LEARNING OBJECTIVES

At the end of this presentation, participants should be able to:
1. Identify medications used in the treatment of diabetes and classify them by mechanism of action
2. Identify basic therapeutic effects and common adverse effects of medications used to treat diabetes
3. Differentiate between injectable medications for diabetes, including long-acting insulins, rapid-acting insulins, and GLP-1 receptor agonists
4. Identify which diabetes medications are most likely to cause hypoglycemia and explain why these medications should be used cautiously in elderly patients.

PHYSIOLOGY & PATHOPHYSIOLOGY: A BRIEF REVIEW
**TYPES OF DIABETES**

**TYPE 1**
- Autoimmune
- Body is unable to produce insulin, complete insulin deficiency
- More common in younger, thinner, and Caucasian patients
- Formerly known as juvenile diabetes

**TYPE 2**
- Metabolic syndrome
- Insulin resistance initially causes a relative insulin deficiency, which eventually can progress to complete insulin deficiency
- More common in adult, overweight, and African American and Hispanic patients

**THE OMINOUS OCTET**

- **HYPERGLYCEMIA**
  - Decreased Insulin Secretion
  - Increased Glucose Production
  - Increased Glucose Transport
  - Decreased Glucose Uptake

**SYMPTOMS**
- Polydipsia
- Polyuria
- Polyphagia
- Dizziness
- Nausea/vomiting
- Lethargy
- Blurry vision
- Urinary tract infections
- Fungal or genital infections
COMPLICATIONS OF DIABETES

- Microvascular
  - Nephropathy
  - Neuropathy
  - Retinopathy
- Macrovascular
  - Myocardial infarction
  - Stroke

DIAGNOSIS

Pre-Diabetes
- Hemoglobin A1c 5.7-6.4%
- Fasting plasma glucose 100-125mg/dL
- 2-hour plasma glucose 140-199 mg/dL during an oral glucose tolerance test

Diabetes
- Hemoglobin A1c ≥ 6.5%
- Fasting plasma glucose ≥126 mg/dL
- 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test
- Random plasma glucose ≥200 mg/dL with symptoms

TREATMENT GOALS

- HbA1c
  - ≤ 7% American Diabetes Association
  - ≤ 6.5% American Association of Clinical Endocrinologists
- Fasting plasma glucose ≤100 mg/dL
- 2-hour post-prandial plasma glucose <180 mg/dL
OVERVIEW OF STANDARDS OF MEDICAL CARE IN DIABETES (ADA GUIDELINES) 2020

TREATMENT OPTIONS

**Type 1**
- Insulin
- Multiple daily injections basal and prandial
- Continuous subcutaneous insulin infusion (pump)
- Pramlintide

**Type 2**
- Biguanides
- Sulfonylureas
- Meglitinides
- DPP-4 Inhibitors
- SGLT2 Inhibitors
- TZDs
- Alpha-Glucosidase Inhibitors
- Pramlintide
- GLP-1 Receptor Agonists
- Insulin

Glucose-lowering medication in type 2 diabetes: overall approach.
MEDICATIONS USED IN THE TREATMENT OF DIABETES

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ORAL MEDICATIONS FOR TYPE 2 DIABETES

15

Citation: Pancreatic Hormones and Antidiabetic Drugs, Jobst EE, Panus PC, Kruidering-Hall M. Pharmacology for the Physical Therapist, 2e; 2020. Available at: https://accessphysiotherapy.mhmedical.com/content.aspx?bookid=2753&sectionid=232009036 Accessed: June 18, 2020

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**BIGUANIDES (METFORMIN)**

- **MOA:** reduce hepatic gluconeogenesis, reduce intestinal absorption of glucose, and enhance insulin sensitivity
- **Route of administration:** oral once daily (ER) or twice daily
- **Adverse effects:** nausea/diarrhea (>20%), lactic acidosis, vitamin B12 deficiency
- **Place in therapy:** 1st line, preferred initial agent for all patients with T2DM without contraindications

---

**Medications in class**

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Metformin (Glucophage)</th>
<th>Metformin ER (Glucophage XR, Fortamet, Glumetza)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

---

**SECRETAGOGUES**

- **MOA:** stimulate pancreatic beta cells to increase endogenous insulin secretion
- **Route of administration:** oral 1-3 times daily
- **Advise:** effective hypoglycemia, weight gain
- **Place in therapy:** add-on to metformin
SULFONYLUREAS

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Glipizide (Glucotrol)</th>
<th>Glipizide XL (Gluconor XL)</th>
<th>Glyburide (Diabeta, Micronase)</th>
<th>Glimepiride (Amaryl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Inexpensive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MEGLITINIDES

