New Medications on the Horizon

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Disclosure to Participants

- Notice of Requirements For Successful Completion
  - Please refer to learning goals and objectives
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

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  - Presenter: Diana Isaacs, PharmD, BCPS, BC-ADM, CDE – Advisory Board: Sanofi; Becton, Dickinson & Co.
  - Presenter: Andrew Bzowyckyj, PharmD, BCPS, CDE – No COI/Financial Relationship to disclose

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Session Objectives

- Describe new agents approved and in the pipeline for type 1 and type 2 diabetes.
- Compare and contrast new diabetes medications and formulations to what was previously available.
- Discuss factors to consider when adding these new medications for specific patient populations.

Drug Selection Factors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Risk of Hypoglycemia</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on Glucose</td>
<td>Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>CV Benefits</td>
<td>Effects on Weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Route of Administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient Preferences</td>
<td></td>
</tr>
</tbody>
</table>

ADA. Standards of Care. Diabetes Care 2019;42(Suppl. 1):S90–S10
How many medication classes are available to treat diabetes?

Drug Options for Diabetes

- Biguanide
- Sulfonylureas
- Meglitinides
- Thiazolidinediones (TZD’s)
- Dipeptidylpeptidase-4 (DPP-4) inhibitors
- Glucagon-like-peptide-1 (GLP-1) receptor agonists
- Sodium glucose cotransporter-2 (SGLT-2) inhibitors
- Bile acid sequestrant
- Dopamine-2-agonist
- Amylin mimetic
- Alpha-glucosidase inhibitors
- Insulin
- Glucagon

What’s New?

- Oral semaglutide
- GLP/GIP dual agonist
- Glucagon receptor antagonist
- Sotagliflozin
- Insulin devices
- Insulin formulations
  - Ultra-rapid
  - Generic
- Glucagon

7/31/2019
GLP-1 Receptor Agonists

GLP-1 Receptor Agonist Mechanism

GLP-1 Receptor Agonist Comparison

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Dosing</th>
<th>Administration</th>
<th>Pre-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>0.75mg SC weekly, may increase to 1.5mg SC weekly after 1 month</td>
<td>Without regard to meal</td>
<td>Single use, needle only</td>
</tr>
<tr>
<td>ExenatideIR</td>
<td>5mcg SC BID, may increase to 10mcg SC BID after 1 week</td>
<td>Within 60 minutes before evening meal</td>
<td>Multi-use, attach needle</td>
</tr>
<tr>
<td>ExenatideER</td>
<td>2mg SC weekly</td>
<td>Without regard to meal</td>
<td>Single use, needle only</td>
</tr>
<tr>
<td>Liraglutide*</td>
<td>0.6mg SC daily for 1 week, then 1.2mg SC daily; May increase to 1.8mg SC if needed after 1 week</td>
<td>Without regard to meal</td>
<td>Multi-use, attach needle</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10mcg SC daily for 14 days, then increase to 20mcg SC daily</td>
<td>Within 60 minutes before evening meal</td>
<td>Multi-use, attach needle</td>
</tr>
</tbody>
</table>

* Liraglutide is FDA-approved to reduce the risk of major adverse cardiovascular events (cardiovascular death, MI, stroke) in adults with type 2 diabetes and established CVD.

GLP-1 Receptor Agonist Devices

- 5mcg or 10mcg pen 1 pen/month Requires Rx for needles
- Contains 14 doses (20mcg) 2 pens/month Requires Rx for needles
- 0.5mg, 1 pen/month 1mg, 2 pens/month [ Comes with needles
- 2mg pen 4 pens/month Shake 15 seconds Never see needle
- 0.75mg or 1.5mg pens 4 pens/month Never see needle
- 1.2mg, 2 pens/month 1.8mg, 3 pens/month Requires Rx for needles

Oral Semaglutide

- Barriers to GLP-1 oral absorption:
  - Degradation by gastrointestinal enzymes
  - pH induced conformational changes
  - Limited protein permeability of the intestinal membrane
- Semaglutide co-formulated with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), an absorption enhancer
- Absorbed in stomach where SNAC causes a localized increase in pH, leading to higher solubility and protection against proteolytic degradation
- Phase 3 PIONEER (Peptide InnovatioN for Early diabEtes iReatment) studies
- Submitted to the FDA in early 2019 with priority review voucher

