Trends in Diabetes Medication Management

CAPT Christopher Lamer, PharmD, MHS, BCPS, CDE
Objectives

• At the end of this presentation, participants will be able to:
  • Describe the changes in treatment goals for type 2 diabetes mellitus.
  • Explain the pros and cons of commonly prescribed glucose lowering medications.
  • Synthesize reasons for selecting glucose lowering medications.
  • Reinforce the importance of assessing for medication adherence among people with type 2 diabetes mellitus.
Diabetes is a Progressive Disease

- Normal
- Pre-DM
- 0-5 years
- 5-10 years
- > 15 years

Insulin Secretion

Nutrition and Physical Activity

Non-Insulin Medications

Insulin
Changes in Treatment Targets

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C</strong></td>
<td>&lt;7%</td>
<td>Individualize targets (Many &lt;7%)</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>&lt;100mg/dL</td>
<td>Statin if at risk of ASCVD</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>Age &gt;40 yrs</td>
<td>If at risk of ASCVD</td>
</tr>
</tbody>
</table>
# A1C Targets

<table>
<thead>
<tr>
<th>Situation</th>
<th>A1C Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Early Disease</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Most non-pregnant Adults</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Clinically Complex Adults</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>Very Complex or Adults in Poor Health</td>
<td>&lt;8.5%</td>
</tr>
</tbody>
</table>
Selecting Medications (circa 2007)

1. Metformin → 2. Sulfonylurea → 3. TZD

4. Insulin
More Medication Options

Alpha Glucosidase Inhibitors
Amylin Analog
Bile Acid Sequestrants
Incretin Mimetics
  Glucagon Like Peptide
  DPP-4 Inhibitor

Sulfonylurea Meglitinide
  Pancreas

Intestines

Glucose  Insulin

Urine
  Kidney

Liver

Metformin

SGLT-2 Inhibitors

Muscles
  Fat Cells

Indian Health Service
Division of Diabetes Treatment and Prevention
Medication Selection in 2017
Step 1: Metformin

- A1C <9%  Metformin monotherapy
- A1C 9-10%  Metformin + second agent
- A1C >10%  Consider insulin therapy +/- Metformin
Metformin

- Decrease A1C 1-2%
- Decrease Weight
- Low Risk of Hypoglycemia
- Taste Disturbances
- Monitor B12
- GI Upset
Metformin Dosing

• Start with 500mg once a day with largest meal of the day.

• Regular Release
  • Increase to 1 tablet 2 times a day for at least 1 week.
  • Increase by 1 tablet weekly if able.
  • Maximum dose 2500mg per day (5 tablets)

• XR (Extended Release)
  • Increase to 2 tablets with largest meal for at least 1 week.
  • Increase by 1 tablet weekly if able.
  • Maximum dose 2000mg per day (4 tablets)
Metformin Dosing (cont.)

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

4/2017 Update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letters and latest prescribing information by searching for metformin at Drugs@FDA

Safety Announcement

[4-8-2016] The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin’s use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. We were asked1,2 to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function3-14 and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. We have concluded our review, and are requiring changes to the labeling of all metformin-containing medicines to reflect this new information.
Metformin Contraindications and Cautions

- Lactic Acidosis
  - **Contraindications**
    - Severe renal impairment: eGFR < 30 mL/min
    - Acute or chronic metabolic acidosis
  - **Temporarily discontinue**
    - Radiologic studies using iodinated contrast media
    - Hold for non-minor surgery – restart when eating and renal function normal
  - **Cautions**
    - Hypoxia (shock, CHF, AMI)
    - Hepatic dysfunction
    - Excessive alcohol intake
    - Severe renal impairment: eGFR 30-45 mL/min
### Step 2: Add Another Agent

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea</th>
<th>TZD</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT2 Inhibitor</th>
<th>GLP-1 Agonist</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C Lowering</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Hypoglycemia risk*</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Weight gain</td>
<td>↑↑</td>
<td>↑↑</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cost</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low-high</td>
</tr>
</tbody>
</table>

* when used alone
Sulfonylureas

- Stimulates insulin release
  - Requires functional pancreas and ability to create insulin
<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Max Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide (Diabeta®, Micronase®)</td>
<td>1.25-10mg daily (single or divided dose)</td>
<td>20mg daily</td>
<td>24 hours</td>
<td>Metabolized by the liver. Excreted in urine and bile.</td>
</tr>
<tr>
<td>Glyburide (Glynase®)</td>
<td>0.75-12mg daily</td>
<td>12mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide (Glucotrol®, Glucotrol XL®)</td>
<td>2.5-20mg daily (single or divided dose)</td>
<td>40mg (20mg if XL)</td>
<td>12-16 hours</td>
<td>Metabolized by the liver. Excreted in the urine. Take on empty stomach.</td>
</tr>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td>1-4mg daily</td>
<td>8mg daily</td>
<td>24 hours</td>
<td>2 major metabolites. Hepatic &amp; renal elimination. Take with first main meal</td>
</tr>
</tbody>
</table>
Thiazolidinediones

- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)
Thiazolidinediones (cont.)

