Type 2 Diabetes Pharmacotherapy Update 2015

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OBJECTIVES

• Describe the current therapies for type 2 diabetes including insulin, metformin, sulfonylureas, thiazolidinediones, GLP-1 agonists, DPP-IV inhibitors, and SGLT2 Inhibitors

• Utilize a patient centered approach when selecting therapy for a patient with type 2 diabetes
UPDATED GUIDELINES

• Standards of Medical Care in Diabetes 2015. *Diabetes Care* 2015;38(Suppl 1)


DIABETES MEDICATIONS

<table>
<thead>
<tr>
<th>Year</th>
<th>Medication</th>
</tr>
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<tbody>
<tr>
<td>1922</td>
<td>Insulin</td>
</tr>
<tr>
<td>1957</td>
<td>SUs</td>
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<tr>
<td>1957</td>
<td>Metformin</td>
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<tr>
<td>1995</td>
<td>AGIs</td>
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<tr>
<td>1997</td>
<td>Glinides</td>
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<tr>
<td>1997</td>
<td>TZDs</td>
</tr>
<tr>
<td>2000</td>
<td>Sitagliptin</td>
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<tr>
<td>2005</td>
<td>Saxagliptin</td>
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<tr>
<td>2005</td>
<td>Liraglutide</td>
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<tr>
<td>2009</td>
<td>Linagliptin</td>
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<tr>
<td>2009</td>
<td>Albiglutide</td>
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<tr>
<td>2010</td>
<td>Dapagliflozin</td>
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<tr>
<td>2010</td>
<td>Empagliflozin</td>
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<tr>
<td>2011</td>
<td>Canagliflozin</td>
</tr>
<tr>
<td>2014</td>
<td>Afrezza</td>
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<tr>
<td>2014</td>
<td>Inhaled insulin</td>
</tr>
</tbody>
</table>
LONG ACTING/BASAL INSULIN

Insulin detemir (Levemir®)
- Once or twice daily dosing
- Pens or Vials

Insulin glargine (Lantus®)
- Once daily dosing
- Pens or vials

INSULIN GLARGINE 300 UNITS/ML (TOUJEO® SOLOSTAR PEN)

- Higher concentration of Insulin Glargine
- Only available in pen form
- Same efficacy and dosing as Lantus®
  - Just requires 1/3 less volume of insulin for the same number of units
  - Lasts slightly longer than 24 hours

*You will not see the plunger until you have injected a few doses
INTERMEDIATE-ACTING INSULIN - NPH

- Neutral Protamine Hagedorn (NPH)
- Novolin® N
- Humulin® N

Onset: 1 to 2 hrs
Peak: 6 to 10 hrs
Duration: 12-18 hours
Cloudy insulin: suspension
BID dosing when used as basal coverage
Cheaper option for basal coverage when needed

SHORT ACTING INSULIN - REGULAR

- Novolin® R
- Humulin® R

Onset: 30 minutes
Peak: 2 to 5 hrs
Duration: 4 to 6 hrs
Inject 30 minutes before meals
Good option for gastroparesis
RAPID-ACTING INSULIN

• Insulin Lispro (Humalog®)
  • Humalog U-200 Pens now available also
• Insulin Aspart (Novolog®)
• Insulin Glulisine (Apidra®)

  • Onset 5-15 minutes
  • Peak effect: 1 to 3 hrs
  • Duration 3- 5 hours
  • Inject 5-15 min before meals

