Real World Strategies to Reduce and Treat Hypoglycemia

Debbie Hinnen
APN, BC-ADM, CDE, FAAN
University of Colorado Health
Colorado Springs
Deborah.Hinnen@uchealth.org

Diana Isaacs
PharmD, BCPS, BC-ADM, CDE
Clinical Pharmacy Specialist
Cleveland Clinic Diabetes Center
Cleveland, OH
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 credits/hours

- Conflict of Interest (COI) and Financial Relationship Disclosures:
  - Presenter: Diana Isaacs, PharmD, BCPS, BC-ADM, CDE – Advisory Board: Sanofi, BD
  - Presenter: Debbie Hinnen, APN, BC-ADM, CDE, FAAN, FAANP – Speaker/consultant: Lily, Novo, Sanofi, Janssen, Merck
  - Non-Endorsement of Products:
    - Accredited status does not imply endorsement by AADE, ARCC, APNCC or COIR of any commercial products displayed in conjunction with this educational activity

- Off-Label Use:
  - Participants will be notified by speakers to any product used for a purpose other than for which it was approved by the Food and Drug Administration

- Some slides adapted/collated with permission IMNE, 5-2019

Learning Objectives

- Describe the clinical consequences and implications of hypoglycemia
- Discuss newer options for treatment and prevention of hypoglycemia
- Design a treatment regimen that enhances glycemic management while reducing hypoglycemic risk

Hypoglycemia Causes More Hospitalizations than Hyperglycemia

JAMA Intern Med. 2014 July; 174(7): 1116–1124


**CV Death From Hypoglycemia**

- **Dead in Bed Syndrome**
- **Possible Mechanisms:**
  - Neuroglycopenia
  - CNS depression
  - Decreased respiration/hypoxemia
  - Hypokalemia
  - Seizures
  - Myocardial infarction
  - Cardiac arrhythmias

---

**Treatment and Prevention**

---

**Medications that Cause Hypoglycemia**

- Insulin
- Sulfonylureas
- Meglitinides

---

All other diabetes medications do not typically cause hypoglycemia when used alone.
Preventing Hypoglycemia

- Patient education
- Dietary intervention
- Exercise management
- Glucose monitoring
- Medication adjustment
- Clinicians asking about hypoglycemia at every visit


---

Recognizing Hypoglycemia From Glucose Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>BG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>6:00 AM</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>6:00 PM</td>
<td>140</td>
</tr>
<tr>
<td>Tue</td>
<td>4:40 AM</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>7:20 AM</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>12:45 PM</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>10:20 PM</td>
<td>87</td>
</tr>
<tr>
<td>Weds</td>
<td>6:00 AM</td>
<td>160</td>
</tr>
</tbody>
</table>

---

Hypoglycemia in CGM Downloads

<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
</tr>
<tr>
<td>62%</td>
</tr>
<tr>
<td>31%</td>
</tr>
<tr>
<td>7%</td>
</tr>
</tbody>
</table>

---

Handwritten SMBG Diary

Downloaded Glucose Meter
Proactively Discuss Hypoglycemia at Every Visit

- How many times have you had glucose < 70 mg/dL in the past 2 weeks?
- How low is your glucose when you feel symptoms?
- How do you treat low glucose?
- What do you carry with you at all times in case you need to treat low glucose?
- What do you do to prevent low glucose?


Treating Hypoglycemia: Rule of 15

- If the person is conscious, they should eat or drink glucose
- Use the rule of 15: repeat up to 3 times

- May if the person is not conscious:
  - Glucagon and call 911
  - Dextrose or glucose IV may be administered by emergency personnel

Patients and Their Close Contacts Need to Know How to Use Glucagon for Severe Hypoglycemia

- Glucagen HypoKit
- Glucagon Emergency Kit and App

When?:
- Unconscious and/or having seizure
- Unable to eat or drink a sugar-containing product
- Sugar does not improve condition

Where?:
- Available by prescription from local pharmacies; request in budgel, such as 8mg (2 vials)

How?:
- Expires powder to be reconstituted and drawn up
- downloadable app has audio instructions to talk care partners through the process of injection
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


Time to Administer Nasal Glucagon

- 16 instructed caregivers and 15 non-instructed acquaintances administered nasal vs injectable glucagon to manikins
- Tons of mistakes with IM glucagon
  - Injected partial dose, injected diluent only, bent needle,

