The Insulin Toolbox: Understanding the Options

National Diabetes Education Program
Quarterly Webinar Series
Tuesday, September 30, 2014
2-3 PM ET
Webinar Logistics

• All lines are muted
• Two ways to ask questions during Q&A period:
  1. Type your question into the question section and we will read your question aloud.
  2. Click the “raise hand” icon and we will call your name and unmute your line allowing you to ask your question.
Presenters

Francine R. Kaufman, M.D.
Distinguished Professor Emerita of Pediatrics and Communications, The University of Southern California and Children’s Hospital Los Angeles

Chief Medical Officer and VP of Global Clinical, Medical and Health Affairs, Medtronic Diabetes

Joanne Gallivan, M.S., R.D.
Director, National Diabetes Education Program
National Institutes of Health
The Insulin Toolbox: Understanding the Options

Francine R. Kaufman, M.D.

Distinguished Professor Emerita of Pediatrics and Communications
The University of Southern California and Children’s Hospital Los Angeles

Chief Medical Officer and VP of Global Clinical, Medical and Health Affairs, Medtronic Diabetes
Types of Insulins on the Market, US

- Ultra-rapid
- Short, rapid acting
- Intermediate
- Basal, long
- Mixed
<table>
<thead>
<tr>
<th>Insulin preparation</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>5 to 15 minutes</td>
<td>1 to 2 hours</td>
<td>4 to 5 hours</td>
<td>—</td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td>5 to 15 minutes</td>
<td>1 to 2 hours</td>
<td>4 to 5 hours</td>
<td>—</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>5 to 15 minutes</td>
<td>1 to 2 hours</td>
<td>4 to 5 hours</td>
<td>—</td>
</tr>
<tr>
<td>Regular (recombinant) (Humulin R)</td>
<td>30 to 60 minutes</td>
<td>2 to 4 hours</td>
<td>8 to 10 hours</td>
<td>Inject 30 minutes before meal</td>
</tr>
<tr>
<td><strong>Intermediate-acting insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane (NPH) (Humulin, Novolin N)</td>
<td>1 to 2 hours</td>
<td>4 to 8 hours</td>
<td>10 to 20 hours</td>
<td>—</td>
</tr>
<tr>
<td><strong>Basal insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir (recombinant) (Levemir)</td>
<td>1 to 2 hours</td>
<td>Relatively flat</td>
<td>12 to 20 hours</td>
<td>Smoother curve than NPH; administered 1-2/d; pen form; without refrigeration up to 42 d</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>1 to 2 hours</td>
<td>Relatively flat</td>
<td>20 to 24 hours</td>
<td>Available in pen form</td>
</tr>
<tr>
<td><strong>Mixed insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple preparations (e.g., Humulin 70/30)</td>
<td>30 minutes</td>
<td>Dual peak</td>
<td>Up to 24 hours</td>
<td>Mixed insulin preparations may hinder tight glycemic control</td>
</tr>
</tbody>
</table>

*Am Fam Physician. 2009 Jan 1;79(1):29-36*
Afrezza® Inhaled Human Insulin

* Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Afrezza + OAD N= 177</th>
<th>Placebo + OAD N= 176</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HgbA1c (%)</td>
<td>-0.82</td>
<td>-0.42</td>
<td>(-0.57, -0.23)</td>
</tr>
<tr>
<td>% Patients achieving HgbA1c ≤ 7%</td>
<td>32.2</td>
<td>15.3</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Inhaled insulin + basal insulin n = 174</th>
<th>Insulin aspart + basal insulin n = 170</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HgbA1c (%)</td>
<td>-0.21</td>
<td>-0.4</td>
<td>(-0.57, -0.23)</td>
</tr>
<tr>
<td>% Patients achieving HgbA1c ≤ 7%</td>
<td>13.8</td>
<td>27.1</td>
<td>-</td>
</tr>
</tbody>
</table>
New Insulin Products on the Horizon

- New basal, longer acting
  - Reduce hypo and hyperglycemia
- Ultra-rapid insulin
  - Improve post meal hyperglycemia
  - Use in artificial pancreas systems
- Bio-engineered, “biosimilars”
  - Reduce cost
- Concentrated insulin
  - Inject less often
  - Reduce cost?
Methods of Insulin Delivery

• Syringes
• Pens
• Pumps
  – Artificial pancreas systems
• Inhaled
• Oral, Buccal, Intradermal
• Intraperitoneal
  – Through pump or peritoneal catheter
• Smart insulin
Insulin Pens

• More discreet
• Combines insulin container and syringe into a single modular unit
• More convenient than carrying insulin vials and syringes
• More accurate
  – Insulin-dose setting dial, audible clicks
• High patient satisfaction
Insulin Pumps