NEW INHALED INSULIN

• Afrezza: approved 6-27-14
  • Human insulin inhalation powder
  • Rapid acting insulin
  • Boxed warning advising about acute bronchospasm risk in patients with asthma or COPD
  • Single use cartridges of 4, 8, and 12 units
Older Oral Therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Precautions</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (Metformin)</td>
<td>• Activates AMP-kinase&lt;br&gt; • ↓ Hepatic glucose production&lt;br&gt; • ↑ insulin sensitivity&lt;br&gt; • ↓ GI absorption of glucose</td>
<td>• Extensive experience&lt;br&gt; • No hypoglycemia&lt;br&gt; • Weight neutral&lt;br&gt; • ? ↓ CVD</td>
<td>• GI side effects&lt;br&gt; • Lactic acidosis&lt;br&gt; • B-12 deficiency&lt;br&gt; • Contraindications (renal impairment-GFR &lt;30)&lt;br&gt; • If GFR &lt;45, use ½ max dose</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonlureas (Glyburide, Glipizide, Glimepiride)</td>
<td>• Closes KATP channels&lt;br&gt; • ↑ Insulin secretion</td>
<td>• Extensive experience&lt;br&gt; • Good A1C reduction at initiation&lt;br&gt; • Glipizide XL, Glimepiride once daily dosing</td>
<td>• Hypoglycemia&lt;br&gt; • Weight gain&lt;br&gt; • Low durability</td>
<td>Low</td>
</tr>
<tr>
<td>TZDs (Pioglitazone, Rosiglitazone)</td>
<td>• PPAR-g activator&lt;br&gt; • ↑ insulin sensitivity</td>
<td>• No hypoglycemia&lt;br&gt; • Durability&lt;br&gt; • Once daily dosing&lt;br&gt; • ↓ TGs, ↑ HDL-C</td>
<td>• Weight gain&lt;br&gt; • Edema / heart failure risk&lt;br&gt; • Bone fractures&lt;br&gt; • ↑ MI risk(rosi)&lt;br&gt; • ↑ Bladder cancer (pio)…retracted by company 9-2014</td>
<td>mid</td>
</tr>
</tbody>
</table>

*Diabetes Care 2012 June;35(6): 1364-79*
GLP-1 Agonists

THE INCRETIN EFFECT

Ingested glucose results in a more robust insulin response than glucose administered intravenously, indicating the presence of substances within the gastrointestinal tract that stimulate insulin release in a glucose-dependent manner.

**GLP-1 Secretion and Inactivation**

Mixed meal → Intestinal GLP-1 release → GLP-1 active → DPP-4 → GLP-1 inactive (>80% of pool)

**GLP-1 PHYSIOLOGY**

GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

- Promotes satiety and reduces appetite
- Enhances glucose-dependent insulin secretion
- Postprandial glucagon secretion
- Liver: reduces hepatic glucose output
- Stomach: regulates gastric emptying

EXENATIDE (BYETTA®)

• Dosing:
  • 5 mcg SC twice daily within 60 min of start of a meal
  • Increase to 10 mcg bid after 4 weeks
  • Need to prescribe pen needles
• FDA approved for type 2 diabetes as monotherapy or in combination with a sulfonylurea, TZD, metformin, or insulin glargine

LIRAGLU TIDE (VICTOZA®)

• FDA approved for type 2 diabetes in combination with metformin, sulfonylurea, TZD, or insulin detemir
• Dosing: 0.6 mg SQ once daily x 1 week
  • Then 1.2 mg SQ daily x 1 week
  • Can increase to 1.8 mg daily if needed
• Timing of doses, independent of meals
• Need to prescribe pen needles
EXENATIDE LONG ACTING (BYDUREON®)

- 2 mg subq once a week
  - Without regard to meals or time of day
  - New Pen device just FDA approved 3-2014
    - Available in pharmacies this year

ALBIGLUTIDE (TANZEUM™)

- 30 mg SQ once a week
  - Can increase to 50 mg once weekly
  - Without regard to meals or time of day
DULAGlutide (Trulicity™)

- 0.75 mg SQ once weekly
  - Can increase to 1.5 mg once weekly
  - Each pen is single use
  - Patient does not see the needle when performing the injection

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GLP-1 Agonist Comparative Trials

- **LEAD-6**: Liraglutide vs. Exenatide BID x 26 wks
  - A1C reduction: -1.12% vs. -0.79% (P<0.0001)

- **DURATION-1 AND DURATION-5**: Exenatide LAR vs. Exenatide BID x 24 weeks
  - A1C reduction: -1.6% vs. 0.9% (P<0.0001)

- **DURATION-6**: Liraglutide vs. Exenatide LAR x 26 weeks
  - A1C reduction: -1.5% vs. -1.3% (P=0.02)

DURATION-5. J Clin Endocrinol Metab. 2011;96(5):1301-10
GLP-1 AGONIST COMPARATIVE TRIALS

