New and Improved?
New Drug Update

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Disclosure

• Melinda C. Joyce declares that she is a member of the Advisory Board of Cumberland Pharmaceuticals and is on their Speaker’s Bureau.
• She will not be discussing any of their products in this presentation.

Objectives

• Discuss new medications that have been recently approved by the FDA, focusing on indications for use, potential adverse reactions, and contraindications
• Review safety concerns for existing medications and how these concerns may impact their use
• Evaluate the place in therapy of new medications compared to existing therapies.
NEW DRUG APPROVAL PROCESS

What is Happening in the Pharmacy World?

• Drug spending is continuing to increase
  – Price increases on branded drugs
  – New medications
  – Decreased impact from patent expirations
  – Huge increases in drug spending from specialty drugs
    • Hepatitis C medication spend increased 743% in 2014

• New drug development is skewed towards specialty drugs and orphan drugs
  – 50% of all new drugs approved during the past five years have been specialty drugs
  – More than half of the new drugs approved in 2015 would be considered specialty drugs

• Specialty drugs are those more likely to be initiated by a specialist and are usually more likely to be:
  – High cost
  – Used to treat complex, chronic conditions
  – Require
    • Special handling, distribution, and/or administration
    • Significant patient education and monitoring
  – Specialty drug spending expected to quadruple by 2020
FDA Drug Approvals - 2015

Classifications

- New Molecular Entities (NMEs) can be classified as:
  - First-In-Class
  - Noteworthy First-In-Class
  - Rare Disease Drugs (Orphan Drugs)
  - Fast Track
  - Breakthrough
  - Priority Review
  - Accelerated Approval

- Many agents will be designated in more than one category
First-In-Class

• 36% of those approved in 2015 were identified as First-In-Class
  – A new and unique mechanism of action for treating a medical condition
  – One indicator of the innovative nature of the drugs
• Noteworthy First-In-Class are those agents that are likely to quickly make a positive impact on care
  – Sugammadex – to reverse post-surgical neuromuscular blockade caused by certain kinds of anesthesia
  – Palbociclib – to treat advanced (metastatic) breast cancer
  – Idarucizumab – to reverse adverse anticoagulant effects caused by the blood thinner, dabigatran

Fast Track

• 31% of the NMEs approved in 2015 were designation as Fast track
  – Drugs with the potential to address unmet medical needs
• Fast Track speeds new drug development and review
  – Allows developers to use a “rolling review” process where the FDA can review portions of an application ahead of the submission of the full application
  – The 14 medications with this designation were for a variety of conditions from infection to heart failure to multiple agents for the treatment of cancer

Breakthrough

• 22% were designated as Breakthrough therapies
  – Preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy
  – A Breakthrough designation conveys all of the Fast Track features as well as more intensive FDA guidance on an efficient drug development program
• The ten Breakthrough drugs:
  – Alectinib –ALK-positive lung cancer
  – Lumacaftor/ivacaftor – cystic fibrosis
  – Daratumumab – multiple myeloma patients who have received at least one prior treatment
  – Idarucizumab – reverse the anticoagulant effects of dabigatran
  – Elotuzumab – multiple myeloma patients who have received one to
Notable Patent Expirations in 2015

- Albuterol/ ipratropium (Combivent)
- Aripiprazole (Abilify)
- Glatiramer (Copaxone)
- Imatinib (Gleevec)
- Insulin glargine (Lantus)
- Linezolid (Zyvox)
- Memantine (Namenda)
- Pegfilgrastim (Neulasta)
- Testosterone (AndroGel)

SPECIFIC MEDICATIONS

New Drugs

Cardiac Medications
  - Alirocumab
    - PCSK9 inhibitor for cholesterol
  - Cangrelor
    - P2Y12 Antiplatelet
  - Edgarsun
    - Factor Xa inhibitor – Atrial fibrillation or deep vein thrombosis (DVT)/ pulmonary embolism (PE) treatment
  - Enotocumab
    - PCSK9 inhibitor for cholesterol
  - Idarucumab
    - Monoclonal antibody fragment that binds to dabigatran for reversal
  - Ivabradine
    - Heart failure
  - Sacubitril/ Valsartan
    - Heart failure
New Drugs

Antimicrobial Agents

- Ceftazidime/avibactam
  - Complicated intra-abdominal and urinary tract infections
- Isavuconazonium
  - Azole antifungal for invasive aspergillosis and mucormycosis
- Ceftolozane/tazobactam
  - Complicated intra-abdominal and urinary tract infections

Psychotropic Medications

- Brexpiprazole
  - Atypical antipsychotic agent for depression and schizophrenia
- Cariprazine
  - Atypical antipsychotic agent for schizophrenia and bipolar disorder
- Suvorexant
  - Orexin receptor antagonist for insomnia

Miscellaneous

- Eluxadoline
  - Mu-opioid receptor agonist for irritable bowel disease with diarrhea (IBS-D)
- Filbanserin
  - Serotonin agonist/antagonist for premenopausal women with hypoactive sexual desire disorder
- Naloxegol
  - Opioid antagonist for opioid-induced constipation
Homozygous Familial Hypercholesterolemia (HoFH)

- Most severe form of familial hypercholesterolemia
- Caused by genetic defects inherited from both parents that affect the function of the low-density lipoprotein (LDL) receptor
  - Responsible for removing LDL cholesterol from the body
- Frequency is 1 in 1 million
- Characterized by extremely high levels of LDL
- Serum cholesterol ranges from 650 to 1000 mg/dL
- Patients with HoFH respond very poorly to currently available therapies
  - Apheresis is the current standard of care
    - Circulates a portion of the blood outside the body and passes it through a special adsorber column, which removes the LDL cholesterol and then returns the treated blood back to the body
    - Removes LDL and triglycerides, but only a small effect on HDL

