financial disclosure
• “i have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation”

pharmacist learning objectives
• identify signs and symptoms of hypothyroidism and hyperthyroidism
• indicate the onset of action for different insulin products

Technician Learning Objectives
• Identify the correct brand and generic names for thyroid products
• Explain appropriate storage requirements for insulin products

thyroid disorders
hypothyroidism/ hyperthyroidism
Hypothalamic-Pituitary-Thyroid Axis

- TRH = thyrotropin-releasing hormone
- TSH = thyroid-stimulating hormone
- T3 = triiodothyronine
- T4 = thyroxine

Thyroid Hormones

- Normal TSH: 0.45 - 4.12 mIU/L
- Growth & development
  - Role in brain development
  - Thermogenesis
- Cardiovascular effects
  - Hypothyroid: bradycardia
  - Hyperthyroid: tachycardia
- Metabolic effects
  - Hypothyroid: hypercholesterolemia, decreased insulin requirements

Thyroid Disorders

- Primary: thyroid gland dysfunction (Elevated TSH, Low free T4)
  - Hashimoto's disease: autoimmune (most common)
  - Antithyroid peroxidase antibodies and antithyroglobulin antibodies
  - Radiation, surgical treatment for hyperthyroidism, thyroid cancer
  - Medications: amiodarone, lithium, sulfonylureas, iodides

Signs/ Symptoms of Hypothyroidism

- Cold sensitivity
- Dry skin
- Fatigue
- Bradycardia
- Constipation
- Goiter
- Weight gain
- End-stage myxedema coma (hypothermia, decreased consciousness, respiratory depression)

Signs/ Symptoms of Hyperthyroidism

- Heat intolerance
- Increased sweating
- Agitation, nervousness, anxiety
- Tachycardia
- Diaphoresis
- Insomnia
- Tremor
- Thyroid storm
Types of Hypothyroidism

- **Secondary**: hypothalamic/pituitary dysfunction
  - Hypothalamic disease (Low TRH)
  - Pituitary disease (Low to normal TSH, Low T4)

Levothyroxine (Levo-T®, Levothroid®, Levoxyl®, Synthroid®, Unithroid®)

- **Mechanism of Action**: Synthetic form of thyroxine (T4) which can be converted to the active metabolite, T3
- **Dosage Forms**:
  - Oral capsule: 13mcg, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 137mcg, 150mcg
  - Reconstituted intravenous solution: 100mcg, 200mcg, 500mcg
  - Tablets: 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 137mcg, 150mcg, 200mcg, 300mcg
- Taken 60 minutes prior to breakfast or bedtime (3 hours or more after the evening meal)

Liothyronine (Cytomel®)

- **Mechanism of Action**: synthetic salt of T3
- **Dosage Forms**:
  - Intravenous solution: 10 mcg/ml
  - Oral tablet: 5mcg, 25mcg, 50mcg
- Short term data: 3 times daily dosing may be beneficial to weight and lipids
- Longer-term controlled trial needed with long-acting formulation
- Euthyroid patients with depression
- More robust trials needed
- Euthyroid patients with obesity
- Lack of data showing efficacy

Liotrix (Thyrolar®)

- **Mechanism of action**: uniform mixture of synthetic T4 and T3 in a 4:1 ratio
- **Dosage Forms**:
  - Levothyroxine 12.5 mcg/ liothyronine 3.1 mcg
  - Levothyroxine 25 mcg/ liothyronine 6.25 mcg
  - Levothyroxine 50 mcg/ liothyronine 12.5 mcg
  - Levothyroxine 100 mcg/ liothyronine 25 mcg
  - Levothyroxine 150 mcg/ liothyronine 37.5 mcg
- No strong evidence of superiority over levothyroxine alone
- Combination therapy showed conflicting results comparing therapy to levothyroxine alone
Thyroid Extract (Armour Thyroid®, Nature Throid®, NP Thyroid®)