- Delivery is customizable, flexible, adjustable, precise and reproducible
- Uses only rapid insulin with less variability in absorption
- Advanced features – dosage calculators, integrated with CGM, suspend feature
- Durable, patch
ADA Standards of Care

Glycemic Targets Differ by Age, Patient Characteristics

- Glycemic targets used to be fixed
- Now by age and patient characteristics
- Pediatrics - <7.5%
- Adult if possible <7%
- If Issues:
  - Avoid fixed insulin regimens
  - 3-4 injections of basal and prandial insulin or CSII (grade of evidence, A)
  - Match prandial insulin dose to carbohydrate intake, pre-meal glucose and anticipated activity (grade of evidence, E)
  - Use insulin analogs (grade of evidence, A)
The Type 1 Exchange – Real Life US Type 1 Diabetes Data from the 2013 Annual Report

- 26,293 participants
- 73 sites
- 59% use insulin pump therapy, CSII
- 41% use multiple daily injections, MDI
The Type 1 Exchange Data Shows Target A1C Not Achieved

Mean HbA1c by Age Group

- <6: 8.3%
- 6-12: 8.3%
- 13-17: 8.7%
- 18-25: 8.5%
- 26-49: 7.7%
- ≥ 50: 7.6%

Goal A1C < 7.5%
Goal A1C < 7%
Unacceptable Rates of DKA and Severe Hypoglycemia

12-month frequency of diabetic ketoacidosis* according to age

12-month frequency of severe hypoglycemia*

*1 or more events in 12 mo
Insulin Delivery Method in the Type 1 Exchange By Age

Age (years)

<table>
<thead>
<tr>
<th>Age</th>
<th>Pump</th>
<th>Injections/Pens</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>6-13</td>
<td>54%</td>
<td>46%</td>
</tr>
<tr>
<td>13-18</td>
<td>51%</td>
<td>49%</td>
</tr>
<tr>
<td>18-26</td>
<td>49%</td>
<td>51%</td>
</tr>
<tr>
<td>26-31</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>31-50</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>50-65</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>≥65</td>
<td>47%</td>
<td>53%</td>
</tr>
</tbody>
</table>
Insulin Delivery Method in the Type 1 Exchange By Race/Ethnicity and A1C Outcomes

HbA1c according to Insulin Method Stratified by Race/Ethnicity

*Means and P value adjusted for confounders
Insulin Pump Combined with Continuous Glucose Monitor
Improved A1C Outcome without Increasing Hypoglycemia

Values are means ± SE. Comparisons between SAP group and MDI group are significant for each time period (P<0.001).

The Suspend Feature of the Sensor-Augmented Pump

In the ASPIRE In-Home study, the MiniMed™ sensor-augmented insulin pump with low suspend feature prevented more nocturnal hypoglycemic events than an insulin pump without that feature. (n=247, age 16 to 70 years)


37.5% reduction in the combined magnitude and duration of nocturnal hypoglycemia events.

31.8% fewer nocturnal hypoglycemic events.

**Mean Area Under the Curve of Nocturnal Hypoglycemia Events**

<table>
<thead>
<tr>
<th></th>
<th>Low Suspend</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In Phase</td>
<td>1,547</td>
<td>1,406</td>
</tr>
<tr>
<td>Study Phase</td>
<td>980</td>
<td>1,568</td>
</tr>
</tbody>
</table>

37.5% reduction (p<0.001)

**Nocturnal Hypoglycemia Events**

<table>
<thead>
<tr>
<th></th>
<th>Low Suspend</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In Phase</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Study Phase</td>
<td>1.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

31.8% reduction (p<0.001)
Clinical Evidence for Suspend Feature: **ASPIRE In-Home**

**Sensor Glucose Distribution <70 mg/dL**

- **Threshold Suspend**: 1.8%, 2.8%, 3.0%
- **Control**: 4.1%, 3.1%, 1.2%

- 40% reduction, p<0.001
- 36% reduction, p<0.001

- **Nocturnal**
  - Threshold Suspend: 1.2%
  - Control: 3.1%

- **Combined Day and Night**
  - Threshold Suspend: 2.8%
  - Control: 3.7%

*There were fewer SG values in hypoglycemic ranges in the Threshold Suspend Group.*

**Glycated Hemoglobin (A1C)**

- **Threshold Suspend**
  - 3-month: 7.26
  - Randomization: 7.24

- **Control**
  - 3-month: 7.21
  - Randomization: 7.14

ΔA1C was similar in the two groups. The 95% CI of the difference in ΔA1C (-0.05, 0.15) did not include the non-inferiority limit of 0.4%.

Study conducted with Veo pump. Not FDA approved and not commercially available in the US.