Heterozygous Familial Hypercholesterolemia (HeFH)

- Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder that affects about 1 in 500 people
- HeFH is characterized by:
  - Cholesterol deposits affecting the corneas, eyelids, and extensor tendons
  - Elevated plasma concentrations of LDL cholesterol
  - Accelerated vascular disease, especially CAD
Proprotein Convertase Subtilisin/Kexin type 9 (PCSK) Enzymes

- **LDL-C Receptors**
  - Expressed on the surface of the liver
  - Function as the primary mechanism to reduce LDL-C from the bloodstream
- **Proprotein convertase subtilisin/kexin type 9 (PCSK9) enzymes**
  - Enzyme that is responsible for degrading the LDL-C receptors on the liver to remove LDL from the bloodstream
- By blocking PCSK9, a higher number of LDL receptors are available to clear LDL

Alirocumab (Praluent)

- **Indications:**
  - Subcutaneous agent as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease who require additional lowering of their LDL-cholesterol
  - First-in-class designation
- **Advantages:**
  - Extremely effective in lowering LDL-C
  - Has a unique mechanism of action
  - Less likely to cause adverse effects
  - Less likely to interact with other drugs
- **Disadvantages:**
  - Must be administered by subcutaneous injection

Alirocumab

- **Adverse Effects:**
  - Nasopharyngitis (11%); Injection site reactions (7%); Influenza (6%)
- **Availability:**
  - Single-dose, pre-filled syringes – 75 mg and 150 mg doses
  - The medication should be stored in the refrigerator and allowed to warm to room temperature for 30 to 40 minutes prior to administration
  - Should not be used if out of the refrigerator for more than 24 hours
Alirocumab

- **Dose:**
  - 75 mg once every 2 weeks by subcutaneous injection
  - Can take up to 20 seconds to administer entire (full) dose
  - If LDL-C control not adequate, then can increase to the maximum dose of 150 mg once every 2 weeks
  - If a dose is missed, the patient should administer the dose within 7 days from the missed dose and then resume the regular dosing schedule
  - If the missed dose is not administered within 7 days, the patient should wait until the next regularly scheduled dose

- **Monitoring:**
  - LDL-C should be determined within 4 to 8 weeks of initiating treatment or changing the dose

Evolocumab *(Repatha)*

- **Indications:**
  - Subcutaneous agent as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of their LDL-cholesterol
  - Also for the treatment of homozygous familial hypercholesterolemia
  - The second agent in the PCSK9 inhibitor group

- **Advantages:**
  - Labeled indications includes HoFH
  - Can be administered as once a month injections

- **Disadvantages:**
  - When the higher, once a month dosage is used, it does require multiple (3) injections

- **Adverse Effects:**
  - Nasopharyngitis (11%); Upper respiratory tract infections (9%); Influenza (8%); Back pain (6%); Injection site reactions (6%)

Evolocumab

- **Availability:**
  - Single-use prefilled auto-injectors and syringes containing 140 mg
  - For longer dating, should be stored in the refrigerator and allowed to warm for at least 30 minutes at room temperature
  - Product can be stored at room temperature, if stored in the original packaging and must be used within 30 days

- **Dose:**
  - 140 mg every 2 weeks or 420 mg monthly, administered by subcutaneous injection
  - Can take up to 15 seconds to administer entire dose.
  - If 420 mg is administered, the three injections must be given within a 30 minute timeframe
PCSK9 Summary Points

**Pro**
- Robust reductions in LDL-C have best potential to significantly lower cardiovascular events
- Every 2 to 4 week dosing that is well tolerated
- Preliminary outcome data has positive trends and early benefit, but complete data is not yet available
- Best option for those patients with HoFH or HeFH

**Con**
- Still need to determine the true impact on cardiovascular events
- Injectable agent requiring proper patient selection for self-administration
- High annual acquisition cost is problematic
  - Over $14,000 per year
- Cost effectiveness studies comparing various options are needed

Antiplatelet Therapy

- Platelet activation, which occurs in response to vessel injury, produces coronary occlusion either by formation of a platelet plug through release of vasoactive compounds from the platelet
- Antiplatelet drugs inhibit platelet aggregation → decreases production of coronary occlusions
  - Inhibits formation of cyclo-oxygenase
  - The P2Y12 receptor also plays a key role in platelet aggregation
- Current guidelines recommend aspirin plus an oral P2Y12 platelet inhibitor for all patients undergoing percutaneous coronary intervention (PCI)

Cangrelor (Kengreal)

- **Indications:**
  - Administered IV as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of peri-procedural myocardial infarction, repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor
  - Direct-acting P2Y12 platelet inhibitor that blocks adenosine diphosphate (ADP)–induced platelet activation and aggregation

- **Advantages:**
  - Could be beneficial in those patients that may need urgent surgery or if there is a concern about inadequate platelet inhibition at the time of the PCI
  - Is more effective than clopidogrel in reducing the occurrence of MI and ST and the need for repeat coronary revascularization, although it did not reduce the risk of death
Cangrelor

- **Disadvantages:**
  - More likely than clopidogrel to cause bleeding
  - Administered IV
  - Expensive
  - When cangrelor was administered concurrently with a loading dose of clopidogrel or prasugrel, cangrelor blocked the antiplatelet effect of the oral agents
    - Treatment with clopidogrel or prasugrel should only be started after discontinuation of the cangrelor infusion
  - Ticagrelor does not interact with cangrelor and can be given during or immediately after the cangrelor infusion