- **Mechanism of Action:** animal-derived T3 and T4
  - Porcine or bovine origin
  - May contain variable amounts of T3 and T4
- **Dosed in grains:**
  - 1 grain=60-65 mg, ½ grain = 30-32.5 mg, ¼ grain= 15-16.25 mg
- **Oral Tablets:**
  - Armour Thyroid®: 15mg, 30mg, 60mg, 90mg, 120mg, 180mg, 240mg, 300mg
  - Nature Throid®: 16.25mg, 32.5mg, 48.75mg, 65mg, 81.25mg, 97.5mg, 113.75mg, 144.25mg, 162.5mg, 182.5mg, 213mg, 260mg, 325mg
  - NP Thyroid®/generic: 15mg, 30mg, 60mg, 90mg, 120mg

Types of Hyperthyroidism

- **Low TSH, elevated T4 and T3**
- **Subclinical:** low TSH, normal T4
- **Excess thyroid hormone production and release**
- **Inflammation and release of hormone by the gland**
- **Endogenous**
  - Grave’s disease (most common): Thyrotropin receptor antibodies (TRAb)
- **Exogenous**
  - Amiodarone: 3 mg iodine/100 mg of amiodarone
- **Thyroid Storm**
  - Untreated hyperthyroidism: exaggerated symptoms - fever, tachycardia, coma, death

**Thionamides**

<table>
<thead>
<tr>
<th>Methimazole (Tapazole®)</th>
<th>Propylthiouracil (PTU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action:</strong> Inhibits synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland; PTU also inhibits conversion of T4 to T3</td>
<td></td>
</tr>
<tr>
<td>5 mg, 10 mg tablet</td>
<td>50 mg tablet</td>
</tr>
<tr>
<td>- Drug of choice</td>
<td>- Used during first trimester of pregnancy, thyroid storm, and if methimazole not tolerated</td>
</tr>
<tr>
<td>- Used during 2nd and 3rd trimester</td>
<td>- Hazardous drug</td>
</tr>
</tbody>
</table>

**Iodides**

<table>
<thead>
<tr>
<th>Potassium iodide and iodine solution (Lugol’s Solution®)</th>
<th>Saturated solution of potassium iodide (ThyroShield®, SSKI®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action:</strong> Temporarily inhibits secretion of thyroid hormones; T4 and T3 levels will be reduced for several weeks but not maintained</td>
<td></td>
</tr>
<tr>
<td>Oral solution used in preparation for thyroidectomy for 10 days prior to surgery. Helps to decrease the vascularity, size, and fragility of thyroid gland.</td>
<td></td>
</tr>
<tr>
<td>Dosage Forms: Oral Solution</td>
<td>Dosage Forms: Oral Solution, Oral Tablet</td>
</tr>
</tbody>
</table>
Radioactive Iodine (RAI)

- Colorless, odorless liquid
- Rapidly absorbed, concentrated by the thyroid, and incorporated into storage follicles
- Destruction is noted by epithelial swelling and necrosis, follicular disruption, edema, and leukocyte infiltration
- Easy administration, efficacious, low expense, and absence of pain
- Contraindicated in pregnancy

Diabetes

- Type 1: 5-10% of diabetics, autoimmune destruction of the B-cells in the pancreas
- Type 2: 90-95% of diabetics, insulin resistance or B-cell destruction

Hyperglycemia

- Polyuria - excessive urination
- Polydipsia - excessive, abnormal thirst
- Polyphagia - excessive, uncontrolled eating

Hypoglycemia

- Shakiness
- Sweating
- Hunger
- Nausea
- Blurred vision/ Headache
- Weakness/ Fatigue
- Confusion
Complications

Microvascular
• Retinopathy
• Neuropathy
• Nephropathy

Macrovascular
• Coronary artery disease
• Diabetic cardiomyopathy
• Peripheral vascular disease
• Stroke

Biguanide:
Metformin (Glucophage®, Riomet®)
Metformin XR (Glucophage XR®, Fortamet®, Glumetza®)