**HARMONY 7**: Albiglutide vs. liraglutide x 32 weeks non inferiority study
- A1C reduction -0.78% vs. -0.99% p=0.0846 (did not meet non-inferiority criteria)
- Weight loss greater with liraglutide
  - -2.19 kg vs -0.64 kg p<0.0001


GLP-1 AGONIST ADVERSE EFFECTS/CONTRAINDICATIONS

**Adverse Effects**
- N/V, diarrhea
- Weight loss (a good side effect)

**Contraindications/Precautions**
- Type 1 diabetes
- CrCl < 30 ml/min (exenatide)
- Gastroparesis
- History of pancreatitis
- History of medullary thyroid carcinoma
- Multiple endocrine neoplasia syndrome 2
GLP-1 AGONIST BENEFITS

• Low risk of hypoglycemia
  • Slightly higher risk when used with sulfonylureas or insulin
• Weight loss
• Potential for once daily or once weekly dosing
  • Numerous studies now supporting their use with insulin (or instead of insulin)

FUTURE INCRETIN MIMETICS

• Lixisenatide- Once daily
  • Lixisenatide + insulin glargine fixed dose combo (Lixilan)
Inhibition of DPP-4 Increases Active GLP-1

Mixed meal → Intestinal GLP-1 release → GLP-1 (7-36) active → DPP-4 → DPP-4 inhibitor → GLP-1 (9-36) inactive
AVAILABLE DPP-IV INHIBITORS

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza™)
- Linagliptin (Tradjenta™)
- Alogliptin (Nesina™)

DPP-IV INHIBITORS

- Efficacy: ↓ A1C 0.5-0.7%
  - Similar efficacy for all four drugs
  - Less A1C reduction than with the GLP-1 agonists
- Weight neutral
- Adverse effects: very well tolerated
  - Low risk of hypoglycemia
  - Post-marketing reports of pancreatitis
  - One study showed increased CHF hospitalizations with saxagliptin, but not with the others
DPP-IV INHIBITOR COMPARATIVE TRIALS

• **DURATION-2** and **DURATION-4**: Exenatide LAR vs. Sitagliptin x 26 weeks
  - A1C reduction when added to metformin: -1.5% vs. 0.9% (p<0.0001)

• **Sitagliptin 100 mg vs. Saxagliptin 5 mg**
  - As add-on therapy to metformin x 18 weeks
  - -0.6% vs. -0.5% (NS)

COMBINATION PRODUCTS

• Sitagliptin/metformin (Janumet®)
  - Sitagliptin/metformin XR (Janumet® XR)
  - Saxagliptin/metformin XR (Kombiglyze™)
  - Linagliptin/metformin (Jentadueto™)
  - Alogliptin/Metformin (Kazano)
  - Alogliptin/Pioglitazone (Oseni)
  - Canagliflozin/Metformin (Invokamet™)
  - Dapagliflozin/Metformin XR (Xigduo XR™)
  - Empagliflozin/Linagliptin (Glyxambi™)
# MAJOR DIFFERENCES IN INCRETIN THERAPIES

<table>
<thead>
<tr>
<th>Properties/Effect</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-dependent stimulation of insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Glucose-dependent reduction of increased glucagon</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect on body weight</td>
<td>Weight neutral</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>minimal</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral Once daily</td>
<td>Subcutaneous Once or twice daily or once weekly</td>
</tr>
</tbody>
</table>

**SGLT2 Inhibitors**

Glucose normally reabsorbed into body

Glucose flow to kidneys

Blocked by SGLT inhibitor

Glucose now passed in urine
SGLT2 INHIBITORS – 1ST AGENT APPROVED 3/29/13

• Sodium-glucose co-transporter inhibitors (SGLT2)
• Increase urinary glucose excretion

SGLT2 INHIBITORS

• Canagliflozin (Invokana™)
• Dapagliflozin (Farxiga™)
• Empagliflozin (Jardiance™)
  • Once daily oral medications
  • Low risk of hypoglycemia
  • Weight loss
• Adverse Effects:
  • Female genital mycotic infections
  • UTI
  • Increased urination
  • 2015 FDA warning about ketoacidosis
  • Fracture risk?
SGLT2 INHIBITORS

• EMPA-REG OUTCOME study
  • Cardiovascular safety study
• 7020 patients with established CVD randomized to empagliflozin or placebo
  • Primary composite outcome: death from CV cause, nonfatal MI, or nonfatal stroke
  • 10.5% in empagliflozin group vs. 12.1% placebo p=0.04 for superiority
  • Death from CV causes:
    • 3.7% empagliflozin 5.9% in placebo
    • 38% relative risk reduction

Zinman B, et al. NEJM 2015. published online September 17, 2015

ADA Management of Hyperglycemia in Type 2 Diabetes

Standards of Medical Care in Diabetes 2015. Diabetes Care 2015;38(Suppl 1)

GLYCEMIC GOALS

ADA Guidelines

- A1C < 7.0%
  - Less stringent A1C goal <8% appropriate for certain patients… see guidelines
- Fasting/premeal glucose 80-130 mg/dl
- Peak postprandial glucose <180 mg/dl
- 1-2 hours after the start of the meal

<table>
<thead>
<tr>
<th>A1C</th>
<th>Mean Plasma glucose mg/dl</th>
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<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
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<tr>
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<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

Approach to management of hyperglycemia:

- Patient attitude and expected treatment efforts:
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - 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. mild vs. severe
- Established vascular complications:
  - absent vs. mild vs. severe
- Resources, support system:
  - readily available vs. limited

*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*

**MONITORING**

- **Self monitoring of blood glucose (SMBG)**
  - At least 3 times/day if on insulin injections
  - If on orals, just use SMBG to help them achieve their glycemic goals
  - Use the data to make decisions on what therapy to add
- **A1C**
  - Every 3 months in patients whose therapy has changed or aren’t meeting treatment goals
  - At least twice a year in patients who are at goal
METFORMIN 1ST LINE

• Metformin, if not contraindicated, is the preferred 1st line agent
  • Low risk of hypoglycemia, no weight gain, cheap
• Titrate metformin to max dose over 1-2 months
  • Start with 500 mg once or twice a day
  • After 5-7 days if GI effects haven’t occurred, increase to 1000 mg BID
  • If GI effects as dose is increased reduce dose and try to increase again at a later time
• Consider adding other agents if there is persistent hyperglycemia
• Use eGFR to dose metformin
  • <45 cut dose in half
  • <30 do not use

CONSIDERATIONS WHEN ADDING ON THERAPY TO METFORMIN

• Choice is based on patient and drug characteristics
  • Use ADA algorithm and knowledge of pharmacology, cost, patient preference, and side effect profile
• Consider insulin 2nd line (or 1st line + metformin) when patient presents with significant hyperglycemia
  • Glucose >300 and/or A1C >10% or symptomatic
• No evidence for using DPP-IV inhibitor with GLP-1 agonist
• Consider insulin as 3rd agent especially when A1C is >9% and patient is already on 2 non-insulin drugs
HOW TO ADD INSULIN FOR TYPE 2 DIABETES

- Long-acting Basal insulin typically started alone initially
  - 0.1-0.2 units/kg once a day
    - Alternative is NPH dosed BID
    - Used in conjunction with 1-2 non-insulin agents
- If fasting glucose is at goal, but A1C remains elevated, consider pre-meal insulin OR GLP-1 agonist
  - 4 units or 0.1 units/kg before meals
  - Also consider pre-meal insulin if the basal dose has exceeded 0.5 units/kg and glucose still isn’t at goal
- Discontinue sulfonylureas when starting a pre-meal insulin

APPROACH TO STARTING AND ADJUSTING INSULIN IN TYPE 2 DIABETES
KEY POINTS

• After metformin, little data to guide treatment decisions
• **Insulin should be considered with metformin for initial therapy when A1C >10%**
  • Consider insulin as second or third add-on agent when A1C >9%
  • Use insulin pens when possible
  • Discontinue sulfonylureas when initiating a prandial insulin
• Glycemic targets and glucose lowering therapies should be individualized
• Include lifestyle modifications with all drug therapies

Questions