- **Adverse Effects:**
  - Bleeding (15.5% with serious, life-threatening bleed at 2.5%)

- **Availability:**
  - Single-use vials of 50 mg as a lyophilized powder that should be reconstituted with 5 ml of sterile water

- **Dose:**
  - 30 mcg/kg as an IV bolus (over less than 1 minute) followed immediately by a 4 mcg/kg/min IV infusion
    - IV bolus should be initiated and completely administered prior to PCI
    - Administer rapidly over less than 1 minute
    - Maintenance infusion should be continued for at least 2 hours or for the duration of the PCI, whichever is longer
    - An oral P2Y12 inhibitor should be administered immediately after discontinuation of cangrelor

Heart Failure

- The only cardiovascular disease that is increasing in prevalence
- Approximately 6 million people currently diagnosed with HF in the United States (1-2% of population)
- More Medicare dollars are spent on HF diagnosis and treatment than any other diagnosis
  - Reason behind the various CMS quality measures related to heart failure
- Most common hospital discharge diagnosis for people over age 65
- National average of 30 day readmissions is 25%
  - Costs of $37 billion/year
    - More costly than all forms of cancer combined
- Progression of HF is not smooth or predictable
  - 1 year mortality rate of 10-15%
  - 5 year mortality rate approaches 50%
- HF mortality has increased 35% over the last decade
Neprilysin

• Neprilysin is a natural endopeptidase that degrades select vasoactive peptides, such as natriuretic peptides, bradykinin, and others
• Inhibiting neprilysin increases BNP concentrations
  – Also increases bradykinin and substance P
    • Increase bradykinin levels may lead to an increase in angioedema
    – All vasodilatory substances
• By inhibiting neprilysin, these vasoactive peptides produce decreases in vasoconstriction and reductions in sodium retention and maladaptive remodeling

Sacubitril/ Valsartan (Entresto)

• Indications:
  – First-in-class medication
  – To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction
  – Sacubitril – neprilysin inhibitor
  – Valsartan – angiotensin II receptor blocker
• Advantages:
  – More effective based on comparison with enalapril
    • Study endpoint of cardiovascular death or hospitalization

Sacubitril/ Valsartan

• Disadvantages:
  – Has a greater risk of causing angioedema
    • Due to the degradation of bradykinin
    – Is more likely to cause hypotension
      • Especially in patients treated with high doses of diuretics
    – Expensive, especially as compared to traditional therapies, which are generic
    – Currently not part of heart failure guidelines
• Adverse Effects:
  – Hypotension (18%); Hyperkalemia (12%); Cough (9%); Dizziness (6%); Renal failure/acute renal damage (5%)
  – Contraindicated in patients with a history of angioedema related to a
Sacubitril/ Valsartan

- **Availability:**
  - 24 mg/26 mg; 49/51 mg, 97/103 mg tablets (sacubitril/valsartan)

- **Dose:**
  - Should not be administered within 36 hours of switching from or to an ACE-I
  - 49/51 mg (sacubitril/valsartan) twice daily and after at least 2 to 4 weeks, increase to the target dose of 97/103 mg twice daily
  - Reduced starting dose of 24/26 mg twice daily
    - *Moderate hepatic impairment

Ivabradine (Corlanor)

- **Indications:**
  - First-in-class, fast-track medication
  - To reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or lower, who are in sinus rhythm with resting heart rate of at least 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use
  - Causes a dose-dependent reduction in heart rate as a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker

Ivabradine

- **Advantages:**
  - Contributes to greater effectiveness in reducing the risk of hospitalization for worsening heart failure
  - Has a unique mechanism of action
  - Seems to be effective in stable heart failure patients with a heart rate \( \geq 70 \) bpm taking multiple therapies
  - May be useful for patients with a beta-blocker contraindication
Ivabradine

Disadvantages:
- Is not more effective in reducing risk of cardiovascular death
  - Advantage is in reducing hospitalisations
- Use is associated with a greater risk of bradycardia
- Is more likely to cause visual disturbances
- Several contraindications to use
- Expensive as most other agents are available generically
- May interact with more medications
  - Strong CYP3A4 inhibitors are contraindicated
    - Acute antifungal agents
    - Macrolides
    - HIV protease inhibitors
  - Moderate CYP3A4 inhibitors should be avoided
    - Diltiazem, verapamil, grapefruit juice
  - CYP3A4 inducers should be avoided
    - St. John’s Wort, rifampin, phenytoin
- Negative chronotropes
  - Digoxin, amiodarone

Adverse Effects:
- Bradycardia (10%); Hypertension (9%); Atrial fibrillation (8%);
  Luminous phenomena (3%)
  - Enhances brightness in the visual field brought on by sudden variations in light intensity
  - Kaleidoscopic effects - colored lights
  - Multiple images
  - Onset is generally within the first 2 months of treatment but may occur repeatedly

Contraindications:
- Pregnancy
- Acute decompensated heart failure
- BP < 90/50 mmHg
- Resting heart rate < 60 bpm
- Pacemaker dependence
- Severe hepatic impairment

Availability:
- 5 mg and 7.5 mg tablets

Dose:
- 5 mg twice daily with meals, adjust dose to a resting heart rate between 50 and 60 beats per minute
- Based on heart and patient tolerability, the dose can be titrated up in 2 to 4 weeks to the maximum dose of 7.5 mg twice daily
- A reduced starting dose of 2.5 mg twice daily if bradycardia could be problematic
Atrial Fibrillation (AF)