• Mechanism of Action: Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity
• Dosage Forms:
  - Oral Solution (Riomet®): 500mg/5ml
  - Oral Tablet: 500mg, 850mg, 1000mg
  - Extended Release Oral Tablet: 500mg, 750mg, 1000mg
• Adverse effects: diarrhea, nausea
  • Taken with food to decrease stomach upset

Second Generation Sulfonylureas:
Glyburide, Glyburide-micronized (Micronase®, Glynase®), Glipizide (Glucotrol®), Glipizide XL (Glucotrol®XL), Glimepiride (Amaryl®)

• Mechanism of Action: Stimulates insulin secretion from the pancreas by binding to the sulfonylurea receptor and inhibiting ATP K+ channels of the beta cells
  • Only effective in those with endogenous insulin production
  • Taken 30 minutes prior to meals

Dosage Forms

• Glyburide Oral Tablets:
  - Glynase®: 1.5mg, 3mg, 6mg
  - Generic: 1.25mg, 1.5mg, 2.5mg, 3mg, 5mg, 6mg
• Glipizide Oral Tablets:
  - Glucotrol®/generic: 5mg, 10mg
  - Glipizide Extended Release Tablets:
    - Glucotrol®XL/generic: 2.5mg, 5mg, 10mg
  - Glimepiride Oral tablets:
    - Amaryl®/generic: 1mg, 2mg, 4mg
Meglitinides: Repaglinide (Prandin®), Nateglinide (Starlix®)
- **Mechanism of Action**: Stimulates insulin secretion from the pancreas by binding to the sulfonylurea receptor and inhibiting ATP K+ channels of the beta cells
- *Only effective in those with endogenous insulin production*
- *Taken 30 minutes prior to meals*

  - **Oral Tablets**:
    - Prandin®: 1mg, 2mg
    - Generic: 0.5mg, 1mg, 2mg
    - Starlix®/generic: 60mg, 120mg

Thiazolidinediones (TZDs): Pioglitazone (Actos®), Rosiglitazone (Avandia®)
- **Mechanism of Action**: Improves target cell response to insulin by activating peroxisome proliferator activated receptors (PPAR), without increasing pancreatic insulin secretion
- *May take 8-12 weeks to see full effect of the medication*

  - **Oral Tablets**:
    - Actos®/generic: 15mg, 30mg, 45mg
    - Avandia®: 2mg, 4mg

α-Glucosidase Inhibitors: Acarbose (Precose®), Miglitol (Glyset®)
- **Mechanism of Action**: Inhibits the enzyme alpha-glucosidase in the brush border of the small intestine, resulting in delayed carbohydrate digestion and glucose absorption
- *Taken with the first bite of each large meal*

  - **Oral Tablets**:
    - Precose®/generic: 25mg, 50mg, 100mg
    - Glyset®/generic: 25mg, 50mg, 100mg

Glucagon-like peptide-1 (GLP-1) Receptor Agonists
- **Mechanism of Action**: Stimulates the production of insulin in response to high blood glucose levels, inhibits the release of glucagon after meals, slows the rate of gastric emptying, and increases satiety

  - Exenatide (Byetta®): Twice daily (short acting)
  - Liraglutide (Victoza®): Once daily (long acting)
  - Exenatide LAR (Bydureon®), Albiglutide (Tanzeum®), Dulaglutide (Trulicity®): Once weekly (long acting)
GLP-1 Receptor Agonists

Exenatide (Byetta®)
Exenatide LAR (Bydureon®)

Storage/ Stability:
- Byetta® (5mcg, 10mcg pens)
  • Prior to initial use store under refrigeration (2°C-8°C), may store at room temperature up to 30 days
- Bydureon® (2mg pen)
  • Store under refrigeration, if necessary may store at room temperature for up to 30 days

Byetta®

Exenatide (Byetta®)
Exenatide LAR (Bydureon®)


GLP-1 Receptor Agonists

Tanzeum® (30mg, 50mg pen-injector)

• Store unused pens under refrigeration; may be stored at room temperature for ≤4 weeks prior to reconstitution. Use within 8 hours of reconstitution.