Oral Semaglutide – PIONEER 1 (n=703)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=175</th>
<th>3 mg N=175</th>
<th>7 mg N=175</th>
<th>14 mg N=178</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>-0.1%</td>
<td>-0.8%</td>
<td>-1.3%</td>
<td>-1.5%</td>
</tr>
<tr>
<td>A1C &lt; 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Baseline 8%)</td>
<td>34%</td>
<td>59%</td>
<td>72%</td>
<td>80%</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Baseline 88 kg)</td>
<td>-1.5 kg</td>
<td>-1.7 kg (NS)</td>
<td>-2.5 kg (NS)</td>
<td>-4.1 kg</td>
</tr>
</tbody>
</table>

- Oral tablet administered once daily; 30 minutes before first meal
- Advantages: long half-life; lower molecular weight; high potency; molecular stability
- NS: Not statistically-significant


PIONEER 3: Compared to DPP4 Inhibitor

- RCT comparing oral semaglutide to sitagliptin (N=1864)
- Primary endpoint: change in A1C
- Baseline A1C=8.3%, BMI=32.5


Semaglutide is different from other GLP-1 agonists because:

- A. An oral formulation is currently in development
- B. It is available as a once-monthly injection
- C. It requires a prescription for pen needles
- D. The pen needle is never visible to the patient

PIONEER 6: CV Outcomes

- RCT comparing oral semaglutide 14mg vs placebo, N=3183 adults
- Primary outcome: first occurrence of CV death, non-fatal MI, non-fatal stroke
- Median follow-up: 16 months
- Demonstrated non-inferiority of major CV events (MACE)
  - Overall MACE (HR 0.79 favoring semaglutide, P<0.05)
  - CV death reduction (HR 0.49, P<0.03)
  - All cause mortality (HR 0.49, p=0.008)
- Novo applied for CV indication based on PIONEER 6 and SUSTAIN-6

GLP-1/GIP Dual Agonist

GLP-1: Glucagon-like peptide-1
GIP: Glucose-dependent Insulinotropic Polypeptide

- Can increase glucagon AND insulin
  - Glucose-dependent
  - Dose-dependent
- Responsible for majority of insulinotropic effect
- Therapeutic utility diminished in hyperglycemia
- Role in regulating body weight?
**Tirzepatide (LY3298176)**

- Once weekly subcutaneous injection
  - Peak concentration within 24-48 hours
  - Half-life approximately 5 days
- High affinity for GIP AND GLP-1 receptors

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**A1C Reduction by Dose**

Baseline A1C ~ 8%; n=318

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**Total Weight Loss**

Baseline weight ~ 91.5 kg; BMI ~32.6; n=318
Tirzepatide (LY3298176)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Phases 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
<th>Phase 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>2.3%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>0.25</td>
<td>2.7%</td>
<td>1.8%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>0.5</td>
<td>5.2%</td>
<td>5.2%</td>
<td>5.2%</td>
<td>5.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>1</td>
<td>7.9%</td>
<td>7.9%</td>
<td>7.9%</td>
<td>7.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>2</td>
<td>10.7%</td>
<td>10.7%</td>
<td>10.7%</td>
<td>10.7%</td>
<td>10.7%</td>
</tr>
</tbody>
</table>

Drop out rate: 17.6% 15.4% 14.5% 13.7% 34.0% 14.8%

Glucagon Receptor Antagonist(s)

- Mechanism of Action:
  - Prevent glycogenolysis & hepatic glucose production
- Limited by adverse effects:
  - Increased liver enzymes
  - Increased hepatic fat fraction
  - Increased BP (?)

FASEB J. 2019;33(1 Supp):514.5
Sodium Glucose co-Transporter (SGLT) Inhibitors

Sotagliflozin (Zynquista)

- Dual SGLT1/SGLT2 inhibitor:
  - SGLT1: small intestine
  - SGLT2: nephron (proximal convoluted tubules)
- Hypothesis:
  - SGLT2 inhibition leads to SGLT1 upregulation
  - Decrease post-prandial glucoses & suppress glucagon


Sotagliflozin: inTandem Trials (T1DM)