- Most common cardiac arrhythmia
- Frequently becomes chronic and associated with a small increase in the risk of death
- Depending on the presence of other risk factors, risk of stroke can be 7x greater in AF patients
- Non-valvular atrial fibrillation
  - Seen in 5% of persons over age 65
  - Seen in 10% of persons over age 75
- Frequently asymptomatic, but can cause dizziness, fainting, chest pain, and heart failure

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

- Very common finding
- Third most common preventable death in the hospitalized patient
- Centers for Medicare and Medicaid (CMS) specific quality measures related to the use of appropriate prophylaxis to prevent DVT and PE

Edoxaban (Savaysa)

- **Indications:**
  - To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - For the treatment of deep vein thrombosis (DVT) an pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant
  - Direct factor Xa inhibitor, similar to rivaroxaban and apixaban
- **Advantages:**
  - Administered once per day
  - Less likely to interact with other medications
Edoxaban

- **Adverse Events:**
  - Clinically-relevant non-major bleeding (9%); rash (4%); abnormal liver function tests (5%)
  - Contraindicated in patients with pathological bleeding or strong risk factors for bleeding
- **Availability:**
  - 15mg, 30mg, and 60 mg tablets
- **Dose:**
  - Non-valvular atrial fibrillation
    - 60 mg once daily
    - Reduce dose to 30 mg once a day in patients with a creatinine clearance of 15 to 50 ml/min

Idarucizumab (Praxbind)

- **Indications:**
  - Considered a first-in-class, breakthrough medication
  - Administered IV in patients treated with dabigatran when reversal of the anticoagulant effects is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding
  - Humanized monoclonal antibody fragment that binds to dabigatran with a higher affinity than the binding affinity of dabigatran to thrombin
  - Clinical studies showed that the anticoagulant activity of dabigatran was fully reversed in 89% of study patients within 4 hours of receiving the medication
- **Advantages:**
  - First agent that reverses the action of dabigatran and neutralizes its anticoagulant activity

Idarucizumab

- **Adverse Effects:**
  - Hypokalemia (7%); delirium (7%); constipation (7%); pyrexia 96%; pneumonia (6%)
- **Availability:**
  - Single-use vials containing 2.5 g of idarucizumab in 50 ml
    - Should be stored in the refrigerator
- **Dose:**
  - 5 grams (two vials) administered IV as two consecutive infusions or bolus injections by injecting both vials consecutively one after another via syringe
  - A repeat dose may be considered in urgent situations
  - Due to the risk of thromboembolic event when the anticoagulant
Edoxaban

- Disadvantages:
  - No specific antidote
  - May be less effective than other agents
  - In clinical studies, was determined to be noninferior to warfarin in reducing the risk of stroke and systemic embolism
  - Noninferior to warfarin with respect to recurrent venous thrombosis
  - Apixaban was found to be superior to warfarin in preventing stroke
  - Should not be used in patients with a creatinine clearance greater than 95 ml/min
  - Found to not be as effective due to high renal clearance
  - Drug exposure > 70% higher in patients with a creatinine clearance < 50

TARGET SPECIFIC ORAL ANTICOAGULANTS (TSOACS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Dosage</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Apixaban</td>
<td>Thromboembolism prevention in patients with A-Rs</td>
<td>5 mg BID; 2.5 mg BID for 15 days (hip); 2.5 mg BID for 12 days (knee)</td>
<td>Dose adjust for renal impairment; No antidote!</td>
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<tr>
<td></td>
<td>VTE prophylaxis – hip and knee replacement</td>
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<td></td>
<td>Treatment of DVT/PE</td>
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<tr>
<td>Dabigatran</td>
<td>Thromboembolism prevention in patients with A-Rs</td>
<td>150 mg BID; 150 mg BID following 5 to 10 days treatment with a parenteral anticoagulant</td>
<td>Dose does need to be adjusted in patients with renal impairment</td>
</tr>
<tr>
<td></td>
<td>Treatment of DVT/PE</td>
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<tr>
<td></td>
<td>VTE prophylaxis – hip and knee replacement – not in the US</td>
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*620 mg once daily immediately after surgery - this strength not available in US.
## Anticoagulant Comparison

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<tr>
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<th>Dosage</th>
<th>Considerations</th>
</tr>
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<tbody>
<tr>
<td>Edoxaban</td>
<td>• Thromboembolism prevention in patients with A-fib&lt;br&gt;• Treatment of DVT/PE</td>
<td>• 60 mg once daily in patients with CrCl 50 to 95 ml/min&lt;br&gt;• Treatment dose is the same following 5 to 10 days of parenteral anticoagulation&lt;br&gt;• Should not be used in patients with normal renal function&lt;br&gt;• VTE prophylaxis, continue for at least 3 months&lt;br&gt;• No antidote!</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>• Thromboembolism prevention in patients with A-fib&lt;br&gt;• Treatment of DVT/PE&lt;br&gt;• VTE prophylaxis – hip and knee replacement</td>
<td>• 20 mg once daily&lt;br&gt;• 10 mg once daily for 35 days (hip)&lt;br&gt;• 10 mg once daily for 12 days (knee)&lt;br&gt;• Not recommended for patients with CrCl &lt; 30 ml/min&lt;br&gt;• Take with evening meal for best absorption&lt;br&gt;• No antidote!</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>• Prevention/treatment of DVT or PE&lt;br&gt;• Thromboembolism prevention in patients with A-fib&lt;br&gt;• Secondary prevention post-MI</td>
<td>• Dose based on INR – goal of 2 to 3&lt;br&gt;• 14 days for lone&lt;br&gt;• Many potential drug and food interactions&lt;br&gt;• Lab monitoring necessary&lt;br&gt;• Antidote is available</td>
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## Target Specific Oral Anticoagulants

- **Advantages**
  - Direct anticoagulants
  - Predictable pharmacokinetics
  - Most agents will not need significant bridging
  - No monitoring needed
  - Few diet/ drug interactions

- **Disadvantages**
  - Renal/ hepatic excretion
  - No antidote except for dabigatran
  - Unable to monitor directly
  - Limited experience
  - Lack of long-term safety data
  - Cost
To Use Or Not Use?

