td>sitagliptin</td>
<td>Merck &amp; Co.</td>
<td>DPP-IV</td>
<td>8.5bn</td>
<td>2.7bn</td>
</tr>
<tr>
<td>Victoza</td>
<td>liraglutide</td>
<td>Novo Nordisk</td>
<td>GLP-1</td>
<td>3.6bn</td>
<td>1.9bn</td>
</tr>
<tr>
<td>Lantus</td>
<td>insulin glargine</td>
<td>Sanofi</td>
<td>Insulin</td>
<td>8.0bn</td>
<td>1.4bn</td>
</tr>
<tr>
<td>Novolog/NovoRapid</td>
<td>insulin aspart</td>
<td>Novo Nordisk</td>
<td>Insulin</td>
<td>4.1bn</td>
<td>1.3bn</td>
</tr>
<tr>
<td>Nesina</td>
<td>alogliptin</td>
<td>Takeda</td>
<td>DPP-IV</td>
<td>1.3bn</td>
<td>1.3bn</td>
</tr>
<tr>
<td>Bydureon</td>
<td>exenatide</td>
<td>BMS/AstraZeneca</td>
<td>GLP-1</td>
<td>1.3bn</td>
<td>1.2bn</td>
</tr>
<tr>
<td>Tradjenta</td>
<td>liraglutin</td>
<td>Eli Lilly/BI</td>
<td>DPP-IV</td>
<td>1.4bn</td>
<td>1.2bn</td>
</tr>
<tr>
<td>Tresiba</td>
<td>insulin degludec</td>
<td>Novo Nordisk</td>
<td>Insulin</td>
<td>1.1bn</td>
<td>1.1bn</td>
</tr>
<tr>
<td>Onglyza</td>
<td>saxagliptin</td>
<td>BMS/AstraZeneca</td>
<td>DPP-IV</td>
<td>1.8bn</td>
<td>1.1bn</td>
</tr>
<tr>
<td>Humalog</td>
<td>insulin lispro</td>
<td>Eli Lilly</td>
<td>Insulin</td>
<td>3.2bn</td>
<td>830m</td>
</tr>
<tr>
<td>Galvus</td>
<td>vildagliptin</td>
<td>Novartis</td>
<td>DPP-IV</td>
<td>1.6bn</td>
<td>720m</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>canagliflozin</td>
<td>J&amp;J</td>
<td>SGLT</td>
<td>680m</td>
<td>680m</td>
</tr>
<tr>
<td>Lantus/Lyxumia</td>
<td>insulin glargine/lixisenatide</td>
<td>Sanofi</td>
<td>Insulin</td>
<td>660m</td>
<td>660m</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>semaglutide</td>
<td>Novo Nordisk</td>
<td>GLP-1</td>
<td>590m</td>
<td>590m</td>
</tr>
<tr>
<td>RyzeDeg</td>
<td>insulin degludec/aspart</td>
<td>Novo Nordisk</td>
<td>Insulin</td>
<td>525m</td>
<td>525m</td>
</tr>
</tbody>
</table>

Source: FirstWord
What about Medicare patients?

What you will pay in 2020 and beyond when the Donut Hole is “closed”
Based on the CMS defined standard Medicare Part D plan

- **Initial Deductible**: you pay 100%
- **Initial Coverage Phase**: you pay 85%
- **Coverage Gap**: you pay 25%
- **Catastrophic Coverage**: you pay approx. 5%

Donut Hole Discount 2020 and Beyond:
- **Initial Deductible**
- **Initial Coverage Phase**
- **Coverage Gap**
- **Catastrophic Coverage**

Who’s profiting?

It’s not just insulin...

Table 8.5—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

<table>
<thead>
<tr>
<th>Class</th>
<th>Compounds</th>
<th>500 mg (IR)</th>
<th>1,000 mg (IR)</th>
<th>500 mg (SR)</th>
<th>1,000 mg (SR)</th>
<th>Median AWP</th>
<th>Median NADAC</th>
<th>Maximum approved dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>$84 (54, 160)</td>
<td>$95 (70, 160)</td>
<td>$80 (50, 160)</td>
<td>$95 (70, 160)</td>
<td>$2,000 mg</td>
<td>$3,000 mg</td>
<td>$2,000 mg</td>
</tr>
<tr>
<td>Sulfonuranes (2nd generation)</td>
<td>Glyburide</td>
<td>$65 (50, 100)</td>
<td>$80 (50, 100)</td>
<td>$65 (50, 100)</td>
<td>$80 (50, 100)</td>
<td>$2,000 mg</td>
<td>$3,000 mg</td>
<td>$2,000 mg</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>$67 (50, 80)</td>
<td>$82 (50, 100)</td>
<td>$67 (50, 80)</td>
<td>$82 (50, 100)</td>
<td>$2,000 mg</td>
<td>$3,000 mg</td>
<td>$2,000 mg</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Exenatide</td>
<td>$6,566</td>
<td>$7,000</td>
<td>$6,566</td>
<td>$7,000</td>
<td>$2,000 mg</td>
<td>$3,000 mg</td>
<td>$2,000 mg</td>
</tr>
</tbody>
</table>

average wholesale prices (AWP) and National Average Drug Acquisition Costs (NADAC)


ADA guidelines - 2019

Cost is a major issue...

If FPG above target:
- Start metformin with lowest escalation cost
- OR
  - Consider FPP in DN

If FPG above target:
- Insulin therapy based on clinical data and insulin-escalation plan
- OR
  - Consider FPP in DN

[Flowchart image showing cost considerations and treatment options for diabetes management]
What can we do?

- Always ask about costs - Do you have difficulty affording insulin? Are you rationing?
- Don’t give samples of a medication you know won’t be covered
- Consider Wal-mart/Relion 70/30 - it’s not that bad
- Use cost as a motivator to change diet/exercise/get off insulin
- Think - how much addition “value” is this medication for the patient?
- Make sure those heading into Medicare know about “donut hole”
- Medicare Low Income Subsidy program - [https://secure.ssa.gov/i1020/start](https://secure.ssa.gov/i1020/start)
- Advocate with the ADA Insulin Access and Affordability Working Group - [https://makeinsulinaffordable.org](https://makeinsulinaffordable.org)

Clinical case

- Angela is 58 yo with a 20 year history of T2DM. She has HTN, HLD, and weighs 260 pounds (BMI 39). She is on Metformin 1000mg BID and Glargine insulin 80 units daily. Despite multiple visits to the CDE and frequent counseling about diet and exercise, her Hemoglobin A1c is 8.7%.
  - Glimepiride
  - Aspart
  - Canagliflozin
  - Liraglutide
  - Sitagliptin
  - Would any of these be preferred?
  - Would any of these be contraindicated?
Clinical case - what ifs?

• She has a history of hypertriglyceridemia, and despite an aggressive medical regimen, her TG levels are 700-1200

• 4 years ago she had a heart attack and had 3 stents placed

• She has frequent CHF admissions

• She has no microvascular disease

Clinical case - what ifs?

• She has a history of breast cancer 7 years ago from which she is deemed clear of disease.

• 4 years ago she had a heart attack with 3 stents placed.

• 3 years ago, she developed an ulcer on her right foot which failed to heal due to PAD and neuropathy, and had to undergo TMA.
Clinical case - what ifs?

- Years ago, while on prandial insulin, she had frequent unpredictable hypoglycemia including a seizure.
- She has CKD with a GFR ~ 50.
- 4 years ago she was diagnosed with Papillary thyroid cancer, currently with no recurrence.
- She has about 4-5 yeast infections per year.

References

THANK YOU!!