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

1. 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 lies with the patient.
Approach to Management of Hyperglycemia

- **Patient attitude and expected treatment efforts**: More stringent (highly motivated, adherent, excellent self-care capacities) vs. less stringent (less motivated, non-adherent, poor self-care capacities).
- **Risks potentially associated with hypoglycemia, other adverse events**: Low vs. high.
- **Disease duration**: Newly diagnosed vs. long-standing.
- **Life expectancy**: Long vs. short.
- **Important comorbidities**: Absent vs. few/mild vs. severe.
- **Established vascular complications**: Absent vs. few/mild vs. severe.
- **Resources, support system**: Readily available vs. limited.
Healthy eating, weight control, increased physical activity

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonlurea</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
<td>high</td>
<td>low risk</td>
<td>variable</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>high</td>
<td>low risk</td>
<td>loss</td>
<td>Insulin (usually basal)</td>
</tr>
<tr>
<td>Insulin (usually basal)</td>
<td>highest</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea
- Metformin + Thiazolidinedione
- Metformin + DPP-4 Inhibitor
- Metformin + GLP-1 receptor agonist
- Metformin + Insulin (usually basal)

If combination therapy that includes basal insulin has failed to achieve HbA1c goal after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

**Insulin** (multiple daily doses)

Additional strategies:
- Initial drug monotherapy (Efficacy, Hypoglycemia, Weight, Side effects, Costs)
- Two drug combinations (Efficacy, Hypoglycemia, Weight, Major side effect(s), Costs)
- Three drug combinations
- More complex insulin strategies

*Diabetes Care, Diabetologia.* 19 April 2012 [Epub ahead of print]
Insulin Regimens in Type 2 Diabetes

- Non-insulin regimens
- Basal insulin only (usually with oral agents)
  - Basal insulin + 1 (meal-time) rapid-acting insulin injection
  - Premixed insulin twice daily
- Basal insulin + ≥2 (meal-time) rapid-acting insulin injections

- Number of injections:
  - 1: low
  - 2: mod.
  - 3+: high

- Flexibility: more flexible to less flexible

Sequential Insulin Strategies in T2DM

*Diabetes Care, Diabetologia.* 19 April 2012 [Epub ahead of print]
**Algorithm for Adding/Intensifying Insulin**

**START BASAL (long-acting insulin)**

- **A1c < 8%**
  - TDD 0.1–0.2 U/kg
  - **Insulin titration every 2–3 days to reach glycemic goal:**
    - Fixed regimen: Increase TDD by 2 U
    - Adjustable regimen:
      - FBG > 180 mg/dL: add 4 U
      - FBG 140–180 mg/dL: add 2 U
      - FBG 110–139 mg/dL: add 1 U
      - If hypoglycemia, reduce TDD by:
        - BG < 70 mg/dL: 10% – 20%
        - BG < 40 mg/dL: 20% – 40%

- **A1c > 8%**
  - TDD 0.2–0.3 U/kg

**INTENSIFY (prandial control)**

- **Glycemic Control Not at Goal**
  - Add GLP-1 RA or DPP-4i
  - TDD: 0.3–0.5 U/kg
    - 50% Basal Analog
    - 50% Prandial Analog
  - Less desirable NPH and regular insulin or premixed insulin

**Insulin titration every 2–3 days to reach glycemic goal:**

- Increase basal TDD as follows:
  - Fixed regimen: Increase TDD by 2 U
  - Adjustable regimen:
    - FBG > 180 mg/dL: add 4 U
    - FBG 140–180 mg/dL: add 2 U
    - FBG 100–139 mg/dL: add 1 U
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose > 180 mg/dL.
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL.
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

**Glycemic Goal:**

- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

---

**Copyright © 2013 AACE** May not be reproduced in any form without express written permission from AACE.
CSII Compared to MDI in Type 2 Diabetes Patients
Not at Target with MDI – Global OpT2miseTrial

A 6-month randomized controlled trial, N=495 adults entered the run-in study phase. With a 6-month extension period.

Reduction of HbA1c:

CSII group: -1.1%
(HbA1c drop from 9.0% to 7.9%)

MDI group: -0.4%
(HbA1c drop from 9.0% to 8.6%)

A difference of 0.7% in favor of CSII group (p<0.001)

Insulin pump therapy (CSII) significantly improved glycemic control compared to multiple daily injections

Key Points of ADA/EASD Type 2 Approach

• Individualized glycemic targets and BG lowering therapies

• Diet, education and exercise are the foundation

• Unless contraindicated, metformin is optimal first-line drug

• After metformin, combination therapy with 1-2 other oral / injectable agents is reasonable, minimize side effects

• Ultimately, many patients will require insulin therapy alone or in combination with other agents

• All treatment decisions should be made in conjunction with the patient – focus on preferences, needs and values