- **Non-Valvular Atrial Fibrillation**
  - Those already on warfarin, with good INR control, may not need to switch
  - New agents may have better safety profile (less intracranial hemorrhage)
  - Consider patient compliance and cost of drug and testing
  - Drug interactions with the new agents and drugs that may be used for atrial fibrillation must be considered

To Use Or Not Use?

- **Prevention of VTE**
  - Dabigatran and edoxaban are not approved in the US for this indication
  - Rivaroxaban and apixaban are good alternatives to low molecular weight heparin/warfarin in this setting
  - Look closely at the trial comparator dose of enoxaparin before choosing agent
  - Approval currently only for total hip replacement and total knee replacement

To Use Or Not Use?

- **Treatment of VTE**
  - Special attention should be given to dosing regimens when prescribing/counseling
  - Patients may no longer require hospitalization but should have careful follow-up
  - Rivaroxaban and apixaban are also indicated for extended treatment of VTE after at least 6 months of treatment but more bleeding than placebo
More Experience Needed

- Malignancy
- Pregnancy
- Mechanical heart valves
- Thrombophilia
- Extremes of body weight
- Those with more than "low" bleeding risk
- Real world compliance (not on studies)

ANTIMICROBIAL AGENTS

Carbapenem-Resistant *Enterobacteriaceae* (CRE)

- CRE are bacteria that are resistant to most antibiotics
- *Enterobacteriaceae* is a family of bacteria that live in the environment, especially soil and water
- These bacteria can cause pneumonia, urinary tract infections, and bloodstream infections
- Resistance is seen with
  - *Klebsiella pneumoniae* (most common)
  - Also seen in *E. coli*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Serratia*, *Pseudomonas* and *Proteus* spp.
- Most often seen in hospitalized, critically ill patients
- About 4% of US hospitals had at least one patient with a CRE infection in 2012 and about 18% of long-term acute care hospitals
- There are very few antibiotics that are available to treat infections
Ceftazidime/Avibactam (Avycaz)

• **Indications:**
  – Fast-track, priority review medication
  – Administered by IV infusion for the treatment of adults with complicated intra-abdominal infections, caused by susceptible organisms and for complicated urinary tract infections, caused by susceptible organisms
    • E. coli
    • Klebsiella sp.
    • Enterobacter
    • Pseudomonas spp.
  – Its use should be reserved for patients who have limited or no alternative treatment options
    • May be more specific for its activity against Gram-negative bacteria that produce

Ceftazidime/Avibactam (Avycaz)

• **Advantages:**
  – Has activity against carbapenem-resistant Enterobacteriaceae

• **Disadvantages:**
  – Has limited activity against gram-positive bacteria and anaerobic bacteria
    • Should be used in combination with metronidazole for intra-abdominal infections
    • Does not cover Acinetobacter
  – Is infused over at least 2 hours
  – Contraindicated in patients allergic to cephalosporins
  – Watch for cross-reactivity with those patients allergic to penicillins
  – Decreased efficacy in patients with a baseline creatinine clearance of

Ceftazidime/Avibactam

• **Adverse Effects:**
  – Vomiting (14%); Nausea (10%); Constipation (10%); Anxiety (10%); Abdominal pain (8%); Dizziness (6%)
  – Central nervous system reactions may occur, especially in patients with impaired renal function

• **Availability:**
  – Single-use vials of 2 grams ceftazidime/0.5 grams avibactam and should be reconstituted with 10 ml of sterile water, 0.9% sodium chloride or 5% dextrose
  – The reconstituted solution should be further diluted to a total volume between 50 ml and 250 ml
**Ceftazidime/Avibactam**

- **Dose:**
  - 2 grams/0.5 grams (ceftazidime/avibactam) every 8 hours by IV infusion over 2 hours for 5 to 14 days for intra-abdominal infections and for 7 to 14 days for complicated UTIs
  - The dose should be reduced to 1 gram/0.25 g every 8 hours for patients with an estimated creatinine clearance of 31 – 50 ml/min

**Ceftolozane/Tazobactam (Zerbaxa)**

- **Indications:**
  - Fast-track, priority review medication
  - Administered by IV infusion for the treatment of adults with complicated intra-abdominal infections, caused by susceptible organisms and for complicated urinary tract infections, caused by susceptible organisms
    - *E. coli*
    - *Klebsiella* sp.
    - *Enterobacter*
    - *Pseudomonas* spp.
    - *Bacteroides* fragilis
    - *Streptococcus* spp. (not *Strep pneumoniae*)
  - Its use should be reserved for patients who have limited or no alternative treatment options

- **Indications (continued):**
  - Ceftolozane – fifth generation cephalosporin
    - Specially designed to treat infections caused by resistant Gram-negative organisms
  - Tazobactam – beta-lactamase inhibitor