Glucagon-like peptide-1 receptor agonists: Liraglutide (Victoza®)

Storage/Stability:
- Prior to initial use store under refrigeration; after initial use, may be stored under refrigeration or room temperature. Discard after 30 days
- Pen-injector: 18mg/3ml

Pictures available from: http://www.drugsdb.com

Amylin agonists: Pramlintide (Symlin®)

Storage/ Stability:
- Mechanism of Action: Synthetic form of human amylin; Reduction in postprandial glucose by prolongation of gastric emptying, reduction of postprandial glucagon secretion, and reduction of caloric intake through appetite suppression
- Pen-injector: SymlinPen®60 (1500 mcg/1.5ml), SymlinPen®120 (2700 mcg/2.7ml)
- Store under refrigeration; after initial use may be kept refrigerated or at room temperature. Discard after 30 days.
Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors): Sitagliptin (Januvia®), Saxagliptan (Onglyza®), Linagliptin (Tradjenta®), Alogliptan (Nesina®)

- **Mechanism of Action**: Inhibits dipeptidyl peptidase 4, the enzyme responsible for degrading incretin hormones. An increase of GLP-1 leads to insulin release and reduction in glucagon secretion.

- **Oral Tablets**:
  - Januvia®: 25mg, 50mg, 100mg
  - Onglyza®: 2.5mg, 5mg
  - Tradjenta®: 5mg
  - Nesina®/generic: 6.25mg, 12.5mg, 25mg

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT-2 Inhibitors): Dapagliflozin (Farxiga®), Canagliflozin (Invokana®), Empagliflozin (Jardiance®)

- **Mechanism of Action**: Inhibition of SGLT-2 in the proximal renal tubules, reduces glucose reabsorption and increases glucose excretion in the urine.

- **Oral Tablets**:
  - Farxiga®: 5mg, 10mg
  - Invokana®: 100mg, 300mg
  - Jardiance®: 10mg, 25mg

Rapid Acting Insulin Products: onset 10-30 minutes

- **Insulin glulisine** (Apidra®)
  - **Storage/Stability**:
    - Unopened vials/prefilled pens: refrigeration (2°C-8°C) until expiration date or at room temperature for 28 days.
    - Opened vials: refrigeration/room temperature for 28 days.
    - Opened prefilled pens: room temperature and used within 28 days.
    - Continuous subcutaneous insulin infusion (CSII): replaced every 48 hours at room temperature.

- **Insulin lispro** (Humalog®)
  - **Storage/Stability**:
    - Unopened vials/prefilled pens: refrigeration (2°C-8°C) until expiration date or at room temperature <30°C for 28 days.
    - Opened vials: refrigeration/room temperature for 28 days.
    - Opened prefilled pens: room temperature for 28 days.
    - CSII: changed every 7 days.
    - Prefilled: stable in HS for 48 hours refrigerated, then an additional 48 hours at room temperature while in use.
Rapid Acting Insulin Products: onset 10-30 minutes

**Insulin aspart (Novolog®)**

**Storage/ Stability:**
- Unopened vials/prefilled pens: refrigeration (2-8°C) until expiration date or room temperature <30°C for 28 days
- Opened vials: refrigeration/room temperature for 28 days
- CSII: replaced every 6 days
- IV infusion: stable in NS for 24 hours at room temperature

Inhaled Insulin (Afrezza®)

**• Rapid Acting Insulin: onset ~12 minutes**
**• Contraindication: chronic lung disease such as asthma or COPD, due to risk of bronchospasm**
**• Spirometry (FEV1) test prior to initiation**

**Storage/ Stability:**
- Prior to Use (sealed): refrigerated (2-8°C), if not refrigerated must be used in 10 days
- In Use: room temperature (25°C), open strips must be used in 3 days

Short Acting Insulin: onset 30 minutes

**Regular insulin (Humulin R®, Novolin R®)**

**Storage/ Stability:**
- Humulin R®: unopened vials: refrigeration (2-8°C) until expiration date
- Opened vials: refrigeration/room temperature for up to 42 days
- Novolin R®: unopened vials: refrigeration until expiration date or at room temperature for up to 42 days
- Opened vials: room temperature for up to 42 days
- Unopened FlexPen: refrigeration until expiration date or at room temperature for up to 28 days
- Opened FlexPens: room temperature for up to 28 days