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Trial Population</th>
<th>Efficacy</th>
<th></th>
</tr>
</thead>
</table>
| inTandem 1 (USA) | 793 | 46 years; 95% white | A1C ~ 7.57%; BMI ~ 29 kg/m²  
Insulin pump: 60%  
Sota 200 or 400 vs. PBO x 52 weeks |   |
|          |     |                   | A1C change vs. placebo:                      |   |
|          |     |                   | 200 mg: -0.36% (p<0.001)  
400 mg: -0.41% (p<0.001) |   |
| inTandem 2 (Europe) | 782 | 43 years; 96% white | A1C ~ 7.8%; BMI ~ 30 kg/m²  
Insulin pump: 25%  
Sota 200 or 400 vs. PBO x 52 weeks |   |
|          |     |                   | A1C change vs. placebo:                      |   |
|          |     |                   | 200 mg: -0.37% (p<0.001)  
400 mg: -0.35% (p<0.001) |   |
| inTandem 3 (Global) | 1402 | 43 years; 86.4% white | A1C ~ 8.2%; BMI ~ 28 kg/m²  
Insulin pump: 40%  
Sota 400 mg vs PBO x 24 weeks | Percent achieving A1c < 7% with no severe hypoglycemia or DKA |
|          |     |                   | Sota: 28.6% vs. PBO: 15.2% (p<0.001) | NNT: 8 people x 6 months |
Sotagliflozin & DKA: inTandem Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>FBO</th>
<th>Sota 200 mg</th>
<th>NNH (vs. 200 mg)</th>
<th>Sota 400 mg</th>
<th>NNH (vs. 400 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>inTandem 1 (USA)</td>
<td>793</td>
<td>0.4%</td>
<td>3.4%</td>
<td>33</td>
<td>4.2%</td>
<td>26</td>
</tr>
<tr>
<td>inTandem 2 (Europe)</td>
<td>782</td>
<td>0%</td>
<td>2.3%</td>
<td>43</td>
<td>3.4%</td>
<td>29</td>
</tr>
<tr>
<td>inTandem 3 (Global)</td>
<td>1402</td>
<td>0.6%</td>
<td>N/A</td>
<td>N/A</td>
<td>3.0%</td>
<td>41</td>
</tr>
</tbody>
</table>


Updates: SGLT Use in T1DM

- **Dapagliflozin** submitted to EU and FDA
  - EMA recommended approval for use in T1DM who meet certain criteria:
    - Adjust to insulin therapy
    - BMI ≥ 27kg/m²
    - Supplemental ketone monitoring
    - Additional patient selection criteria
    - Patient Alert Card
  - Waiting on decision from FDA
- **Sotagliflozin** submitted to EU and FDA
  - Jan 2019: FDA advisory committee voted 8-8 if benefits outweigh risks
  - Mar 2019: FDA issues Complete Response Letter (not approved)
  - Feb 2019: EU approved with same criteria as dapagliflozin
- **Ipragliflozin** approved for use in T1DM in Japan

Mitigating DKA Risk – STICH Protocol

<table>
<thead>
<tr>
<th>ST</th>
<th>I</th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST</td>
<td>I</td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>Stop SGLT inhibitor</td>
<td>Inject bolus insulin</td>
<td>Consume 30 grams carbohydrates</td>
<td>Hydrate with water</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitor Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Use Not Recommended</th>
<th>Studied in Type 1</th>
<th>CV Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100-300mg QAM</td>
<td>eGFR &lt;65ml/min</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5-10mg QAM</td>
<td>eGFR &lt;65ml/min</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10-25 mg QAM</td>
<td>eGFR &lt;65ml/min</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>5-15mg QAM</td>
<td>eGFR &lt;60ml/min</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Which of the following statements best applies to using SGLT inhibitors in T1DM?

A. Just don’t; never ever ever do it, ever
B. They are most effective for people with BMI < 25
C. Remember to check for ketones and STICH
D. Sotagliflozin has an FDA-approved labeling for this use

Insulin Devices

#AADE
New Insulin Devices
- NovoPen Echo
- DiabNext Clipsulin
- InPen

NovoPen Echo
- Durable (non-disposable) pen
- Records last dose & time since last injection
- Dosing in half-unit increments
- Available in two colors
- End-of-dose click for reassurance
- Compatible with insulin aspart cartridges

DiabNext Clipsulin
- Connects to most insulin pens (1-unit increments)
  - Insulin dose calculator app
  - Insulin dose tracker
- Transmits information via Bluetooth
InPen
• Durable (non-disposable) pen
• Syncs with smartphone app via Bluetooth
• Helps calculate doses & track injection data
• Dosing in half-unit increments
• Compatible with insulin aspart or lispro cartridges
• Healthcare provider inputs:
  – Patient-specific glucose targets
  – Carb:insulin ratio
  – Correction factor
• Insulin doses calculated based on blood glucose, carb intake, insulin on board