- **Advantages:**
  - Has activity against carbapenem-resistant Enterobacteriaceae
  - Can be used in renally impaired patients with dosage adjustment

- **Disadvantages:**
  - Has limited activity against gram-positive bacteria and anaerobic bacteria
    - Should be used in combination with metronidazole for intra-abdominal infections
    - Does not cover *Acinetobacter*
Ceftolozane/Tazobactam

• Adverse Effects:
  – Nausea (8%); Headache (6%); Diarrhea (6%); Pyrexia (6%);
    Constipation (4%); Insomnia (4%); Anxiety (2%)
• Availability:
  – Single-use vials of:
    • 1.5 g: (1 gram /0.5 grams) (ceftolozane/ tazobactam)
    • 750 mg: (500 mg/250 mg)
    • 375 mg: (250 mg/125 mg)
    • 150 mg: (100 mg/50 mg)
  – Vials should be stored in the refrigerator
  – Should be reconstituted with 0.9% sodium chloride or 5% dextrose

Ceftolozane/Tazobactam

• Dose:
  – 1.5 g (1 g ceftolozane/ 0.5 g tazobactam) every 8 hours by IV
    fusion over 1 hour for 7 days for both complicated intra-
    abdominal and urinary tract infections
  – For renal impairment
    • CrCl 30–50 ml/min: 750 mg IV q8h
    • CrCl 15–29 ml/min: 375 mg IV q8h
    • Dialysis: Single loading dose of 750 mg followed by a 150 mg
      maintenance dose q8h for the remainder of the treatment period
      – Administer the dose at the earliest possible time following completion of dialysis

Isavuconazonium (Cresemba)

• Indications:
  – Priority review medication
  – Administered orally or IV for the treatment of invasive aspergillosis or
    invasive mucormycosis
  – Isavuconazonium is a prodrug that is converted to isavuconazole
  – Isavuconazole is an azole antifungal agent with a spectrum similar to
    voriconazole and posaconazole
• Advantages:
  – Labeled indications include invasive mucormycosis
  – Is less likely to cause QT-interval prolongation, visual disturbances,
    hallucinations, and photosensitivity reactions
  – Is more suitable for use in patients with impaired renal function
Isavuconazonium

• **Disadvantages:**
  – Labeled indications for more limited
  – Voriconazole has more labeled indications
  – Efficacy and safety in patients less than 18 years of age have not been established
  – Insoluble particulates may form in IV solutions
  – Many potential drug-drug interactions
    • Strong CYP3A4 Inhibitors can increase the action of the drug
      – Macrolides
      – HIV Protease Inhibitors
    • Strong CYP3A4 inducers should not be used (contraindicated) because

Isavuconazonium

• **Adverse Effects:**
  – Infusion-related reactions may occur and include hypotension and dyspnea
    • Treatment should be discontinued
  – May cause serious hepatic adverse effects and liver function tests should be monitored at the start of therapy and throughout treatment
  – Should be avoided in pregnancy
  – Nausea (26%); Vomiting (25%); Diarrhea (22%); Headache (17%); Hypokalemia (14%); Constipation (13%); Dyspnea (12%); Cough (12%); Peripheral edema (11%); Back pain (10%); Elevated liver function tests (16%)

Isavuconazonium

• **Availability:**
  – 186 mg capsules
    • Should be kept in the original container to protect from moisture
  – Single-dose vials – 372 mg powder for reconstitution and then further diluted
    • Resultant solution should be filtered by an in-line filter to remove any particulates
    • Vials should be stored in the refrigerator
  – Loading dose – 372 mg every 8 hours for 6 doses
  – Maintenance dose – 372 mg once a day starting 12 to 24 hours

**Dose:**

4/27/2016
PSYCHOTROPIC MEDICATIONS

Etiology of Psychotropic Illnesses

- Etiology of many psychiatric disorders is not well understood
- Thought to be due to abnormal functioning of neurotransmitters located in the CNS
  - Serotonin
  - Norepinephrine
  - Dopamine
  - Histamine receptors
  - Muscarinic receptors
- Cannot do a blood test to determine which neurotransmitter is most affected
- Treatment is often “trial and error”
  - Clinical effect often takes several weeks to see
  - Adverse effects may develop much quicker, which may impact compliance
  - May need to use a combination of therapies, especially in more refractory cases

Schizophrenia

- Complex mental illness resulting from dysfunction of dopamine and serotonin
- Positive symptoms
  - Delusions, auditory hallucinations, cognitive impairment, and psychosis
- Negative symptoms
  - Flat or blunted affect and emotion, poverty of speech (alogia); inability to experience pleasure (anhedonia), lack of desire to form relationships (associality), and lack of motivation (avolition)
- Symptom onset usually occurs in late adolescence or early adulthood
Major Depressive Disorder (MDD)

- Severe and debilitating mental illness
- The highest rates of MDD are experienced by adults aged 18 to 29 years of age
- Antidepressants are the first-line agents in the treatment of the disorder, but not all patients will respond to traditional therapies
- In refractory cases, one option is augment antidepressant therapy with a second-generation or atypical antipsychotic medication
  - Generally, the dose of the atypical antipsychotic medication is lower

Bipolar Disorder I

- Severe and debilitating conditions with many symptoms including mood changes (swings) that may range from lows of depression to the highs of mania
- Manic or hypomanic phase
  - Euphoria, poor judgment, rapid speech, racing thoughts, aggressive behaviors, delusions, and psychosis
- Depressive phase
  - Sadness, hopelessness, suicidal thoughts, fatigue, appetite changes, and loss of interest
- Bipolar I Disorder
  - Prolonged (at least 7 days) of severe mania or
  - Mixed episodes (depressed but energized)
  - Most patients with bipolar I disorder will also have periods of depression that will last at least 2 weeks
- Second-generation or atypical antipsychotic medications are often prescribed in conjunction with a mood stabilizer in the treatment of bipolar disorder

