Diabetes Mellitus: Pharmacology and Disease Management

Michael King, MD
Assistant Professor
Residency Program Director
University of Kentucky
Dept. of Family & Community Medicine
Objectives


2. Optimize management of diabetes to decrease potential microvascular and macrovascular complications.
Therapies

- Constantly evolving treatments & evidence
- Important to know the type and physiology of diabetes

**Type 1:**
- Insulin (many types and preparations)
- Some new options (pramlintide)

**Type 2:**
- Oral agents and/or insulin/and or new options
Selecting an Oral Agent

Considerations:
- Efficacy for glycemic reduction
- Mechanism of action
- Side effects/contraindications
- Associated metabolic changes
- Patient adherence
- Cost
## T2DM Treatments and Decrease in A1C

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>HbA1c % Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas (Glyburide, Glipizide, Glimepiride)</td>
<td>1.0 to 2.0</td>
</tr>
<tr>
<td>Meglitinides (Repaglinide, Nateglinide)</td>
<td>0.5 to .5</td>
</tr>
<tr>
<td>Biguanides (Metformin)</td>
<td>1.0 to 2.0</td>
</tr>
<tr>
<td>Glitazones (Rosiglitazone, Pioglitazone)</td>
<td>0.5 to 1.4</td>
</tr>
<tr>
<td>Alpha-Glucosidase Inhib. (Acarbose, Miglitol)</td>
<td>0.5 to 0.8</td>
</tr>
<tr>
<td>Amylin Analogue (Pramlintide)</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Incretin Mimetic (Exenatide)</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>DPP-4 Inhib (Sitagliptin)</td>
<td>0.5 to 0.8</td>
</tr>
</tbody>
</table>
### Pathophysiologies and Pharmacotherapy

#### Mechanisms of Action

<table>
<thead>
<tr>
<th></th>
<th>Insulin deficiency</th>
<th>Insulin Resistance</th>
<th>Excess hepatic glucose output</th>
<th>Intestinal glucose absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Glitazones</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alpha-Glucosidase Inhib.</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DPP-4 Inhib.</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
ADA Algorithm for Management of Type 2 Diabetes

LESS well-validated therapies after lifestyle and **Metformin**

- **Step 2:**
  - Add **Pioglitazone** (if no hypoglycemia, edema, HF, bone loss)
  - OR
  - Add **GLP-1 agonist** (if no hypoglycemia, weight loss, nausea/vomiting)

- **Step 3:**
  - Combination of **preferred Sulfonylurea and Pioglitazone** (no GLP-1 agonist)
  - OR
  - Add **basal insulin** (no sulfonylurea, pioglitazone, or GLP-1)

- **Final:** Add **Intensive Insulin**
Insulin Secretagogues

**Sulfonylureas: Long acting agents**
- Second generation: glipizide, glyburide, glimepiride
- Cheapest oral medication

**Meglitinides: Short acting (<1hr half life)**
- Repaglinide (Prandin), Nateglinide (Starlix)
- Expensive

**Combinations**
- Glyburide/Metformin (Glucovance), Glipizide/Metfomin (Metaglip), Rosiglitazone/Glimepiride (Avandaryl), Pioglitazone/Glimeperide (Duetact)
**Sulfonylureas**

- Little benefit beyond half of max dose
- Risks: Hypoglycemia, weight gain
- Renal Insufficiency/Failure:
  - Avoid Glyburide (active metabolites, renally cleared)
  - Glipizide (Glucotrol), inactive metabolites, and glimepiride (bilary/fecal excretion) preferred
Sulfonylureas

- Many drug interactions:
  - ↑ action (NSAIDs, warfarin, salicylates, allopurinol, alcohol, B-blockers)
  - ↓ action (steroids, diuretics, L-thyroxine, estrogen/progestins)

- Decreases Microvascular endpoints, only trends toward decreasing macrovascular (UKPDS).
Biguanide: Metformin

- Decreases hepatic glucose production (main)
- Increased muscle glucose utilization (less prominent)
- Combines well with SU, acarbose, glitazones, DPP4 inhib or insulin

Preferred Initial Treatment:
- Less hypoglycemia, wt loss, enhances lipids, improves insulin resistance
- Improves macrovascular endpoints (UKPDS)
Metformin : Contraindications

- Renal insufficiency
  - Serum CR >1.5 males, >1.4 females
- Hepatic insufficiency
- CHF
- Dehydration
- ETOH abuse
- Hx of metabolic acidosis
- Type I diabetes
- Category B in Pregnancy
Metformin: Side Effects and Caveats