• Comprehensive CV risk reduction should be a major focus
Provider Barriers that Delay Insulin

- Stepwise "treatment to failure" approach
- Lack of consensus regarding treatment goals and the best practices
- Clinical inertia
- Propensity to delay, until "absolutely necessary"
- Lack of access to team for education and support
  - Underutilization of diabetes education
    - Lack of access (i.e., in rural areas)
    - Inadequate reimbursement
    - Physician unawareness of diabetes education resources
Barriers to Optimal Care – Patient Delay Insulin or Interfere with Adherence

**Educational**
- Low diabetes knowledge
- Low knowledge of services

**Internal physical**
- Physical effects of treatment

**External physical (systems)**
- Personal finance issues
- Poor physical access to service
- Limited range of services
- Poor quality of services
- Lack of community-based services
- Need for more helpful health professionals
- Inappropriate diabetes care

**Psychosocial**
- Group pressure
- Prejudice
- Lack of public awareness
- Lack of family support
- Family demands
- Lack of community support
- Communication difficulties
- Lack of cultural support

**Psychological**
- Health beliefs
- Public health beliefs
- Poor motivation
- Low self-efficacy
- No symptom cues
- Difficulty setting priorities
- Negative perceptions of time
- Emotional issues
- Precontemplative stage of change
Recommendations for the Provider to Enhance Advancement and Adherence to Use of Insulin

- Consider cultural issues, ask what’s important to the patient
- Enhance DSME – diabetes education
- Co-manage with a team
- Refer to social workers, mental health
- Help with financial issues, co-pays, insurance
- Alter insulin dosage as needed, ask about side effects
- Encourage and support glucose monitoring
- Believe in the patient, meet them where they are
Cases 1

• 22 year old female with BMI 28 kg/m2, develops of polyuria, weight loss, polydipsia during graduate school

• Goes to health center, BG 218 mg/dL after lunch
  – Repeat glucose – fasting 189 mg/dL

• What do you do?

• Do you think she will need insulin? (Yes or No)
Case 1

• GAD auto-antibodies come back positive
• What regimen do you start her on?
  A. Fixed 2 shots of premix AM and PM
  B. Basal plus prandial insulin for carbohydrate counting
  C. Basal plus prandial insulin for fixed meals
  D. Basal only at night
Case 1

• 1 year later her A1C is 7.8% and her meter download shows mean glucose of 175 mg/dL, Standard deviation of 98 mg/dL, 12% low glucose and 38% high glucose values.

• She had a fender bender due to low glucose. What do you consider?
  A. Get her license revoked
  B. Insulin pump therapy
  C. Diabetes education, review correcting highs and carb counting
  D. Pump and sensor with threshold suspend
  E. Counsel her to check glucose before driving
Case 2

• A 56 year old man was diagnosed with type 2 diabetes at age 42 years when his BMI was 35 kg/m2
• At diagnosis, he was placed on diet and exercise
• At 3 months, A1C was 9.8%, started metformin, then A1C in low 8 range
• At 5 years, A1C > 9.0%, BMI increased to 37 kg/m2, added second oral, then A1C is mid 8 range
• At 10 years, A1C > 9.0%, added 3rd oral, then A1C in mid-to-high 8 range
• At 14 years, A1C > 9.0%
• What would you do?
Case 2

• What would you do?
  A. Change oral agents
  B. Add basal insulin
  C. Add prandial insulin
  D. Go to MDI regimen
Case 2

• You begin basal insulin at night
• What do you do?
  A. Teach how to count carbohydrate
  B. Educate about recognizing and treating hypoglycemia
  C. BG monitoring not important without prandial insulin
  D. Continue 3 oral medications
Related Resources from NDEP and Partner Organizations

Joanne Gallivan, M.S., R.D.
Director, National Diabetes Education Program
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Related NDEP Resources

www.YourDiabetesInfo.org/Publications
National Diabetes Information Clearinghouse (NDIC) Resources

http://diabetes.niddk.nih.gov/
Preventing Adverse Drug Events

Individualizing Glycemic Targets Using Health Literacy Strategies

- Preventing Adverse Drug Events: Individualizing Glycemic Targets Using Health Literacy Strategies

- Earn continuing education credit (CME, CNE, CEU, CPE)

- Available on the training tab of www.health.gov
Webinar Slides and Evaluation

- Webinar Series Webpage
  - www.YourDiabetesInfo.org/Webinars
- Presentation Slides
- Webinar Evaluation
- Certificate of Completion for Webinar Attendees
  - ndep@hagersharp.com
Thank You

NDEP
National Diabetes Education Program
A program of the National Institutes of Health and the Centers for Disease Control and Prevention

www.YourDiabetesInfo.org
1-888-693-NDEP (1-888-693-6337)
TTY: 1-866-569-1162