Brexpiprazole (Rexulti)

- Indications:
  - Treatment of patients with schizophrenia and as adjunctive treatment of patients with major depressive disorder
  - Atypical antipsychotic agent with partial agonist activity at serotonin and dopamine receptors
    - Structurally similar to aripiprazole
- Advantages:
  - May be less likely to cause extrapyramidal reactions
  - Once daily dosing
Brexpiprazole

**Disadvantages:**
- Labeled indications are more limited
  - No labeled indications for bipolar disorder
- Has not been evaluated in pediatric patients
- Dosage forms are more limited as the medication is an oral form only
- May be more likely to cause weight gain
- Expensive
- Potential drug-drug interactions
  - Strong CYP3A4 inhibitors will increase the action of the medication
    - Macrolides
    - Azole antifungals
  - Strong CYP3A4 inducers will decrease the action of the medication
    - Rifampin

**Adverse Effects:**
- Black boxed warning about the increased risk of death in patients with dementia
- Increased risk of suicidal thoughts and behaviors in patients age 24 and younger
- Potential for metabolic changes that could lead to hyperglycemia or dyslipidemia
- Akathisia (9%); Weight gain (7%)

**Availability:**
- 0.25mg, 0.5mg, 1mg, 2mg, 3mg, and 4mg tablets

**Dose:**
- Schizophrenia
  - 1 mg once a daily for days 1 to 4 with a target dose of 2 to 4 mg once daily
  - Max: 4 mg per day
- Major Depressive Disorder (as adjunctive treatment)
  - 0.5 mg
  - 1 mg once daily with a target dose of 2 mg once daily
  - Max: 3 mg per day

Cariprazine (Vraylar)

**Indications:**
- Atypical antipsychotic for the treatment of schizophrenia
- Treatment of manic or mixed episodes of bipolar I disorder
- Potent partial agonist at dopamine (D3) receptors along with partial antagonist activity of serotonin receptors

**Advantages:**
- Has a three- to ten-fold higher affinity for the human D3 receptor
- No dosage adjustments are required for patients with impaired renal or hepatic function

**Disadvantages:**
- Unknown if there is proven benefit due to the higher affinity of the D3 receptor
Cariprazine

• Adverse Effects:
  – Black-boxed warning about the increased risk of death in patients with dementia
  – Increased risk of suicidal thoughts and behaviors in patients age 24 and younger
  – Potential for metabolic changes that could lead to hyperglycemia or dyslipidemia
  – Akathisia (20%); Tremors (20%); Headache (14%); Insomnia (13%); Nausea and vomiting (10%); Hypertension (5%)

• Availability:
  – 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules

Cariprazine

• Dose:
  – Schizophrenia:
    • 1.5 mg daily, adjusting dose based on response and tolerability to 1.5 to 4.5 mg daily
    • Maximum dose: 6 mg daily
  – Bipolar I Disorder:
    • 1.5 mg daily, adjusting dose based on response and tolerability to 3 to 6 mg daily
    • Maximum dose: 6 mg daily
  – May need to decrease the starting dose in half for patients that are taking a strong CYP3A4 inhibitor
    • Macrolides
    • Azole antifungals

Epidemiology of Sleep Disorders

• Insomnia is a common disorder that can present in a variety of ways
  • Sleep Latency – difficulty in falling asleep
  • Sleep Maintenance – difficulty staying asleep
  • Sleep Quality – Not feeling rested after a night’s sleep
  • It is estimated that about 1/3 of Americans experience insomnia nightly
  • First-line treatments for insomnia tend to focus on non-pharmacologic interventions with drug therapy added to those approaches if necessary
  • Insomnia may also present with other co-morbid conditions, such as pain, depression or anxiety
  • The underlying issue should be addressed
Suvorexant (Belsomra)

**Indication:**
- Treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- New class of sedative/hypnotic classified as an orexin (hypocretin) receptor antagonist
- Orexin neuropeptide signaling system in a central promoter of wakefulness
  - Narcolepsy/cataplexy caused by a deficiency in orexin (no wake drive)
  - Insomnia may be caused by an abundance of orexin (signals wakefulness)
- Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to the orexin-1 receptor and orexin-2 receptor

*Adverse effects!*
- Is more likely to cause cataplexy-like symptoms and is contraindicated in patients with narcolepsy
- Must watch carefully for daytime drowsiness and/or impaired

**Advantages:**
- Has a unique mechanism of action
- May be less likely to cause withdrawal effects when treatment is discontinued
- Has not been associated with rebound insomnia

**Disadvantages:**
- Adverse effects!
Suvorexant

- **Adverse Effects:**
  - Drowsiness/ somnolence (7%)
  - Sleep paralysis
  - Hypnagogic and hypnopompic hallucinations
  - Vivid, highly disturbing hallucinations
  - Cataplexy-like symptoms
    - Cataplexy – loss of muscle tone often after an emotional response (falling to floor after laughing)
  - Alcohol can intensify the adverse effects of the medication