- Nausea, diarrhea: may be self limited
- Lactic acidosis; Identify risk factors
- Hold with IV contrast (48 hrs before)
- Uncommon to see benefit past 2000mg per day (max of 2550 mg)
Metformin: New Preparations

- Glucovance = metformin + glyburide
- Metaglip = metformin + glipizide
- Avandamet = metformin + rosiglitazone
- Actosplus met = metformin + pioglitazone
- Janumet = metformin + januvia

The same precautions apply
Thiazolidendiones

- Increases peripheral insulin sensitivity
  - Activates PPAR (peroxisome proliferator activated receptor gamma)

- Combination therapy with insulin, SU, metformin (mentioned previously)
Glitazones: General considerations

- Do not use if baseline LFTs >3x normal
- Can precipitate clinical heart failure so use cautiously
- Contraindicated with NYHA HF Class III-IV
- CVD? Black box warning
Glitazones: A Benefit or Harm?

- Data is clear to support A1C reduction (disease surrogate)

- No clear difference clinically in other oral hypoglycemic therapies

- No clear evidence to support improved patient oriented outcomes (mortality, MI, CVA)

- Some evidence supports increased CV risk of events, edema and HF episodes/hospitalization

Remember Glucagon?

- Effects of glucagon in glucose metabolism and utilization
- Supressing something instead of increasing something
- Homoestasis = sum of the parts
  - Alpha $\alpha$ + Beta $\beta$ = Glucose Control
  - Glucagon and Insulin
- Newer products focus on this physiology:
  - Amylin analogue, Incretin Mimetic and DPP-4 Inhibitors
Pramlintide (Symlin): Synthetic Amylin

Amylin:
- Produced with insulin (beta cells)
- Works with insulin and glucagon to maintain normal blood glucose
- As beta cell function declines, diabetics become Insulin and Amylin deficient

Effects:
- suppress glucagon excretion
- control postprandial hyperglycemia
- delay gastric emptying, promote satiety

Approved:
- Type 1 diabetes, not achieving goal A1C
- Type 2 diabetes, using insulin and not at goal.
Pramlintide

- SC Injection before meals
  - Lowers post prandial glucose
  - Less fluctuation during the day
  - Less mealtime insulin necessary
  - Cannot be combined with insulin.

- Improves A1C control compared to insulin alone.

- Reduction in body weight compared to insulin alone.

- Expensive
Pramlintide: Side Effects

- Mainly nausea (Dose dependent)
- Hypoglycemia with insulin
- Others: fatigue, abd pain

- No Cardiac, Hepatic or Renal toxicity
- No lipid abnormalities
Medical School Revisited?

- **Incretins**: intestinal hormones released during eating
  - GIP: glucose dependent insulino-tropic peptide
  - GLP1: glucagon-like peptide

- ~60% of post-meal insulin secretion due to incretins (impaired in T2DM)

- **Dipeptidyl peptidase-4 enzyme (DPP-4)**: inactivates GLP1 and GIP
GLP-1 and Glucose Homeostasis

- Enhances *glucose dependent* insulin secretion, **AND**
- Suppresses glucagon secretion
- Promotes satiety, leading to reduction of food intake
- Regulates the rate of gastric emptying, limiting postprandial glucose excursions
Incretin Mimetic: Exenatide (Byetta)

- Amino acid sequence partially overlaps that of the human incretin hormone GLP-1

- T2DM, not achieved target A1C levels with metformin, sulfonylurea, or combination.

- Approved in combination with Metformin and Sulfonylureas

- No hypoglycemia unless taken with a sulfonylurea.
  - Consider decreasing sulfonylurea dose
Exenatide: Caveats

- Not an insulin substitute in insulin-requiring patients
- Not for use Type 1 DM or with DKA
- Not recommended in patients with end-stage renal disease or renal impairment (GFR <30), or severe gastrointestinal disease
- Pancreatitis??
- Category C in Pregnancy
DPP4 Inhibitors

- Sitagliptin (Januvia, 2006) and Saxagliptin (Onglyza, 2009)
- DPP4 inhibitors
  - Improves A1C, fasting and post-prandial glycemia
- Oral Monotherapy, with metformin or a glitazone
- Not for Type 1 DM
- Recommended doses:
  - Sitagliptin 100 mg PO QD
  - Saxagliptin 5 mg PO QD
DPP-4 Inhibitors
Side Effects and Cautions