New Insulins

Biosimilars & Follow-on Biologics
• Highly similar to the reference product
• Analogous to generics, but NOT generics
• Similar manufacturing techniques
• Same amino acid sequence
• May differ slightly in molecular characteristics and clinical profiles
Making Insulin

Gene inserted into vector

Transferred to living host (yeast, bacteria, plant)

Precursor insulin product

Insulin precursor purified & modified

Purified again

Formulated and transferred into syringe & devices


Biosimilars & Follow-on Biologics

- Insulin glargine
  - Basaglar® (Lilly; approved Dec 2015)
- Insulin lispro
  - Admelog® (Sanofi; approved Dec 2017)

Costs: Biosimilar Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Median Average Wholesale Price (AWP; per unit of insulin)</th>
<th>Median National Average Drug Acquisition Cost (NADAC; per unit of insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 Glargine (Sanofi)</td>
<td>$0.32</td>
<td>$0.26</td>
</tr>
<tr>
<td>U-100 Glargine (Lilly)</td>
<td>$0.26</td>
<td>$0.21</td>
</tr>
<tr>
<td>U-100 Lispro Vial (Lilly)</td>
<td>$0.33</td>
<td>$0.26</td>
</tr>
<tr>
<td>U-100 Lispro Vial (Sanofi)</td>
<td>$0.28</td>
<td>$0.23</td>
</tr>
<tr>
<td>U-100 Lispro Pen (Lilly)</td>
<td>$0.42</td>
<td>$0.34</td>
</tr>
<tr>
<td>U-100 Lispro Pen (Sanofi)</td>
<td>$0.36</td>
<td>$0.30</td>
</tr>
</tbody>
</table>

Approximately 15-20% reduction in overall cost

The Rising Cost of Insulin

- **GENERIC insulin lispro (Lilly)**
  - Interchangeable at pharmacy
  - $137.35/vial ($0.14/unit)
  - $362.50 x 5 pens ($0.18/unit)
  - Cash pay only
- **Novo Nordisk/Walmart ReliOn Insulin (N/R)**
  - $25 per vial or box of pens
  - Max 4 vials/boxes per transaction
  - Cash pay only
- **Sanofi VALyou program**
  - Valid on all Sanofi insulins
  - $99/vial (max 10 vials/fill)
  - $149/pack of pens (max 10 packs/fill)
  - One fill per product per month
  - Cash pay only
- **Cigna / Express Scripts**
  - Employer plans ONLY (must opt-in)
  - $25 copay cap

https://www.diabeteseducator.org/practice/educator-tools/app-resources/affordability-resources

Which of the following statements related to insulin affordability is true?

A. Biosimilar insulins have decreased prices by 50%
B. People with Medicare Part D have a capped copay of $25 for insulin
C. Lantus is the only product covered under the Sanofi VALyou program
D. Generic insulin lispro can be substituted at the pharmacy, but not biosimilar Admelog
Ultra Rapid Insulin

The “Perfect” Insulin

Insulin Release:
1st phase: peak 1-2 minutes, duration 10 minutes, suppresses hepatic glucose production
2nd phase: duration 1-2 hours

Choice of Bolus Insulin

1. Slowest onset/longest duration
2. Rapid-acting, similar onset/duration
3. Fastest onset, inhaled is quickest
Are Rapid Acting Insulins Rapid Enough?

<table>
<thead>
<tr>
<th></th>
<th>Regular</th>
<th>Rapid Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>0.25-0.5 hr</td>
<td>0.2-0.3 hr</td>
</tr>
<tr>
<td>Peak Effect</td>
<td>3.5-5.5 hr</td>
<td>3-3.5 hr</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>4-12 hr</td>
<td>3.5 hr</td>
</tr>
<tr>
<td>Onset</td>
<td>0.2-0.5 hr</td>
<td>0.2-0.5 hr</td>
</tr>
<tr>
<td>Peak Effect</td>
<td>1.5-2 hr</td>
<td>0.5-2 hr</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>3-4 hr</td>
<td>≤5 hr</td>
</tr>
</tbody>
</table>