Glucagon Pen

- Room temperature stable, non-aqueous liquid form of glucagon
- Proprietary formulation technology (XeriSol™)
- 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 ± 19.7 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>12.1 ± 7.9 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 2/11/19

### Prevention with CGM Alerts, Basal Suspend/Hybrid-Closed Loops


### Counseling Patients About Common But Avoidable Errors When Using Insulin Therapy

- Top 3 error in insulin administration:
  - Dosing irregularity in last 30 days: 38%
  - Mis-timing the dose relative to meals: 24%
  - Missing a dose: 22%

- Top 3 errors preceding a hypoglycemic emergency:
  - Missing a meal: 46%
  - Using the wrong insulin: 22%
  - Using the wrong dose: 12%

Insulin pens are associated with lower risk of dosing errors and less hypoglycemia than vial-and-syringe administration.
Patients Miss Doses, Mis-Time and Reduce Insulin to Reduce Hypoglycemia Risk

NPH Requires Extra Precautions to Use Safely

Outcomes After Basal Insulin Initiation: Detemir vs NPH in Insulin-Naive T2DM
Current Basal Insulins vs U-100 Glargine: Clinical Characteristics in T2DM

<table>
<thead>
<tr>
<th></th>
<th>U-300 NPH (^1)</th>
<th>U-300 Detemir (^2)</th>
<th>U-300 Glargine Equivalent (^3)</th>
<th>U-300 Degludec (^4,5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ A1C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall hypoglycemia</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼</td>
</tr>
</tbody>
</table>

Newer basal insulin analogues are associated with less hypoglycemia

Arrows indicate statistically significant differences at \( P < .05 \) or better.


Outcomes After Initiating U-100 Degludec or U-300 Glargine in Insulin-Naive T2DM: Head-to-Head Randomized Trial: BRIGHT

Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mo</th>
<th>Baseline</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-300 GLAR</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>U-100 DEG</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
</tbody>
</table>

Overall Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>▼ ▼ ▼ ▼</th>
<th>▼ ▼ ▼ ▼</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-300 GLAR</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
</tr>
<tr>
<td>U-100 DEG</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
</tr>
</tbody>
</table>

Only one episode of severe hypoglycemia occurred (in the U-300 glargine group), attributed to a patient skipping her evening meal and not reducing her insulin dose after an episode of non-severe hypoglycemia 2 days earlier.

Outcomes After Switching From Glargine or Detemir to U-300 Glargine or U-100 or U-200 Degludec in T2DM: Real-World Evidence

Glycemic Control

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mo</th>
<th>Baseline</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-300 GLAR</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>U-100 DEG</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼</td>
</tr>
</tbody>
</table>

Severe Hypoglycemia Requiring Medical Care

<table>
<thead>
<tr>
<th></th>
<th>▼ ▼ ▼ ▼</th>
<th>▼ ▼ ▼ ▼</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-300 GLAR</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
</tr>
<tr>
<td>U-100 DEG</td>
<td>▼ ▼ ▼ ▼</td>
<td>▼ ▼ ▼ ▼</td>
</tr>
</tbody>
</table>

Newer basal insulin analogues are effective, and switching from older to newer basal insulin analogues may reduce the risk of hypoglycemia, but precautions are still necessary.


Outcomes After Switching From Glargine or Detemir to U-300 Glargine or U-100 or U-200 Degludec in T2DM: Real-World Evidence
**Patient Case**

- Alex is a 66 year old male with type 2 diabetes x 10 years, A1C=6.7%, BMI=33kg/m², Scr=1.5mg/dL, eGFR=42
- Checks glucose 2x daily; FBG: 53-180, Bedtime: 110-175
- Comorbidities: Obesity, Hypertension, CKD
- Medications:
  - Lisinopril 40mg daily
  - Carvedilol 25mg BID
  - Metformin 500mg BID
  - Glipizide 10mg BID
  - Insulin glargine 60 units QPM
  - Atorvastatin 40mg daily
  - Aspirin 81mg daily

**Patient Case Questions**

- Which of these medications could mask the symptoms of hypoglycemia?
- Which medications are most likely to contribute to hypoglycemia?
- What changes would you recommend?
- How would you counsel Max about hypoglycemia?

**Summary**

- Hypoglycemia is a serious, life-threatening complication of diabetes treatment.
- Discuss hypoglycemia at every visit by asking questions and reviewing glucose data.
- New technology helps with prevention efforts.
- New glucagon formulations make treatment easier.
- Choose medications with lower hypoglycemia risks.