- Adverse reactions was similar to placebo, including hypoglycemia, some concern of slight increase in upper respiratory infections

- Renal Insufficiency
  - No renal toxic effects but is efficacious at lower doses in renal insufficiency and ESRD (even hemodialysis)
  - Sitagliptin:
    - 50mg: Moderate RI, CrCl <50 but >30 mL/min
      (Cr >1.7 in men, >1.5 in women)
    - 25mg: Severe RI, Cr Cl <30 mL/min
      (Cr >3.0 in men, >2.5 in women)
  - Saxagliptin:
    - 2.5 mg daily, Moderate or Severe RI, CrCl ≤50 mL/min
Insulin: Sometimes a Necessary Therapy

β-cell function

Normal

Absent

Disease progression (years)

Type 1

Type 2

Diet Exercise

PLUS Oral agents

PLUS Combination oral agents

PLUS Insulin
Insulin Therapy

- Useful for both type 1 and type 2
- Basal bolus
- Mimic normal physiology
- Know the timing
- Basal or longer acting: NPH, glargine
- Bolus: regular, lispro, aspart
ADA Algorithm for Management of Type 2 Diabetes

Well-Validated Core Therapies

- **Step 1**: at Diagnosis
  - Lifestyle Modification and **Metformin**

- **Step 2**: Add **Basal Insulin** OR
  - Add **preferred Sulfonylurea**
    - Not glyburide or chlorpropamide
    - If fails then stop sulfonylurea and add **basal insulin**

- **Step 3**: Add **Intensive Insulin**
Oral Agents + Insulin
Type 2 Diabetes:

- Improves glycemic control
- Lower doses of exogenous insulin
- Addresses multiple causes of hyperglycemia
# Insulin Initiation and Titration

1. **Start q hs** \(\textit{NPH or Glargine (10 U or 0.2 U/kg)}\)

2. **Daily BS**, \(\uparrow 2U \text{ q3d}\) until fasting controlled, or \(\uparrow 4U \text{ q3d}\) if \(>180\)

3. **A1C >7, Fasting BS 70-130**, then need **2\textsuperscript{nd} Injection of Insulin**
   - **BS**
     - \(\uparrow \text{ pre-Lunch}\)
     - \(\uparrow \text{ pre-Dinner}\)
     - \(\uparrow \text{ pre-Bed}\)
   - **Add 2\textsuperscript{nd} Injection**
     - **Rapid Insulin at Breakfast**
     - **NPH at Breakfast or Rapid Insulin at Lunch**
     - **Rapid Insulin at Dinner**

4. **A1C >7, recheck pre-meal BS**, may need **3\textsuperscript{rd} Injection of Insulin** as above

5. **A1C >7, check 2hr postprandials and adjust preprandial** \(\textit{Rapid-Insulin}\)

---

Diabetes Care, Vol. 32; 2009; 193-203
<table>
<thead>
<tr>
<th>Insulins</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-Acting Analogues:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>2-3 hrs</td>
<td>None</td>
<td>24+ hrs</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1 hr</td>
<td>None</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td><strong>Intermediate Acting:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-3 hrs</td>
<td>4-10 hrs</td>
<td>10-18 hrs</td>
</tr>
</tbody>
</table>
## Insulins: Bolus Therapy

Prandial Control

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting Analogues:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>10-15 mins</td>
<td>1-2 hrs</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short Acting:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1 hr</td>
<td>2-4 hrs</td>
<td>4-8 hrs</td>
</tr>
</tbody>
</table>
### Insulins: Premixed Prandial Control

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humalog Mix 75/25 = 75% Lispro Protamine / 25% lispro</td>
<td>10-15 mins</td>
<td>1-3 hrs</td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>Humalog Mix 50/50 = 50% Lispro Protamine / 50% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolog mix 70/30 = 70% Aspart Protamine / 30 % aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70/30 = 70% NPH / 30% regular</td>
<td>0.5-1 hr</td>
<td>2-10 hrs</td>
<td>10-18 hrs</td>
</tr>
<tr>
<td>50/50 = 50% NPH / 50% regular</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Diabetes management is individualized and involves the patient and a provider-directed team
• Establishing tight glycemic control is the key to management
• Lifestyle changes to prevent onset of diabetes and CVD are the first step
• Type 2 diabetes is progressive; management will likely ultimately require insulin
• Providers should employ an aggressive, treat-to-target strategy