Insulin Management Interventions at the Pharmacy Level

Presented by:
Ron Scott, R.Ph., Ph.C., BCACP

Learning Objectives (Pharmacists)
• Identify patients who could benefit from adjustments to insulin therapy
• Identify strategies and interventions leading to improvements in insulin therapy
• Describe patient specific factors pertinent to the selection of insulins
• Implement evidence-based screening, diagnostic, and therapeutic actions in their daily practice to help patients to get the most benefit from their insulin

Learning Objectives (Technicians)
• Assist the pharmacist in identifying patients who could benefit from adjustments to insulin therapy
• Participate in the process of implementing changes to therapy
• Recognize when there may be more cost effective ways for patient to get their insulin

ISMP: “For many years, insulin has been shown to be associated with more medication errors than any other type or class of drugs.”
• Patients who self-administer U-500 insulin using a vial and syringe are taught to use only a U-500 syringe and communicate their doses in terms of the name and concentration of the insulin and the actual dose in units using only the U-500 syringe.
• An insulin pen cartridge is never used as a vial.
• An individual insulin pen is never used for more than one patient.
• Eliminate the use of sliding scale insulin doses based on blood glucose values as the only strategy for managing hyperglycemia.
• Use standard insulin order sets (Tall Man, spell units out)

Manufacturer Data Reporting on Errors
• Clinician errors
• Self-administration errors
• Self-monitoring errors
• Improper insertion techniques
• Bad drawing up procedure
• Insulin timing
• Using the wrong insulin
• Miscalculating insulin sensitivity factor
• Using an incorrect carbohydrate ratio
• Not checking blood glucose 2 hrs after injection

From APhA:
Classification and Diagnosis of Diabetes

Classification

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune ß-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of ß-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
Greatest Historical Breakthroughs in Insulin Therapy

- 1973: Development of mono-component “Human” insulin
  - Purified pork insulin; new standard in purity
  - Enzymatic conversion: Alanine (B30) → Threonine
  - Identical in structure to human insulin

- 1978: Advancement of Recombinant DNA “Human” Insulin
  - Gene manipulation of E. Coli to produce bio-synthetic human insulin
  - Eliminated insulin allergy and immune-mediated lipodystrophy.
  - Humulin R and Humulin N (Eli Lilly)

- 1995: Expansion to Insulin Analogues
  - Laboratory grown (E. coli/yeast) but genetically altered amino acid sequence
  - Pharmaco-kinetic/dynamic features striving to simulate “endogenous” insulin
  - Lispro is the first analogue produced – FDA approved 1996

Primary Goal of Insulin Treatment Strategies

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Primary Goal of Insulin Treatment Strategies
Insulin Pump Technology: A Brief History

- Delivery of insulin and glucagon
- Battery-operated syringe delivers continuous release of insulin
- Medtronic’s first pump: DOX (improves user communication)
- Omnipod’s first pump: Omnipod EROS version

Insulin Pump Technology

PROS
- "Micro-Management" of insulin delivery: Less glucose variability (standard deviation)
- Reduction in number and severity of hypoglycemic episodes: Improved quality of life
- No injections: Discreteness of insulin administration
- Reduced hospitalizations due to hypoglycemia/DKA
- Patient generally becomes better educated & more independent
- Refuse injections, prefers insulin delivery: Provides precise delivery: up to 25-30% less insulin

CONS
- Mechanical device attached to body
- Perception of weight gain (not necessarily so)
- Extra cost of pump and supplies
- Time and personnel needed to initiate, supervise, and fine-tune therapy (patient participation crucial)
- More rapid (not more frequent): onset of DKA if insulin delivery interrupted for extended periods
- Infusion site infections (PIA) or irritations, leading to inadequate insulin absorption (minimized by maintaining scheduled visits for remedial care and education)

CGMS Technology reflects Interstitial Glucose

The Ideal Analogue Insulin

Rapid-acting agents:

<table>
<thead>
<tr>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>SPECIFICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular insulin</td>
<td>5-10 min</td>
<td>30-60 min</td>
<td>Neutral insulin crystals, clear solution</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>15-30 min</td>
<td>4-6 hr</td>
<td>34-amino acid of Lys and Arg</td>
</tr>
<tr>
<td>Lispro insulin</td>
<td>5-15 min</td>
<td>20-40 min</td>
<td>Single-chain substitution Proline2-Aspartic acid</td>
</tr>
<tr>
<td>Aspart insulin (Lispro FLEX)</td>
<td>10 min</td>
<td>40-70 min</td>
<td>Single-chain substitution Proline2-Aspartic acid</td>
</tr>
<tr>
<td>Glulisine (AbiMark)</td>
<td>2-5 min</td>
<td>1-3 hr</td>
<td>Neutral, rapid absorption = Aspart insulin stabilizer</td>
</tr>
</tbody>
</table>

24-hour Basal agents:

<table>
<thead>
<tr>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>SPECIFICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapered basal</td>
<td>6 hr</td>
<td>24-36 hr</td>
<td>COMPACT SQ DEPOT reduces re-dissolution rate 13x</td>
</tr>
<tr>
<td>Tapered basal</td>
<td>1-4 hr</td>
<td>No Peak</td>
<td>up to 42 hr</td>
</tr>
<tr>
<td>Lispro insulin</td>
<td>2-4 hr</td>
<td>Material Peak</td>
<td>SQ PRECIQINAT, near-patient profile, 50% intra-patient variability</td>
</tr>
<tr>
<td>Lanreotide insulin</td>
<td>2-3 hr</td>
<td>Material Peak</td>
<td>SQ PRECIQINAT, near-patient profile, 50% intra-patient variability</td>
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Impact of HB 292

- New Mexico Becomes Third State to Cap Monthly Insulin Costs
- House Bill 292, introduced by Rep. Michaela Cadena (D-33rd) and Sen. Daniel Ivey-Soto (D-15th), passed the New Mexico House on a 61-2 vote and in the Senate 40-1. The legislation caps co-pay and out-of-pocket expenses for insulin at $25 per prescription for a 30-day supply.

Impact of HB 292

- Centennial Care – No change
- Commercial Plans – Capped at $25 per 30 day supply for preferred insulins. This cap also applies to High Deductible Plans, so patient will pay $25 for insulins prior to deductible being met.
- Exchange Plans – If insurance was sold on the federal exchange, this cap does not apply as the state does not regulate federally funded plans. If it is an exchange plan that was sold internal to NM, the cap does apply.
- Medicare Plans – Cap doesn’t apply, as this is federally funded. Some insurer(s) are exploring plans with CMS to offer insulin at a lower cost for their Medicare Advantage plans in 2021, but final costs are yet to be determined. Those costs to be available to the public during open enrollment later this year.

3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Insulins
  - Human Insulins
    - Neutral protamine Hagedorn (NPH)
    - Regular human insulin
    - Pre-mixed formulations
  - Insulin Analogs
    - Basal analogues (glargine, detemir, degludec)
    - Rapid analogues (lispro, aspart, glulisine)
    - Pre-mixed formulations

- Glycemic targets
  - HbA1c < 7.0% (mean PG = 150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG < 130 mg/dl (7.2 mmol/l)
  - Post-prandial PG < 180 mg/dl (10.0 mmol/l)

- Individualization is key:
  - Tighter targets (6.0 – 6.5%) - younger, healthier
  - Looser targets (7.5 – 8.0%) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia
PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Intensifying to injectable therapies (2 of 2)

Support

Diabetes Self-management Education and Support

Four critical time points have been defined when the need for DSMES is to be evaluated by the medical care provider and/or multidisciplinary team, with referrals made as needed:

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) arise that influence self-management
4. When transitions in care occur

Abstract:
The DEC7 Your established HbA1C as the gold standard of glycemic control, with levels ≤7% deemed appropriate for reducing the risk of macrovascular complications...

Should minimal blood glucose variability become the gold standard of glycemic control?

If B. Hack and Michael Brownlee

New, even when A1Cs were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progressive-to-severe hypoglycemia.

Our speculative explanation, based on the discovery that hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage, was that glycemic excursions were of greater frequency and magnitude among conventionally treated patients, who received fewer insulin injections.