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Nateglinide (Starlix)</th>
<th>Repaglinide (Prandin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Gain</td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

- MOA: Prolong the activity of endogenous incretins, GLP-1 and GIP
- Route of administration: oral once daily
- Adverse effects: headache, nasopharyngitis, may increase risk of pancreatitis
- Place in therapy: add-on to metformin

Accessed: June 18, 2020
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Linagliptin (Tradjenta)</th>
<th>Saxagliptin (Onglyza)</th>
<th>Sitagliptin (Januvia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Neutral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Not as monotherapy, increased with risk with insulin or secretagogue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

- MOA: increase urinary excretion of glucose
- Route of administration: oral once daily
- Adverse effects: dehydration, increased risk of urinary & fungal genitourinary infections, increased risk of foot and leg amputation (canagliflozin)
- Place in therapy: add-on to metformin, preferred for patients with renal or cardiovascular disease

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Canagliflozin (Invokana)</th>
<th>Dapagliflozin (Farxiga)</th>
<th>Empagliflozin (Jardiance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Intermediate</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Not as monotherapy, increased with risk with insulin or secretagogue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The image contains a table and a diagram illustrating the mechanisms of action for these inhibitors. The text is a summarization of the key points covered in the image.
THIAZOLIDINEDIONES (TZDs)

- MOA: decrease insulin resistance in muscles and adipose tissue
- Route of administration: oral once daily
- Adverse effects: edema (avoid in heart failure), hepatotoxicity (avoid in liver disease), increased risk of fractures
- Place in therapy: add-on to metformin

Medications in class

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Effect on Weight</th>
<th>Risk of Hypoglycemia</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (Actos)</td>
<td>High</td>
<td>Gain</td>
<td>No</td>
<td>Inexpensive</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>High</td>
<td>Gain</td>
<td>No</td>
<td>Inexpensive</td>
</tr>
</tbody>
</table>

ALPHA-GLUCOSIDASE INHIBITORS

- MOA: delay the breakdown and absorption of complex carbohydrates
- Route of administration: oral 3 times daily
- Adverse effects: abdominal pain, flatulence and diarrhea
- Place in therapy: rarely used
**ALPHA-GLUCOSIDASE INHIBITORS**

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Acarbose (Precose)</th>
<th>Miglitol (Glyset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>None - but change treatment</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

**INJECTABLE MEDICATIONS FOR DIABETES**

**INSULIN**
INSULIN INJECTION TECHNIQUE

- Recommended subcutaneous sites: abdomen, thigh, buttock, upper arm
  - Abdomen preferred – fastest absorption
- Rotate sites of injection to avoid lipohypertrophy
  - Do not need to rotate different sites of body from day to day
  - Only preferred site: into quadrants, use one quadrant per week, and rotate clockwise
  - Within quadrant, space at least 1 cm (width of a finger) from previous injection
- Insert needle perpendicular to skin (90 degree angle)
- Skin pinching should be used for children, adolescents, and frail or thin adults
- When using insulin pens, count to 10 after fully depressing button before withdrawing needle from skin

CHOOSING THE RIGHT SYRINGE

<table>
<thead>
<tr>
<th>Syringe Volume</th>
<th>Maximum # units per syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3ml</td>
<td>10</td>
</tr>
<tr>
<td>0.5ml</td>
<td>16</td>
</tr>
<tr>
<td>1ml</td>
<td>70</td>
</tr>
</tbody>
</table>

Showing prominent bulge on either side of the lower abdomen (side view)
CHOOSING THE RIGHT NEEDLE

- Gauge: larger number = thinner needle
- Length: larger number = longer needle
- Recommended lengths:
  - Pen needles: 4mm
  - Syringe needles: ~6mm
- Pen needles screw onto the end of the insulin pen like a bottle cap.

