New Medications for Diabetes

BARRETT CHAPIN, MD, FACP, FACE, CDE
Diabetes medications - Timeline

- Insulin isolated (1922)
- Sulfonylureas (1955)
- Metformin (1995)
- Humalog Insulin (1996)
- Thiazolidinediones (1997)
- GLP-1 Agonist FDA Approved (2005)
- SGLT-2 Inhibitor FDA Approved (2013)
- Inhaled insulin FDA Approved (2014)
- U-300 glargine, U-200 Humalog, and Degludec FDA Approved (2015)
New Diabetes medications - Overview

- **Incretin medications**
  - GLP-1 Agonists - 2005
  - DPP-4 Inhibitors - 2006
- **SGLT-2 Inhibitors** - 2013
- **Insulins**
  - Short-acting / Inhaled (Afrezza) - 2014
  - Long-acting U-300 Glargine (Toujeo) – 2015
  - U-200 Humalog – 2015
  - Degludec (Tresiba) and 70/30 Degludec/Aspart (Ryzodeg) 9/2015
New Diabetes medications - Incretins

- Incretin medications
  - GLP-1 Agonists
  - DPP-4 Inhibitors
Incretin - Physiology and Action

- **In response to food:**

  - **Gastric Inhibitory polypeptide (GIP)**
  - **Glucagon-like peptide-1 (GLP-1)**

  Secreted into the Blood stream.
Incretin Physiology and Action of GLP-1 and GIP Function

**Glucagon-like peptide-1 (GLP-1)**
- Stimulates Insulin release from the pancreas (only when the glucose is elevated)
- Inhibits Glucagon release from the pancreas (which stops the liver from making glucose, when the glucose is elevated)

**Gastric Inhibitory polypeptide (GIP)**
- both
Incretin Physiology and Action of GLP-1 and GIP

Glucagon-like peptide-1 (GLP-1)

Gastric Inhibitory polypeptide (GIP)

Dipeptidyl Peptidase-4 Enzyme (DPP-4)
Breaks down GLP-1 and GIP.

Half life of GLP-1 and GIP is just a few minutes

Inactive Degradation Products
Incretin medication - Categories

**GLP-1 Agonists**
- Glucagon-like peptide-1 (GLP-1)
- Gastric Inhibitory polypeptide (GIP)

**DPP-4 Inhibitors**
- Dipeptidyl Peptidase-4 Enzyme (DPP-4)
  - Breaks down GLP-1 and GIP.

Half life of GLP-1 and GIP is just a few minutes

Inactive Degradation Products
DPP-4 Inhibitors and GLP-1 Agonists

**DPP-4 Inhibitors (“gliptins”)**
- Sitagliptin (Januvia) – FDA approved 2006
- Saxagliptin (Onglyza) – FDA approved 2009
- Linagliptin (Tradjenta) – FDA approved 2011
- Alogliptin (Nesina) – FDA approved 2013
  - Pills
  - Weight neutral
  - Q day dosing
  - Ave. A1c reduction ≈1
  - Head-to-head A1c reduction same for all

**GLP-1 agonists**
- Exenatide (Byetta) – FDA aprvd 2005
- Liraglutide (Victoza) – FDA aprvd 2010
- Exenatide (Bydureon) – FDA aprvd 2012
- Albiglutide (Tanzeum) – FDA aprvd 4/15/14
- Trulicity (Dulaglutide) – FDA aprvd 9/18/14
  - Injectables
  - Weight loss (5-10#s)
  - BID (Byetta), Q day (Victoza), or Q week (Bydureon, Tanzeum, and Trulicity)
  - Ave. A1c reduction ≈1-2
  - Head-to-head A1c reduction
    - Victoza > Bydureon > Byetta
    - Victoza > Aliglutide
    - Trulicity > Byetta
    - Victoza = Trulicity

• Pills
• Weight neutral
• Q day dosing
• Ave. A1c reduction ≈1
• Head-to-head A1c reduction same for all
DPP-4 Inhibitors and GLP-1 Agonists
Cost/month at max dose

DPP-4 Inhibitors ("gliptins") §
Sitagliptin (Januvia) – $343
Saxagliptin (Onglyza) – $337
Linagliptin (Tradjenta) – $343
Alogliptin (Nesina) – $355

