Learning Objectives

- Describe the general treatment approaches for glycemic control (hyperglycemia) in people with type 2 diabetes.
- Review the different types of medications people with type 2 diabetes can use for glycemic control.
- Describe the mechanism of action and unique characteristics of the various classes of type 2 diabetes medications.
- Discuss warnings, precautions for use, and side effect profiles of these medications. Describe general dosing principles for the oral and non-insulin injectable medications.
- Review how to tailor a person’s medication regimen based on patient-specific factors.

Medication Treatment Options To 2000

- Insulin (human and analogs)
- Sulfonylureas (1950's)
- Biguanides (metformin 12/94)
- Alpha-glucosidase inhibitors (Acarbose 9/95)
- Meglitinides or “Glinides” (Repaglinide 12/97; Nateglinide 12/00)
- Thiazolidinediones (Rosiglitazone 5/99; Pioglitazone 7/99)
Medication Treatment Options Since 2005

- Amylin (pramlintide)
- Glucagon-like peptide receptors agonists (GLP-1 RAs)
- Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)
- Bile acid sequestrants (colesevelam)
- Dopamine agonist (bromocriptine)
- Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)
- Combinations of medications
Medication Considerations

- Existing conditions
  - Atherosclerotic cardiovascular disease/ASCVD (heart disease, peripheral arterial disease, cerebrovascular disease)
  - Heart failure
  - Chronic kidney disease
- What is the A1C goal? How much expected ↓ A1C?
- Mechanism of action (how the medication works)
- Risk of low blood glucose (hypoglycemia)
- Side effect profile (e.g., potential for weight gain/loss)
- Conditions that may preclude use (warning vs. precaution for use) such as liver or kidney disease
- Cost

Why Metformin is 1st Line?

- Shown to have long-term impact on diabetes complications
- Decreases sugar release from the liver (hepatic glucose output)
- Reduce A1C 1-2%
- Advantages: no weight gain; no low blood sugar when used alone; inexpensive

Metformin, cont’d

- Dosing
  - Take with meals and/or at bedtime
    - Taking with food may reduce stomach upset & diarrhea
  - Dose is increased slowly generally to target of 1500 mg daily (therapeutic max is 2000 mg)
  - Side effects: diarrhea, nausea, cramping, metallic taste, lactic acidosis (rare), vit B₁₂ deficiency
  - Extended-release formulation available

Metformin, cont’d

- Avoid use in:
  - Severe kidney disease (glomerular filtration rate <30 ml/min)
  - Active liver disease
  - Heart failure, unstable
  - Other serious medical problems (such as severe lung disease, blood infection, conditions of acidosis)
  - Excessive alcohol use or alcoholism
Sulfonylureas (glyburide, glipizide, glimepiride)

- Available for use since the late 1950's
- Stimulate the pancreas to release insulin
- Dosing
  - Taken once or twice daily
  - Start with low dose and increase as required for glucose control
- Side effects: hypoglycemia, weight gain
- Certain SFUs used in elderly or if have kidney disease to lower risk of hypoglycemia: glipizide

Meglininides (repaglinide, nateglinide)

- Stimulate the pancreas to release insulin
- Fast-acting and help control BG at mealtime
- Taken right before eating a meal (within 30 minutes)
- Effect doesn't last as long as SFUs
- Effect on FBG and A1C similar to SFUs (nateglinide less)
- Option in severe kidney disease or erratic eating habits

Actions of GLP-1 Hormone: Incretins

- GLP-1: Secreted upon the ingestion of food
- Stomach: Slows gastric emptying
- Liver: Glucagon reduces hepatic glucose output
- Beta cells: Enhances glucose-dependent insulin secretion
- Alpha cells: Post-meal glucagon secretion
- Beta cells preservation

GLP-1 RAs

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (Byetta)</th>
<th>Liraglutide* (Victoza)</th>
<th>Lixisenatide (Adlyxin)</th>
<th>Exenatide XR (Bydureon BCise)</th>
<th>Dulaglutide (Trulicity)</th>
<th>Semiglutide (Ozempic)</th>
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<tr>
<td>Admin</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once weekly</td>
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- Analogs of human GLP-1. Resistant to DPP-4 breakdown.
- Preferential use in ASCVD