BASAL INSULINS

- Neutral Protamine Hagedorn (NPH) insulin
  - Mechanism of action: suppress hepatic gluconeogenesis while fasting
  - Route of administration: subcutaneous twice daily
  - Onset: ~2 hours
  - Duration: 10-20 hours

NEUTRAL PROTAMINE HAGEDORN (NPH) INSULIN

- Medications in class: Human Insulin isophane (Humulin N, Novolin N)
- Efficacy: High
- Effect on weight: Gain
- Risk of hypoglycemia: Yes
- Cost: Inexpensive
LONG-ACTING INSULIN ANALOGS

- Mechanism of action: suppress hepatic gluconeogenesis while fasting
- Route of administration: subcutaneous once or twice daily
- Onset: 1-4 hours
- Duration: 24 hours

**Medications in class**

- Insulin glargine (Lantus, Basaglar, Semglee)
- Insulin detemir (Levemir)

<table>
<thead>
<tr>
<th>Effect</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on weight</td>
<td>Gain</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

ULTRA LONG ACTING/CONCENTRATED INSULIN ANALOGS

- Mechanism of action: suppress hepatic gluconeogenesis while fasting
- Route of administration: subcutaneous
- Onset: Tojeo 6 hours, Tresiba 1 hour
- Duration: Tojeo >24 hours, Tresiba 42 hours

**Medications in class**

- Insulin degludec U-100 and U-200 (Tresiba)
- Insulin glargine U-300 (Tojeo)

<table>
<thead>
<tr>
<th>Effect</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on weight</td>
<td>Gain</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
</tr>
</tbody>
</table>
TOUJEO AND TRESIBA PEN DEVICES

TOUJEO VS. LANTUS

This study describes the time course effect following product administration. Here AUC0-2h shows no apparent difference of the area under “logarithmic” vs. “linear”.

Source: https://www.toujeopro.com/toujeo-vs-lantus-efficacy-safety

PRANDIAL INSULINS
REGULAR INSULIN

- Mechanism of action: reduce post-prandial hyperglycemia
- Route of administration: subcutaneous 1-3 times daily
- Onset: 30-60 minutes
- Duration: 5-8 hours

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Lispro human regular (Humalog R, Novolin R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>Inexpensive</td>
</tr>
</tbody>
</table>

RAPID-ACTING INSULIN ANALOGS

- Mechanism of action: reduce post-prandial hyperglycemia
- Route of administration: subcutaneous 1-3 times daily
- Onset: 5-15 minutes
- Duration: 3-5 hours

<table>
<thead>
<tr>
<th>Medications in class</th>
<th>Insulin aspart (Novolog, Fiasp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro (Humalog, Admelog, Lyumjev)</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>High</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
</tr>
</tbody>
</table>
INHALED INSULIN

- Mechanism of action: reduce post-prandial hyperglycemia
- Route of administration: inhalation 1-3 times daily
- Onset: 1-2 hours
- Duration: 1-3 hours
- Adverse effects: cough, hypoglycemia

PRE-MIXED INSULIN

- Medications in class: Insulin human (Afrezza)
- Efficacy: High
- Effect on weight: Gain
- Risk of hypoglycemia: No
- Cost: Expensive

Medications in class: Insulin isophane/insulin human (Humulin 70/30, Novolin 70/30)
- Efficacy: High
- Effect on weight: Gain
- Risk of hypoglycemia: Yes
- Cost: Inexpensive (NPH/regular), expensive (analogs)

U-500

- Medications in class: Concentrated human regular insulin
- Efficacy: High
- Effect on weight: Gain
- Risk of hypoglycemia: No
- Cost: Expensive

Medications in class: Concentrated human regular insulin
- Efficacy: High
- Effect on weight: Gain
- Risk of hypoglycemia: No
- Cost: Expensive
**AMYLIN ANALOG (PRAMLINTIDE)**

- **MOA:** Decrease glucagon secretion, delay gastric emptying, promote satiety
- **Route of administration:** Subcutaneous 3 times daily
- **Adverse effects:** Nausea, vomiting, loss of appetite
- **Place in therapy:** Rarely used, but approved in both Type 1 and Type 2

<table>
<thead>
<tr>
<th>Effect on Class</th>
<th>Pramlintide (Symlin)</th>
<th>Effect on Weight</th>
<th>Effect on hypoglycemia</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Low</td>
<td>Loss</td>
<td>Not as monotherapy, increases risk of insulin induced hypoglycemia</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

**GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR AGONISTS**

- **MOA:** Increase insulin secretion, decrease glucagon secretion, delay gastric emptying, promote satiety
- **Route of administration:** SC once daily/weekly, oral once daily (semaglutide)
- **Adverse effects:** Nausea, vomiting, may increase risk of pancreatitis
- **Place in therapy:** Add-on to metformin; preferred injectable agent
GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR AGONISTS

**Medications in class**
- Dulaglutide (Trulicity)
- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin)
- Semaglutide (Ozempic, Rybelsus)