GLP-1 agonists *
Exenatide (Byetta) – $427
Liraglutide (Victoza) – $392
Exenatide (Bydureon) – $440
Albiglutide (Tanzeum) – $326
Dulaglutide (Trulicity) – $488

§From goodrx.com (accessed 10/1/15)
*from The Medical Letter 11/10/14
Incretin Common Side-Effects

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  - Runny nose - about 5%

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  - Runny nose - about 5%
  - GI – roughly 1/3
    - Nausea
    - Dyspepsia
    - Diarrhea
    - Constipation
**Incretin Theoretical Side-Effects**

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- Medullary thyroid cancer
- Pancreatitis
Incretin Side-Effects – Medullary Thyroid Cancer (MTC)

- In rodent studies (rats and mice) Thyroid C-cell Hyperplasia (a precursor to Medullary Thyroid Cancer) was seen in a dose dependent fashion after exposure to Liraglutide and Dulaglutide using concentrations equivalent to human pharmacological doses.

- Some rodents developed Medullary Thyroid Cancer. These animals were exposed to ≥ 8 times the equivalent of the maximum pharmacological dose in humans.

- To date there has been no causal relationship with Liraglutide or Dulaglutide, or any other Incretin medication, with MTC in humans.

- To be cautious do not use any Incretin in a patient with a personal or family history of MTC or MEN2 Syndrome.
Incretin Side-Effects - Pancreatitis

Since released there have been case reports to the FDA of Pancreatitis in patients treated with all the incretin medications.

In Phase III trials there have been more cases of Pancreatitis in Incretin treated subjects than controls but the number of cases have been too low to make the difference statistically significant in any study to date.

The theoretical Pancreatic risk has been extended to pancreatic cancer, but there is even less data supporting this.

Both risks have been perpetuated in the media by commercials from hopeful class action lawyers.
Incretin Potential Beneficial Effects

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• Lower BP
• Possibly Cardio-protective
• Possibly Reno-protective
Incretin medications

Summary

- Physiology and action
  - Gut hormones that increase insulin secretion and suppress glucagon secretion

- GLP-1 Agonists and DPP-4 Inhibitors
  - GLP-1’s are injected and promote weight loss
  - DPP-4’s are pills, less effective at lowering A1c, and weight neutral

- Side-effects (both proven and theoretical)
  - Both can cause runny nose
  - GLP-1’s commonly cause GI side-effects
  - Pancreatitis and MTC are theoretical concerns and at most uncommon
SGLT-2 (Sodium Glucose Transport Protein-2) inhibitor medications

BARRETT CHAPIN, MD, FACP, FACE, CDE
SGLT-2 inhibitor medications

Overview

- Physiology
- The SGLT-2’s
- Side-effects
SGLT-2 - Physiology and Action

- 100% of glucose passes into the nephron
- 90% is reclaimed by SGLT-2
- 10% is reclaimed by SGLT-1
SGLT-2 - Physiology and Action

Your diabetic patient

Your diabetic patient taking an SGLT-2 Inhibitor
SGLT-2 Inhibitors “gliflozins”

Cost (max dose/mo)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval Date</th>
<th>Cost/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>3/29/13</td>
<td>$312</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td>1/8/14</td>
<td>$312</td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td>8/1/14</td>
<td>$301</td>
</tr>
</tbody>
</table>

Ipragliflozin, Tofogliflozin, and Ertugliflozin are in Phase III clinical trials

- Pills
- All are Q day dosing
- Weight loss
- Lower BP
- Ave. A1c reduction ≈1
- No Head-to-head comparisons
- Not effective with eGFR < 45 ml/min

Side Effects
- UTI’s and Urogenital fungal infections – about 10%
- Hypotension
- Dehydration
- Ketoacidosis\(^1\) (FDA warning in May 2015)

\(^1\) J. Clinical Endocrinol Metab. 100(8), p2849-52, Aug 2015.
SGLT-2 Inhibitors
Summary

- Physiology and action
  - Glucose loss through the kidney
- Three FDA approved and more coming
- Benefits
  - Weight loss and lower BP
- Side-effects
  - UTI’s and urinary fungal infections
New Diabetes medications – New Insulins