Subsequent studies correlating the magnitude of oxidative stress with fluctuating levels of glycemia support the hypothesis that glucose variability, considered in combination with A1C, may be a more reliable indicator of blood glucose control and the risk for long-term complications than mean A1C alone.
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Insulins

**Minutes**
- Rapid (Insulin Aspart, Glulisine, Lispro, Glargine)
- Short (Regular)
- Long (Detemir, Degludec, Insulin U40, U100)

**Hours**
- Short (Regular)
- Rapid (Lispro, Aspart, Glulisine)
- Long (Glargine)

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#### Major Adverse Effects of Insulin

- Hypoglycemia (unawareness)
  - DCCT Study (Type 1 Diabetes)
  - Severe hypoglycemia in 36% of patients
  - 43% of episodes nocturnal
- UMPDS Study (Type 2 Diabetes)
  - Blood glucose: 2% of patient with at least 3 severe episode/year
- Weight Gain (over insulinization, hypoglycemia/defensive snacking)
  - DCCT Study (Type 1 Diabetes)
  - Insulin: 7% with +10 lb. increase
- UMPDS Study (Type 2 Diabetes)
  - Insulin: 0% with +10 lb. increase
- Progression of Retinopathy with rapid glycemic control
  - Osmotic Hypertension: rapid death in plasma glucose shifts water from extracellular to intracellular spaces
  - Sympathetic Hypertension: Insulin sensitivity + expression of vascular endothelial growth factor (by ischemic retinal vasoconstriction)
- Higher Risk + proliferative retinopathy + HbA1c ≥ 10%

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#### Hypoglycemia Risk Factors

- Nutritional status
  - Missed meals, delayed meals
- Heart failure, renal disease, hepatic disease
- Malignancy
- Sudden reduction of steroid dose
- Altered patient ability to report symptoms
- Vomiting
- Previous history of hypoglycemia

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#### Hypoglycemia Symptoms

- Variable from patient to patient
  - Trembling
  - Palpitations
  - Sweating
  - Anxiety
  - Nausea
  - Hunger
  - Tingling
  - Tiredness
  - Confusion
  - Difficulty concentrating
  - Weakness
  - Drowsiness
  - Vision changes
  - Difficulty speaking
  - Headache
  - Dizziness

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#### Hypoglycemia in the elderly

- Reduced release of epinephrine and glucagon
- Cognitive impairment/ability to communicate
- Beta Blockers
- Not an absolute contraindication

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#### Hypoglycemia Unawareness

- No warning signals
- First sign may be loss of consciousness
- Confusion

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#### Hypoglycemia Unawareness

- Severe
  - Unresponsive
  - Coma
  - Seizure
- Night Time
  - Crying out
  - Night sweats
  - Morning headache
  - Nightmares
- Severe
GLYCEMIC TARGETS

Hypoglycemia

6.10 Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. C

6.11 In patients taking medication that can lead to hypoglycemia, investigate, screen, and assess risk for or occurrence of unrecognized hypoglycemia, considering that patients may have hypoglycemia unawareness. C

6.12 Glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. B

Hypoglycemia (continued)

6.13 Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals, particularly with the availability of intranasal and stable soluble glucagon available in autoinjector pens. E

6.14 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation of the treatment regimen. E

Hypoglycemia (continued)

6.15 Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. A

6.16 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. B

OLDER ADULTS

Figure 12.1—Algorithm to simplify insulin regimen for older patients with type 2 diabetes.
Management of Hyperglycemia: Managing Safety Concerns

- Both undertreatment and overtreatment of hyperglycemia create safety concerns.
- Areas of risk:
  - Changes in carbohydrate or food intake
  - Changes in clinical status or medications
  - Failure to adjust therapy based on BS patterns
  - Prolonged use of SSI as monotherapy
  - Poor coordination of BG testing with insulin administration and meal delivery
  - Poor communication during patient transfers
  - Errors in order writing and transcription

Steroid Therapy and Glycemic Control

- Steroids are counterregulatory hormones:
  - Impact insulin action (reduce insulin resistance)
  - Appear to diminish insulin secretion
- Majority of patients receiving >2 days of glucocorticoid therapy at a dose equivalent to ≥40 mg/day of prednisone developed hyperglycemia.
- No glucose monitoring was performed in 24% of patients receiving high-dose glucocorticoid therapy.