- Decrease A1C 1-2%
- Low Risk of Hypoglycemia
- Increase Weight
- Stimulation of Ovulation
- Fluid Retention/CHF
### Thiazolidinediones (more)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (Actos®)</td>
<td>15-45 mg daily</td>
<td>45 mg daily</td>
<td>Metabolized by the liver. LFTs every 2 months x first year then periodically.</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia®)</td>
<td>2-8 mg daily</td>
<td>8 mg daily</td>
<td>Metabolized by the liver. LFTs every 2 months x first year then periodically.</td>
</tr>
</tbody>
</table>

- 4mg rosiglitazone daily  =  15mg pioglitazone
- 8mg rosiglitazone daily  =  30mg pioglitazone
- 4mg rosiglitazone BID  =  45mg pioglitazone daily
GLP-1 Agonists (1)
GLP-1 Agonists (2)

- Exenatide (Byetta®, Bydureon®)
  
- Liraglutide (Victoza®)
  
- Albiglutide (Tanzeum®)
  
- Dulaglutide (Trulicity®)
  
- Liraglutide (Saxenda®)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>5 mcg Q12 hours 60 minutes before meals</td>
<td>Increase to 10 mcg after 1 month</td>
</tr>
<tr>
<td>Exenatide Weekly</td>
<td>2 mcg weekly</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg daily x 7 days</td>
<td>1.2 mg daily</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>30 mg weekly</td>
<td>Increase to 50 mg weekly</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75 mg weekly</td>
<td>Increase to 1.5 mg weekly</td>
</tr>
</tbody>
</table>
• HS is a middle aged man with Type 2 Diabetes diagnosed just over 6 years ago. He has been taking Albiglutide 50mg every Monday morning for about 9 months. He calls you on Thursday stating that he forgot to take his medication on Monday and wonders if it is OK to take it now or should he just wait until next Monday?
GLP-1 Agonists (4)

- Missed weekly doses: take when remembered if ≤ 3 days of the next dose

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THUR</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
<th>MON</th>
</tr>
</thead>
</table>

- Switching days: after at least 4 days of last dose

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THUR</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
<th>MON</th>
</tr>
</thead>
</table>
DPP-4 Inhibitors
DPP-4 Inhibitors (cont.)

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

Dosing:  5mg daily
       2.5mg daily if CrCL≤50ml/min or
       strong CYP3A4/5 Inhibitor

Heart failure risk - Heart failure occurred in:
       3.5% of patients taking saxagliptin
       2.7% of patients taking placebo
SGLT-2 Inhibitors

Glucose

SGLT2
90%

Glucose

SGLT1
10%
SGLT-2 Inhibitors (cont.)

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100mg daily before the first meal</td>
<td>300mg daily</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5mg daily with or without food</td>
<td>10mg daily</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10mg daily with or without food</td>
<td>25mg daily</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitors: CVD Benefit

CV death

HR 0.62
(95% CI 0.49, 0.77)
p<0.0001

HbA1c

Basal Insulin

- Intermediate Acting
  - NPH
- Long Acting
  - Glargine
  - Detemir (Levemir®)
- Ultra Long Acting
  - Glargine U300 (Toujeo®)
  - Degludec (Tresiba®)
What Makes Insulin Different?

• How long it takes to work (onset)?
• When (if) the insulin spikes (peak)?
• How long it works (duration)?

• How concentrated is the insulin?
Insulin Concentrations

- 1mL U-100 contains 100 units of insulin
- 1mL U-200 contains 200 units of insulin
- 1mL U-300 contains 300 units of insulin
- 1mL U-500 contains 500 units of insulin
## Intermediate Acting Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>1-2 hours</td>
<td>4-12 hours</td>
<td>12-16 hours</td>
</tr>
</tbody>
</table>
# Long-Acting Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine (Basaglar®, Lantus ®)</td>
<td>1-2 hours</td>
<td>None</td>
<td>20-26 hours</td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>1-2 hours</td>
<td>6-8 hours</td>
<td>18-24 hours</td>
</tr>
</tbody>
</table>
Ultra-Long-Acting Insulin

- Steady insulin levels for over 24 hours
- Injected once daily
- May be combined with short-acting insulin to cover meals

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U300</td>
<td>1-2 hours</td>
<td>None</td>
<td>Up to 36 hours</td>
</tr>
<tr>
<td>(Toujeo®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td>30-90 min</td>
<td>None</td>
<td>&gt;42 hours</td>
</tr>
<tr>
<td>(Tresiba®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Insulin Glargine U300 (Toujeo®)

• Concentrated insulin
  • 1ml of Glarine U100 contains 100 units
  • 1ml of Glargine U300 contains 300 units

• 3ml of Glargine has the same amount of insulin as 1ml of Glargine 300U
Insulin Degludec (Tresiba®)

- Available as:
  - U100 (100 units/mL)
  - U200 (200 units/mL)
- Good for 8 weeks after opening
### Step 2: Add Another Agent

<table>
<thead>
<tr>
<th>Combination with Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td>GLP-1 Agonist</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
</tbody>
</table>
Step 3: Add Additional Agent
Drugs don’t work if….

….people don’t take them!
Medication Adherence

100 Prescriptions written
88 are filled at the pharmacy
76 are taken by the patient
49 are refilled after the prescription runs out
Medication Adherence (cont.)

• Proportion of Days Covered (PDC)

   Days the patient “has” medications
   Jan 1

   Dec 31

   Total days must be \( \geq 80\% \) (> 292 days supply)

• Gaps in Therapy

   Fill A
   Must be \( \leq 30 \) days
   Fill B
Diabetes Medications

Proportion of Days Covered > 80%
Gap in Therapy > 30 days

Biguanide: 38
Sulfonylurea: 40
TZD: 41
DPP IV: 44

Gap in Therapy > 30 days
Proportion of Days Covered > 80%
Cardiovascular Medications

- Beta Blocker: Proportion of Days Covered > 80% (48), Gap in therapy > 30 days (51)
- RASA: Proportion of Days Covered > 80% (47), Gap in therapy > 30 days (52)
- CCB: Proportion of Days Covered > 80% (51), Gap in therapy > 30 days (49)
- Statin: Proportion of Days Covered > 80% (44), Gap in therapy > 30 days (55)
Adherence to Statin Medications 2011-2015

Proportion of Days Covered ≥ 80%  
Gap in Therapy ≥ 30 Days

- 2011 PDC: 49.7
- 2012 PDC: 47.8
- 2013 PDC: 48
- 2014 PDC: 46
- 2015 PDC: 44
- 2011 GAP: 49
- 2012 GAP: 52
- 2013 GAP: 51
- 2014 GAP: 52
- 2015 GAP: 55
Addressing Adherence

• Simplify the regimen
• Impart knowledge
• Modify patient beliefs and human behavior
• Provide communication and trust
• Leave the bias
• Evaluate adherence
Step 4: Add Basal/Bolus Insulin
What to do with other medications when starting Insulin?

- Metformin 500mg
  - Take 2 tablets by mouth two times daily after meals.

- Glyburide 5mg
  - Take 2 tablets by mouth two times daily.

- Pioglitazone 30mg
  - Take 1 tablet by mouth daily.
What to do with other medications when starting Insulin? (cont.)

- **Metformin**: Recommend that it be continued
- **Sulfonylureas**: questionable benefit
- **TZD**: May increase risk of edema and weight gain; may reduce insulin resistance
- **SGLT2 Inhibitors**: Lower risk of hypoglycemia compared with other agents and less weight gain
- **DPP4 Inhibitors**: Modest A1C lowering; may be weight neutral
- **GLP-1 Agonist**: Can reduce A1c and body weight; longer acting have more effect than shorter acting; low risk of hypoglycemia
Diabetes Algorithms

https://www.ihs.gov/diabetes/clinician-resources/dm-treatment-algorithms/
Trends in Diabetes Management:

• Individualize treatment targets and care plans based on the patient’s needs and choices.

• Target treatments that may also enhance health beyond blood glucose lowering.

• Improve the delivery of medications to increase medication acceptance and adherence.
Conclusion

https://www.ihs.gov/MedicalPrograms/Diabetes/RESOURCES/Catalog/index.cfm?module=productDetails&productID=126

Three audio CD set of the book written by Barbara Hora (Paiute/Cree), recorded by the author, complete with audio effects and flute music played by Bob Hora, the author's husband. Barbara talks about her emotional journey with diabetes, and how she battled with denial and depression before learning how to take care of herself and live a joyful life. A valuable inspirational tool for those newly diagnosed with diabetes, those in denial or depressed because of diabetes, and health care providers wanting to better understand the emotional impact of a diabetes diagnosis.
Thank you!

Chris.Lamer@ihs.gov
Regular Insulin U500

<table>
<thead>
<tr>
<th>Units</th>
<th>U-100</th>
<th>U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 units</td>
<td>0.5mL</td>
<td>0.1 mL</td>
</tr>
<tr>
<td>100 units</td>
<td>1 mL</td>
<td>0.2 mL</td>
</tr>
<tr>
<td>200 units</td>
<td>2 mL</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>400 units</td>
<td>4 mL</td>
<td>0.8 mL</td>
</tr>
</tbody>
</table>