**Efficacy**
High

**Effect on weight**
Lose

**Risk of hypoglycemia**
Rare as monotherapy, increased with risk in combination with insulin or sulfonylurea

**Cost**
Expensive

GLP-1 RECEPTOR AGONIST INJECTION DEVICES

- Victoza
- Ozempic
- Trulicity

MOA: promote storage of glucose in muscle and adipose tissue, inhibit hepatic glucose production, increase insulin secretion, decrease glucagon secretion, delay gastric emptying, promote satiety

Route of administration: SC once daily

Adverse effects: hypoglycemia, nausea, vomiting, may increase risk of pancreatitis

Place in therapy offers more convenient dosing for patients who need dual injectable treatment

REFERENCES:
- Pancr eatic Hormones and Antidiabetic Drugs, Jobst EE, Panus PC, Kruidt M. Pharmacology for the Physical Therapist, 2e; 2020. Available at: https://accessphysioteraphy.mhmedical.com/content.aspx?bookid=2753&sectionid=232009036

Accessed: June 18, 2020
**Fixed Ratio Combinations of Insulin + GLP1-RA**

<table>
<thead>
<tr>
<th>Medication in class</th>
<th>Insulin glargine/lixisenatide (Soliqua 100/33)</th>
<th>Insulin degludec/liraglutide (Xultophy 100/3.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Expensive</td>
<td></td>
</tr>
</tbody>
</table>

Source: [https://www.soliqua100-33.com/getting-started/soliqua100-33-solostar-pen](https://www.soliqua100-33.com/getting-started/soliqua100-33-solostar-pen)


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**Special Populations**

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**Adjusting Medications for Exercise**

- Exercise is critical for T1DM and T2DM.
- Children/adults: 40-60 min moderate-intense aerobic activity per day plus 2-3 days of strength work.
- Adults: 150 mins moderate-vigorous aerobic activity per week spread over at least 2-3 days plus 2-3 days of strengthening.
- Test blood glucose prior to exercise.
- Pre-exercise glucose <70 to prevent hypoglycemia.
- Do not exercise if pre-exercise glucose >300mg/dl, as usual limits.
- Consider how comorbidities, including peripheral and autonomic neuropathies, may impact ability to participate in an exercise program.
GERIATRICS

- Of adults over 65
  - ~1/4 have diabetes
  - ~1/2 have prediabetes
- Considerations
  - Cognitive function
  - Dexterity
  - Vision
  - Polypharmacy
  - Regimen complexity vs. self-management ability
  - Life expectancy vs. timeline of development of complications
  - Relaxed A1c goals: <7.5% without comorbidities, <8-8.5% with comorbidities
- Use meds with low risk of hypoglycemia

PEDIATRICS

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin pump or basal-bolus insulin</td>
<td></td>
</tr>
<tr>
<td>A1c goal &lt;7% for most, but may be less stringent for those who cannot articulate symptoms of hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Need to engage family and caregivers in administration of meds and treatment of hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>As per: 97%</td>
<td></td>
</tr>
<tr>
<td>Metformin is still first line</td>
<td></td>
</tr>
<tr>
<td>Basal insulin can be added on</td>
<td></td>
</tr>
<tr>
<td>Prandial insulin if necessary</td>
<td></td>
</tr>
<tr>
<td>Can consider glucagon in children &lt;18 years</td>
<td></td>
</tr>
</tbody>
</table>

HYPOGLYCEMIA
### FACTORS INCREASING RISK

**Patient Factors**
- Older age
- Renal dysfunction
- Hepatic dysfunction
- Alcohol use
- Inconsistent eating habits

**Medication Factors**
- Insulin – especially NPH, regular, and rapid-acting analogs
- Secretagogues – glyburide especially
- Higher doses
- Concomitant use of multiple glucose-lowering medications

### SYMPTOMS

- BG <70mg/dL
- Hunger
- Nausea
- Palpitations
- Sweating
- Shaking
- Irritability
- Tachycardia

If untreated, can progress to: blurred vision, loss of consciousness, convulsions, coma, death

### HYPOGLYCEMIA UNAWARENESS

- Some patients who have frequent episodes of hypoglycemia stop exhibiting these early warning signs.
  - This puts them at risk for development of severe symptoms, including erratic behavior, confusion, weakness, seizures, and coma.
- Should have a medical ID bracelet
- Should carry glucose gel/tablet
- Family/friends should be trained on use of glucagon
TREATMENT

- Treat when BG < 70mg/dL
- Glucose
  - 15-20g glucose
  - Check blood glucose in 15 mins
  - If still <70mg/dL, repeat
- Glucagon
  - Prescribe for anyone who has had severe hypoglycemia <54mg/dL.

QUESTIONS?

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