*FDA indication: “to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease”
GLP-1 RAs, cont’d

- Reduce A1C ~1-1.2%
- Advantages: weight loss, no hypoglycemia (unless with SFU or insulin)
- SEs: nausea/vomiting/diarrhea (↓ over time; dose slowly increased); injection site reaction
- Avoid in:
  - Severe kidney problems (GFR <30 ml/min)
  - Do not use with severe GI disease (e.g., gastroparesis)
- Do not use if personal or family history of MTC (medullary thyroid cancer) or multiple endocrine neoplasia syndrome type 2 (MEN 2)

DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (Januvia)</th>
<th>Saxagliptin (Onglyza)</th>
<th>Linagliptin (Tradjenta)</th>
<th>Alogliptin (Nesina)</th>
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<td>FDA Approved</td>
<td>2006</td>
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- Inhibit DPP-4 and slow breakdown of the body’s incretins (GIP, GLP-1). Primary actions:
  - Increase insulin release (glucose-dependent)
  - Reduce post-meal levels of glucagon, which then reduces hepatic glucose output
  - Vary with respect to caution in kidney problems and drug-drug interaction potential
  - Reduce A1C 0.4-0.8%
  - Advantages: oral; weight neutral; little nausea or hypoglycemia
  - SEs: nausea; join pain

Incretin Therapy and Pancreatitis

- Low risk of pancreatitis
  - Difficult to determine due to:
    - Extremely low event rate
    - Type 2 DM associated with 3-fold increased risk
- Do not use if history of pancreatitis; stones in gallbladder, alcoholism, or significantly elevated blood triglycerides
- What to look out for: abdominal pain (persistent, severe, radiating to back, N/V, anorexia) to contact your provider

SGLT-2 Inhibitors

- Inhibit sodium glucose cotransporter-2 in proximal tubules of the kidneys, where responsible for reabsorption of ~90% of glucose filtered through nephron
- Reduce A1C 0.8-1%
- Common side effects: genital yeast infections and UTIs (bladder infections) due to increased glucose in urine
- Increased chance for dehydration, lower blood pressure, dizziness in 1st few months (diuretic effect)
- Risk of bone fractures
- Can promote weight loss
- Preferential use in heart failure, kidney disease and ASCVD
SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (Invokana)</th>
<th>Dapagliflozin (Farxiga)</th>
<th>Empagliflozin (Jardiance)</th>
<th>Ertugliflozin (Steglatro)</th>
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1FDA indication: “to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease”

2FDA indication “to reduce the risk of major cardiovascular events such as heart attack, stroke, or death in adults with type 2 diabetes who have known heart disease”

Some are being considered for type 1 diabetes.

Thiazolidinediones (TZDs)

- Pioglitazone (Actos), rosiglitazone (Avandia)
- Improve insulin sensitivity (decrease insulin resistance)
  - enhance glucose uptake by muscle and fat tissue
  - decreases hepatic glucose output
- Slow onset to effect: take 4-6 weeks to have an effect on BG (up to 3 to 4 months)
- Can work well in overweight patients
- Dosing: Taken once or twice daily
- Common side effects: fluid retention, weight gain
- Avoid use in heart failure, osteoporosis, bladder cancer (pioglitazone)

Advancing to Combination Therapy:
Combine Agents with Different Actions

General Medication Tips

- Keep an accurate list of all medicines you currently take and carry it with you. Include nonprescription medicines, herbs, vitamins, and dietary supplements.
- Bring and share your medicine list with ALL your health care providers. Bring all your medicine bottles to your visits.
- Try to use only one pharmacy system so the pharmacist has a record of all your medicines (to reduce risk of duplicating medicines and harmful drug interactions).
General Medication Tips, cont’d

- Learn about your medicines
  - Know the purpose of each medicine
  - Read the label carefully
  - Know how to take the medicine and the best time to take it
  - Be familiar with possible side effects
  - Know how to store your medicine
  - Know what to do if you miss a dose

Taking Medications Consistently

- Take your medicines as instructed. If you are taking a medicine differently, inform your health care provider.
- Devise a system that works for you (such as a pillbox)

Questions

Thank you!

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