Faster Aspart: Clinical PK/PD

- Absorption: 2.5 min
- Distribution: <10% protein binding
- Excretion: urine
- Half-life elimination: 1.1 hours

Ultra-Rapid BioChaperone Lispro

- Modified ultra-rapid insulin lispro formulation
  - Citrate increases vascular permeability at the injection site
  - Treprostinil accelerates absorption by local vasodilation
- Randomized, double-blind, crossover phase 1 clinical trials

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>35</td>
<td>Lispro</td>
<td>Reduced 1-2 hr postprandial BG by 10-40%</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>24</td>
<td>Lispro</td>
<td>Faster absorption and 57% reduction in AUC</td>
</tr>
<tr>
<td>Insulin Pump</td>
<td>20</td>
<td>Lispro</td>
<td>Lower 2 hr postprandial glucose</td>
</tr>
</tbody>
</table>
Clinical Trial Results: Ultra-Rapid Lispro


Dosing before the meal associated with more pre-meal hypoglycemia

Which of the following insulins has the quickest onset?

A. Lispro  
B. Fast acting aspart  
C. Glulisine  
D. Inhaled

Rapid-Acting Insulin Comparison

<table>
<thead>
<tr>
<th>Property</th>
<th>Lispro</th>
<th>Lispro U-200</th>
<th>Aspart</th>
<th>Aspart U-200</th>
<th>Glulisine</th>
<th>Inhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>15‐30 min</td>
<td>15‐30 min</td>
<td>10‐20 min</td>
<td>15‐20 min</td>
<td>25 min</td>
<td>12‐15 min</td>
</tr>
<tr>
<td>Peak</td>
<td>30 min‐2.5 hr</td>
<td>30 min‐2.5 hr</td>
<td>40‐50 min</td>
<td>1.5‐2.22 hr</td>
<td>45‐48 min</td>
<td>35 min</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>3‐6.5 hours</td>
<td>3‐6.5 hours</td>
<td>3‐5 hours</td>
<td>6‐9.5 hours</td>
<td>660 min</td>
<td></td>
</tr>
<tr>
<td>Meal Timing</td>
<td>SC up to 15 min before or immediately after meals</td>
<td>SC up to 15 min before or immediately after meals</td>
<td>54 to 30 min before meals</td>
<td>54 to 30 min before meals</td>
<td>SC at start of meal or 20 min after starting meal</td>
<td>Inhaled at beginning of meal</td>
</tr>
<tr>
<td>Units per pen</td>
<td>300 units in 3 mL</td>
<td>300 units in 3 mL</td>
<td>300 units in 3 mL</td>
<td>300 units in 3 mL</td>
<td>300 units in 3 mL</td>
<td>NA</td>
</tr>
<tr>
<td>Max units injected/dose</td>
<td>60 units</td>
<td>60 units</td>
<td>60 units</td>
<td>80 units</td>
<td>80 units</td>
<td>4,8,12 unit cartridges</td>
</tr>
<tr>
<td>Pens/box</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Available as vial?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Expiration</td>
<td>28 days</td>
<td>28 days</td>
<td>28 days</td>
<td>28 days</td>
<td>28 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>
• Severe hypoglycemic events can result in seizure, coma, or death
• ADA recommends prescribing glucagon for all individuals at increased risk of clinically significant hypoglycemia
• Emergency glucagon kits consist of lyophilized glucagon powder that must be mixed with a diluent immediately prior to injection
  • Unstable in solution
  • Administration is complex, intimidating and prone to errors

Nasal Glucagon
• Nasal powder dosing: delivers into patient’s nose by pushing bottom of dispenser
  • Nasal cavity has a large surface area and rich blood supply for absorption
• No need to inhale = consistent dosing
• Found to be non-inferior to 1mg injectable glucagon in a cross-over study with 75 participants
  • Mean time to recovery: 16 min (IN) vs 13 min (IM) (P<0.001)
• Studied in patients with nasal congestion: dosing found to be consistent
• Single-use dose 3mg
• NDA submitted to FDA in 2018

Guzman CB et al. Diabetes Obes Metab. 2018 Mar;20(3):646-653
Time to Administer Nasal Glucagon

- 16 instructed caregivers and 15 non-instructed acquaintances administered nasal vs injectable glucagon to manikins

Glucagon Pen

- Room temperature stable, non-aqueous liquid form of glucagon
- Long-term stability at room temperature
- Pre-mixed solution in auto-injector
  - Doses: 0.5mg, 1mg
- Phase 3 trials completed for severe hypoglycemia
  - NDA submitted to FDA in 2018
- Phase 2 trials for other indications
  - Post-bariatric hypoglycemia, exercise induced hypoglycemia

How Effective is the Glucagon Pen?