Frequency of Hyperglycemia in Patients Receiving High-Dose Steroids

- Patients (%)
- Blood glucose levels:
  - 18-60 <200 mg/dL
  - 20-60 >200 mg/dL

PERIOPERATIVE RECOMMENDATIONS
Pre-Op Recommendations for Patients Admitted Day of Surgery: Patients on Noninsulin Agents

- Withhold noninsulin agents the morning of surgery
- Insulin is necessary to control glucose in patients with BG >180 mg/dL during surgery
- Noninsulin agents can be resumed postoperatively when:
  - Patient is reliably taking PO
  - Risk of liver, kidney, and heart failure are lower

Pre-op Recommendations for Insulin Treated Patients

- Morning of surgery
  - Give 50-75% of home basal insulin dose (NPH/glargine/detemir)
  - Do NOT give prandial insulin
  - Give correction for hyperglycemia
  - For prolonged procedures initiate insulin infusion

Medication Adjustment Before Surgery

<table>
<thead>
<tr>
<th>Oral agents</th>
<th>Dose of glucagon</th>
<th>NPH or premixed insulin</th>
<th>Short or rapid acting insulin</th>
<th>Noninsulin injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day before surgery</td>
<td>AM: usual dose</td>
<td>PM: usual dose</td>
<td>AM: usual dose</td>
<td>PM: 80% of usual dose</td>
</tr>
<tr>
<td>Day of surgery</td>
<td>AM: usual dose</td>
<td>PM: 80% of usual dose</td>
<td>AM: usual dose</td>
<td>PM: usual dose</td>
</tr>
<tr>
<td>Held</td>
<td>80% of usual dose</td>
<td>50% of usual dose if BG =180 mg/dL</td>
<td>Held if nothing by mouth</td>
<td>Held</td>
</tr>
</tbody>
</table>

What else can help the patient?

- To avoid PAs and higher copays, let the prescriber know what the alternative options are that do not require PAs.
- Make sure a patient getting a first insulin order has pen needles or syringes as well
- If a patient is starting insulin, especially prandial insulin, check whether the prescriber really meant to continue the sulfonylurea/secretagogue
- Patients confuse insulins, especially with formulary changes, and sometimes end up getting and using multiple basal/prandial insulins
- Talk about the timing of insulin injections

What else can help the patient?

- Ensure that glucagon is available, if indicated. Assure that patients and caregivers are trained to use it (BG<54)
- Be aware that glucagon can cause vomiting
- Reinforce the rule of 15s (15gm, 15min, repeat if needed) Eat some real food to avoid recurrence (BG>70, or <80 for more frail pts)
- Use liquid sugar to bring BG up rapidly (esp in gastroparesis)
- Do not inject insulin into scar tissue
- Understand and teach carb ratios and correction factors

What else can help the patient?

- If patients can’t afford their copays, advise/help them to access copay cards online
- Be careful with Therapeutic Inertia, i.e. if an insulin dose is the same as it was a year ago, that is likely not correct. Glipizide dose of 40mg daily is likely not correct.
- Counsel on not chasing meals
- “Prandial insulin only” should be a rare occurrence
- Get involved during Transitions of Care
- Start a Diabetes Class
- Don’t assume that the prescriber is thinking at the level of an endocrinologist
What else can help the patient?

- Shares from the audience

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**Statin Treatment—Primary Prevention**

10.19 For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.20 For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. C

10.21 In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. B

10.22 In adults with diabetes and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. C

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**Statin Treatment—Secondary Prevention**

10.23 For patients of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. A

10.24 For patients with diabetes and ASCVD considered very high risk using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost.

10.25 For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. E
Antiplatelet Agents

10.34 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. A

10.35 For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B

10.36 Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome A and may have benefits beyond this period. B

10.37 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. A

Select Diabetes Advocacy Statement

• Diabetes care in the School Setting
• Care of Young Children with Diabetes in the Child Care Setting
• Diabetes and Driving
• Diabetes and Employment
• Diabetes Management in Correctional Institutions

We Talked About...

• Identifying patients who could benefit from adjustments to insulin therapy
• Identifying strategies and interventions leading to improvements in insulin therapy
• Patient-specific factors pertinent to the selection of insulins
• Implementing evidence-based screening, diagnostic, and therapeutic actions in daily practice to help patients to get the most benefit from their insulin
• Technicians assisting the pharmacist in identifying patients who could benefit from adjustments to insulin therapy
• Participating in the process of implementing changes to therapy
• Recognizing when there may be more cost-effective ways for patients to get their insulin

Questions?