- **Insulins**
  - Short-acting / Inhaled (Afrezza) - 2014
  - Long-acting / (Toujeo, aka U-300 Lantus) – 2015
  - Short-acting / Humalog (U-200) – 2015
  - Long-acting / (Tresiba) – 9/2015
New Diabetes medications – New Insulins

- Insulins
  - Short-acting / Inhaled (Afrezza) - 2014
New Diabetes medications - Afrezza

- Short-acting / Inhaled (Afrezza) - 2014
New Diabetes medications - Afrezza

Time to Peak Insulin Level

Data from different studies

2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudalier SR et al. Diabetes Care. 1999;22:1501-1506.
New Diabetes medications - Afrezza

- Contraindicated in smokers or anyone with underlying lung disease.

- FEV1 is recommended at start of Rx, at 6 months, and yearly (as long as FEV-1 is > 80% of predicted treatment use of Afrezza is okay)

- Cost $237 § for 4 unit doses count of 90 (360 units)

§From goodrx.com (accessed 10/1/15)
New Diabetes medications – New Insulins

- Insulins
  - Toujeo – 2015
    - Toujeo is U-300 glargine insulin
    - Lantus is U-100 glargine insulin
New Diabetes medications - Toujeo

- Toujeo is glargine insulin in a U-300 concentration

U-100 = 100 units per ml

U-300 = 300 units per ml

U-500 = 500 units per ml
Toujeo (U-300 glargine insulin)

Lantus (U-100 glargine) vs. Toujeo (U-300 glargine)

Less surface area = slower absorption
Toujeo (U-300 glargine insulin)

Pharmacokinetics

Toujeo (U-300 glargine insulin)

Toujeo  $348 \S\ for 1350 units (box of 3 pens)  ($0.26/unit)
only comes in a pen to avoid dosing errors

Lantus  $385 for 1500 units (box of 5 pens)  ($0.26/unit)
$260 for 1000 unit vial

\S\From goodrx.com (accessed 10/1/15)

Relion Novolin N  = $25 per 1000 unit vial at Walmart
Relion Novolin R
Relion Novolin 70/30
New Diabetes medications – New Insulins

- U-200 Humalog – 2015
U-200 Humalog

- Humalog (Lispro insulin) (U-200) – 2015
- Humalog (Lispro insulin) (U-100) – 1996
U-200 Humalog

- Humalog (Lispro insulin) (U-200)
  - Pen only (to avoid dosing errors)
    - $314§ per 3000 unit box of 5 pens

- Humalog (Lispro insulin) (U-100)
  - $244§ per 1500 unit box of 5 pens
  - $233 per 1000 unit vial

§From goodrx.com (accessed 10/1/15)
U-200 Humalog

- **Humalog (Lispro insulin) (U-200)**
  - The Lilly drug rep tells me it has the same pharmacokinetics as U-100 Humalog
  - There is currently no published data yet
  - If there is a difference U-200 Humalog will be longer in duration due to the decreased surface area of the smaller volume
New Diabetes medications – New Insulins

- Degludec (Tresiba) – 9/2015
Tresiba (degludec)

- FDA approved 9/25/15
- U-100 and U-200 concentrations
  - sold in pen only
- Basal insulin as monotherapy
  - half-life of 25-40 hours
- Combined with Novolog as a 70/30
  - Not yet FDA approved but many studies of a Tresiba/Victoza combination
Tresiba (degludec)

- U-200 degludec compared to U-100 glargine in a meta-analysis of 7 studies of type 2 diabetes\(^1\)
  - Less nocturnal hypoglycemia
  - No difference in A1c

- US cost unknown as yet
  - More expensive than Lantus and Levemir in the UK

\(^1\)Nutr Metab Cardiovasc Dis. 2015 Oct;25(10):898-905
New Diabetes Medications

Summary

- They are expensive
  - competition has not brought prices down
- Incretins are gut hormones that stimulate insulin and suppress glucagon
  - GLP-1 agonists – injected, robust A1c reduction, weight loss
  - DPP-4 Inhibitors – once daily pills, weight neutral
- SGLT-2 Inhibitors – Urinary glucose loss
- Insulins
  - Short-acting
    - Inhaled Afrezza and U-200 Humalog
  - Long-acting
    - U-300 Toujeo and Tresiba (U-200, U-100, and 70/30)