- Phase 3 randomized, controlled, crossover clinical trial compared usual emergency glucagon kit to glucagon rescue pen, N=81

<table>
<thead>
<tr>
<th>Clinical Comparison</th>
<th>Glucagon Pen</th>
<th>Current Glucagon Kit</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug preparation and administration</td>
<td>27.3 ± 10.7 seconds</td>
<td>97.2 ± 45.1 seconds</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Mean time to resolution of hypoglycemia symptoms</td>
<td>11.6 ± 6.5 minutes</td>
<td>13.1 ± 7.0 minutes</td>
<td>NS</td>
</tr>
<tr>
<td>Mean time to resolution of symptoms from decision to dose</td>
<td>12.7 ± 6.5 minutes</td>
<td>15.3 ± 8.0 minutes</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

https://investors.xerispharma.com/static-files/328c34b0-0ed1-42d1-85a1-5d8921ab6024 Accessed 5/30/19
**Dasiglucagon**

- Liquid stable formulation
- Collaboration with beta bionics, iLet, dual hormone insulin pump
- Non-inferior to powdered glucagon formulation
- Pediatric trial underway
- Planned FDA submission late 2019


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**Which of the following is the greatest challenge with the current version of glucagon?**

A. Requires reconstitution  
B. Must be used immediately  
C. Requires multiple steps to prepare  
D. Must be injected

---

**New Combination: Qternmet XR**

- DPP4 inhibitor (Saxagliptin)  
- SGLT2 inhibitor (Dapagliflozin)  
- Metformin

Advantage:
One pill instead of 3, only 1 co-pay
### Combination Options

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generics</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyxambi®</td>
<td>empagliflozin &amp; linagliptin</td>
<td>Once daily</td>
</tr>
<tr>
<td>Invokamet®</td>
<td>canagliflozin &amp; metformin</td>
<td>Twice daily with meals</td>
</tr>
<tr>
<td>Qtern®</td>
<td>dapagliflozin &amp; saxagliptin</td>
<td>Once daily in morning</td>
</tr>
<tr>
<td>Qternmet® XR</td>
<td>dapagliflozin + saxagliptin + metformin ER</td>
<td>Once daily with first meal</td>
</tr>
<tr>
<td>Steglujan®</td>
<td>erugliflozin &amp; sitagliptin</td>
<td>Once daily in morning</td>
</tr>
<tr>
<td>Soliqua®</td>
<td>insulin glargine &amp; lixisenatide</td>
<td>Once daily prior to first meal</td>
</tr>
<tr>
<td>Stuglyt®</td>
<td>insulin degludec &amp; liraglutide</td>
<td>Once daily</td>
</tr>
<tr>
<td>Synjardy®</td>
<td>empagliflozin &amp; metformin</td>
<td>Twice daily with meals</td>
</tr>
<tr>
<td>Xigduo® XR</td>
<td>dapagliflozin &amp; metformin ER</td>
<td>Once daily with first meal</td>
</tr>
<tr>
<td>Xultophy®</td>
<td>insulin degludec &amp; liraglutide</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

### Summary of New Agents

- **Oral semaglutide**
  - Potential option for those hesitant to inject with similar efficacy to injectables

- **GLP/GIP dual agonist**
  - A novel class on the horizon for T2DM & weight loss, if it can overcome side effects

- **Glucagon receptor antagonist**
  - Don’t invest your money quite yet…

- **SGLT inhibitors**
  - Sotagliflozin & dapagliflozin approved for T1DM in Europe; hopefully more real world data coming soon; STICH protocol
  - Sotagliflozin may seek approval for T2DM in US

### Summary of New Agents (continued)

- **Insulin devices**
  - Ability to use smaller doses, record data, and do calculations

- **Generic insulin**
  - The first available earlier this year, will this be a new trend?

- **Ultra-rapid insulin**
  - The quest continues to make insulin that is more physiologic

- **Glucagon**
  - More convenient and easier way to administer glucagon for hypoglycemia
  - Stay tuned regarding FDA approval