**Insulin Regular (Humulin R U-500® (concentrated), Humulin R U-500® KwikPen)**

**Storage/ Stability:**
- Unopened/ Open Vials: refrigerator (2-8°C) until expiration date or may be stored at room temperature <30°C for up to 40 days
- Unopened KwikPen: refrigerator until expiration date or room temperature for up to 28 days
- Open KwikPen: room temperature for up to 28 days
<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset Time</th>
<th>Storage/ Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate Acting</td>
<td>90 minutes</td>
<td>NPH (Humulin N®, Novolin N®)</td>
</tr>
<tr>
<td>Long Acting Insulin</td>
<td>3-4 hours</td>
<td>Insulin glargine (Lantus® or Toujeo®)</td>
</tr>
<tr>
<td>Long Acting Insulin</td>
<td>~1 hour</td>
<td>Insulin detemir (Levemir®)</td>
</tr>
<tr>
<td>Long Acting Insulin</td>
<td>~1 hour</td>
<td>Insulin degludec (Tresiba®)</td>
</tr>
</tbody>
</table>

**NPH (Humulin N®, Novolin N®)**
- **Storage/Stability:**
  - Unopened: Refrigeration (2°C-8°C) until expiration date.
  - Opened: Refrigeration/room temperature <30°C for 31 days.
  - Insulin KwikPen: Refrigeration until expiration date.
  - Opened KwikPen: Room temperature for up to 14 days.

**Insulin glargine (Lantus® or Toujeo®)**
- **Storage/Stability:**
  - Unopened vials/Prefilled pens: Refrigeration (2°C-8°C) until expiration date or at room temperature <30°C for 28 days.
  - Opened vials: Refrigeration for 28 days.
  - Opened Prefilled pens: Room temperature for up to 42 days.

**Insulin detemir (Levemir®)**
- **Storage/Stability:**
  - Unopened pens: Refrigeration (2°C-8°C) until expiration date or at room temperature <30°C for up to 56 days.
  - Opened pens: Refrigeration or at room temperature for up to 56 days.

**Insulin degludec (Tresiba®)**
Mixtures

- Insulin NPH and Regular Insulin 70/30 (Humulin 70/30®, Humulin 70/30® KwikPen, Novolin 70/30®)
- Insulin aspart protamine/insulin aspart 70/30 (Novolog Mix 70/30®, Novolog Mix 70/30® FlexPen)
- Insulin lispro protamine/insulin lispro (Humalog Mix 50/50®, Humalog Mix 50/50® KwikPen, Humalog Mix 75/25®, Humalog Mix 75/25® KwikPen)

Pharmacist Post-test Question

Which of the following is not a symptom of hypothyroidism?

a. Constipation
b. Insomnia
c. Dry Skin
d. Cold Sensitivity

Pharmacist Post-test Question

What is the onset of action of NPH (Humulin N®, Novolin N®)?

a. 10-30 minutes
b. 3-4 hours
c. 6 hours
d. 90 minutes
Pharmacist Post-test Question

What is the onset of action of NPH (Humulin N®, Novolin N®)?

a. 10-30 minutes
b. 3-4 hours
c. 6 hours
d. 90 minutes

Technician Post-test Question

Which of the following thyroid products is correctly matched with its Brand name?

a. Methimazole (ThyroShield®)
b. Liothyronine (Tirosint®)
c. Liotrix (Thyrolar®)
d. Thyroid Extract (Cytomel®)

Technician Post-test Question

How long can unopened insulin detemir (Levemir®) prefilled pens be stored at room temperature?

a. 28 days
b. 42 days
c. 56 days
d. 14 days
How long can unopened insulin detemir (Levemir®) prefilled pens be stored at room temperature?

- 28 days
- 42 days
- 56 days
- 14 days

References:
