Disclosures

• I speak on behalf of the following companies: Astra Zeneca, Boehringer Ingelheim, Johnson & Johnson, Sanofi and Valeritas. I receive funding for clinical research from Medtronic.

Objectives

• Review the most recently approved DM meds
• Discuss how and when to use new medications
• Identify contraindications and precautions of new medications.
• Present case studies identifying appropriate use of new DM meds in specific patient populations.
Explosion of New DM Meds/Technology

- SGLT2 inhibitors
- DPP4 inhibitors
- Combination SGLT2/Metformin
- Combination DPP4/Metformin
- Combination SGLT2/DPP4
- GLP1 receptor agonists
- Inhaled insulin
- U300 glargin
- U200 humling
- VIGO insulin delivery device

- Integrated insulin pumps with CGM:
  - Medtronic 530G + enlite sensor
  - Animas Vibe (Dexcom CGM)

The ominous octet

- SU
- GLP-1R agonists
- T2D
- MET
- GLP-1R antagonists
- GLP-1R inhibitors
- GLP-1R antagonists
- HGP

Hyperglycaemia

Neurotransmitter dysfunction

FDA

U.S. Food and Drug Administration

Glomerulus
Proximal Tubule
Distal Tubule
Collecting Duct

Glomerular filtration
SGLT2 inhibitor
Increased glucose reabsorption
SGLT2 inhibitors (sodium/glucose cotransporter 2)

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>ACTIVE INGREDIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invokana</td>
<td>canagliflozin</td>
</tr>
<tr>
<td>Invokamet</td>
<td>canagliflozin + metformin</td>
</tr>
<tr>
<td>Farxiga</td>
<td>dapagliflozin</td>
</tr>
<tr>
<td>Xigduo XR</td>
<td>dapagliflozin + metformin XR</td>
</tr>
<tr>
<td>Jardiance</td>
<td>empagliflozin</td>
</tr>
<tr>
<td>Glyxambi</td>
<td>empagliflozin + linagliptin</td>
</tr>
</tbody>
</table>

SGLT2-i’s

- **When TO use**
  - DM2 (not approved for DM1), adequate renal function, GFR >45 (Invokana and Jardiance), GFR >60 (Farxiga). Can be used after metformin, added on to any meds as well as insulin. Weight loss (5-10#) positive side effect, low risk of hypoglycemia.

- **When NOT to use**
  - Impaired renal function (GFR <45), history of recurrent UTI’s or yeast infections.

- **Precautions**
  - Hypovolemia (with concomitant diuretics), hypotension (SBP drop of >5-10mmHg), UTI’s, genital mycotic infections, bladder cancer warning on farxiga label, transient increase in cr, recent FDA evaluation of DKA in DM2.
**DPP4 inhibitors**

**dipeptidyl peptidase inhibitor**

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>ACTIVE INGREDIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia</td>
<td>Sitagliptin</td>
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<tr>
<td>Janumet</td>
<td>Sitagliptin + Metformin</td>
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<tr>
<td>Onglyza</td>
<td>Saxagliptin</td>
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<tr>
<td>Kombiglyze XR</td>
<td>Onglyza + Metformin XR</td>
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<tr>
<td>Tradjenta</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Jentadueto</td>
<td>Linagliptin + Metformin</td>
</tr>
<tr>
<td>Glyxambi</td>
<td>Linagliptin + Empagliflozin</td>
</tr>
<tr>
<td>Nesina</td>
<td>Alogliptin</td>
</tr>
<tr>
<td>Oseni</td>
<td>Alogliptin + Pioglitazone</td>
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</table>

**DPP4-inhibitors**

- **When TO use:**
  - DM2, (not approved for DM1), after metformin, added on to any meds, including insulin, low risk of hypoglycemia, weight neutral.
- **When NOT to use:**
  - History of pancreatitis, in conjunction with GLP1-RA
- **Precautions:**
  - Renal impairment requires dose adjustment for all but tradjenta. Post marketing studies of pancreatitis and pancreatic cancer, monitor for signs/symptoms.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Mixing Required</th>
<th>Pre-injection Wait Time</th>
<th>Dosing Smallest Needle Gauge</th>
<th>Needle Included</th>
<th>Approved with Basal Auto Injection</th>
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</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>BID</td>
<td>WO</td>
<td>NO</td>
<td>Drug, filling, 32g, 4mm</td>
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<td>Bydureon Kit</td>
<td>Exenatide</td>
<td>DAILY</td>
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<td>WO</td>
<td>2mg, 32g, 4mm</td>
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<tr>
<td>Bydureon Pen</td>
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<tr>
<td>Tanzeum</td>
<td>Albiglutide</td>
<td>WEEKLY</td>
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<td>YES</td>
<td>30mg, 32g, 5mm</td>
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<tr>
<td>Trulicity</td>
<td>Dulaglutide</td>
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<td>0.75mg, 3.8kg, 5mm, 5mm</td>
<td>YES, part of device, YES</td>
<td>YES, Y</td>
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</tbody>
</table>
GLP1-RAs

- When TO use:
  DM2, (not approved for DM1). After metformin, in addition to other DM meds, including insulin (in some but NOT all). Weight loss a positive side effect, low risk of hypoglycemia.

- When NOT to use:
  History of pancreatitis, pancreatic CA, MEN2, Medullary Thyroid cancer, in conjunction with DPP4i

- Precautions:
  GI side effects (nausea, vomiting, diarrhea) avoid use in gastroparesis, limited data of use in renal impairment but no dosage adjustment for victoza, trulicity, tanzeum. Byetta/Bydureon not to be used w/GFR <30

Inhaled insulin - Afrezza

- Rapid acting inhaled insulin, to be used as bolus insulin

- Not to be used in patients with chronic lung disease such as COPD or asthma, smokers (or those that have smoked in the past 6 months).

- Pulmonary function tests required prior to initiation to ensure FEV1 >70% and again at 6 mos and yearly. Discontinue if FEV1 declines >20% from baseline.

- 4 unit, 8 unit, 12 unit cartridges

Afrezza
**U300 Glargine**

- In all EDITION studies U300 proved non inferior to U100 glargine
- T1D studies (549 pts) showed no convincing hypoglycemia difference, however in a study of 243 Japanese subjects there was a 34% risk reduction for nocturnal and 20% for 24h hypoglycemia
- T2D studies showed reduced risk of severe nocturnal hypoglycemia by 31% achieved with a 10-17% greater insulin dose and less increase in body weight (~0.26kg in T2D, ~0.56kg in T1D).

**U200 Humalog**

- Rapid acting meal time insulin
- Same pharmacokinetics/pharmacodynamics as humalog U100 - bioequivalent
- Only available in pens
- If patients require 20 units, they still draw up "20" units on their pen, however the pen delivers the insulin in 1/2 the volume.
- Useful for patients requiring large doses of mealtime insulin as normal pens provide total of 300 units.
Patch Pumps

V-Go

- Rapid acting insulin infused over 24 hours (20, 30 or 40 units), bolus insulin delivered by patient administering “clicks”
- 1 “click” = 2 units
- New V-Go placed every 24 hrs

Insulin Pumps

Medtronic
Animas
Omnipod
Tandem
Accuchek Spirit

The “bionic pancreas” is a fully automated system that adds glucagon in addition to insulin.

Dr. Steven Russell of Mass General Hospital, Boston presented data at the 2014 ADA conference. Patients wore the bionic pancreas for 5 days, blood sugars improved along with a reduction in hypoglycemia. All patients achieved a projected A1C that fell within goals per the ADA (<7% for adults, <7.5% for adolescents). They hope to have a bionic pancreas on the market by 2017.
Case Study #1

• 73 y/o obese female DM2 x 15 yrs, HTN, HLP, A1C 8.2%, GFR 39. Metformin just stopped by her PCP due to declining renal function. On glipizide 10mg qam, in the past on actos (stopped due to LE edema). Patient doesn’t want to go on insulin.
• What next?
  • DPP4i, SGLT2i, GLP1RA, acarbose, welchol, basal insulin, inhaled insulin...

Case Study #2

• 34 y/o obese F w/DM2, A1c 9.5%, BMI 42, PCOS, normal GFR, recurrent UTI’s. On metformin 1000mg po bid.
• What next?
  • Insulin, GLP1-RA, DPP4i, SGLT2i, glipizide, actos...

Case Study #3

• 72 y/o M w/DM2 x 5 yrs, HTN, BMI 24, A1C 8.4%. On metformin 1000mg bid, GFR>60. Active, bikes 5 miles/day.
• What next?
  • SGLT2i, DPP4i, GLP1RA, insulin, glipizide, actos...
Case Study #4

- 54 y/o M DM2, A1c 9.2%, on invokamet 150/1000mg bid, lantus 40 units qhs, bydureon q week. Compliant with medications but busy work schedule, doesn’t think he will give lunch time bolus. Limited FSBG, but fastings are mostly <120.
- What next?
- Meal time insulin—Afrezza, VGo, novolog, humalog, apidra....

My Bias:
(as of today...)

- Lower blood sugars, avoid hypoglycemia (I typically don’t use sulfonylureas)
- Lower blood sugars, avoid weight gain (I typically don’t use TZDs and choose meds that help with weight loss over others that don’t)
- Simplicity = improved compliance (once weekly, once daily, combo meds, VGO, inhaled insulin, pumps....)
- Do no harm (medication choice tailored to the patient - i.e. history of pancreatitis, UTI’s, gastroparesis, CKD, etc)
- Metformin—->GLP1RA—->SGLT2i—->U300