- **Availability:**
  - 5 mg, 10 mg, 15 mg, and 20 mg tablets

- **Dose:**
  - 10 mg once a night within 30 minutes of going to bed, with at least 7 hours remaining before planned time of awakening
  - Maximum dose is 20 mg once a night
    - Patients should be warned to not drive the next day until the effects from the higher dose are seen
  - 5 mg once a night should be used in patients taking other CYP3A4 inhibitors and in obese females due to a prolonged action of the drug

MISCELLANEOUS NEW AGENTS
Irritable Bowel Syndrome – Diarrhea (IBS-D)

• Functional bowel disorder that is characterized by chronic abdominal pain and frequent diarrhea
  – Loose or watery stools at least 25% of the time
• There are agents to help treat IBS-D but may either be not that effective or have more significant adverse effects

Eluxadoline (Viberzi)

• Indications:
  – Treatment of adult patients with irritable bowel syndrome with diarrhea (IBS-D)
  – The medication has mixed opioid receptor activity
    • It acts as an agonist at the mu and kappa receptors and as an antagonist of delta receptors
• Advantages:
  – Has a unique mechanism of action
  – Labelled indication is not restrictive
    • Some of the agents have labeled indications for women only
  – Less risk of serious gastrointestinal adverse effects

Eluxadoline

• Disadvantages:
  – It is contraindicated in patients with known or suspected biliary duct obstruction
    • Has a greater risk of sphincter of Oddi spasm and pancreatitis
    • Patients without a gallbladder should be monitored for new or worsening abdominal pain
  – Contraindicated in patients with severe hepatic disease
  – Contraindicated in patients with a history of alcoholism or in patients that regularly drink more than three alcoholic beverages per day
  – Is a controlled substance
Eluxadoline

- **Availability:**
  - 75 mg and 100 mg tablets

- **Dose:**
  - 100 mg twice daily with food
  - Dose should be reduced to 75 mg twice daily in patients with no gallbladder
  - The medication should be discontinued in patients who develop severe constipation for more than 4 days

Opioid-Induced Constipation (OIC)

- 40-80% of patients receiving opioids for chronic non-cancer pain will develop OIC
- Can lead to serious effects other than patient discomfort and may be a reason that patients stop taking their medication
- Important to start lifestyle/behavioral modifications when the opioid is initiated
  - Increase in fiber
  - Increase in fluids
  - Physical activity
  - Regular routine for bowel movement
- Next step is generally OTC laxatives, such as lactulose or a stool softener
- Want to try to avoid the stimulant laxatives, such as bisacodyl for occasional use only
- Prescription laxatives should be reserved for more significant cases when the stool softener or lactulose is not effective

Naloxegol (Movantik)

- **Indications:**
  - Treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain
  - Naloxegol is a pegylated derivative of naloxone that is a peripherally-acting mu-opioid receptor antagonist that is effective following oral administration
  - The second oral agent and the third agent to be approved for OIC

- **Advantages:**
  - Is administered orally
  - Is administered once a day
Naloxegol

- **Disadvantages:**
  - Contraindicated in patients with known or suspected gastrointestinal obstruction and at risk for recurrent obstruction
  - Should only be used in pregnancy if the benefit of the medication outweighs the risks to the unborn child
  - Could induce opioid withdrawal
  - More likely to interact with other drugs
    - CYP3A4 inhibitors are contraindicated
      - Macrolides
      - Azole antifungals
    - CYP3A4 inducers should be avoided when possible
      - St. John's Wort
      - Carbamazepine
  - Labeled indications are more limited

- **Adverse Effects:**
  - Abdominal pain (21%); Diarrhea (9%); Nausea (8%); Flatulence (6%); Vomiting (5%)

- **Availability:**
  - 12.5 and 25 mg tablets

- **Dose:**
  - 25 mg once a day in the morning at least 1 hour prior to the first meal of the day or 2 hours after the meal
  - Dose should be reduced to 12.5 mg once daily in patients with moderate, severe, or end-stage renal disease
  - The patient’s maintenance laxative therapy should be discontinued prior to the initiation of naloxegol

- **If inadequate response after 3 days, the maintenance laxatives can be restarted**

Hypoactive Sexual Desire Disorder (HSDD)

- It is estimated that approximately 10% of premenopausal women experience hypoactive sexual desire disorder
- HSDD is designated as “acquired” when it develops in a patient who previously had no problems with sexual desire
- HSDD is designated as “generalized” when it occurs regardless of the type of sexual activity, the situation, or the sexual partner
- Characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical or psychiatric condition, problems with the
Flibanserin (Addyi)

• Indications:
  – First-in-kind treatment
  – Treatment of pre-menopausal women with generalized hypoactive sexual desire disorder (HSDD)
  – It is NOT indicated for treatment of post-menopausal women or men or to enhance sexual performance
  – Works as a partial agonist/antagonist for serotonin, but the exact mechanism of action is not fully understood

• Advantages:
  – First drug to be approved for HSDD
  – In clinical trials, approximately 10% of patients reported

Flibanserin

• Disadvantages:
  – Risk of severe hypotension and syncope
  – Significant CNS depressant effects
    • Should avoid activity requiring full alertness until at least 6 hours after each dose
  – Use of alcohol is contraindicated
  – Is only available through a restricted distribution program

• Adverse Effects:
  – Dizziness (11%); Somnolence (11%); Nausea (10%); Fatigue (9%); Insomnia (5%)

• Availability:
  – 100 mg tablets

• Dose:
  – 100 mg once a day at bedtime
  – If no improvement after 8 weeks, treatment should be discontinued

DIABETES
DPP-4 Inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
- Oral agents that increase the action of "incretins" – naturally occurring hormones that ↑ insulin secretion in the presence of elevated glucose concentrations by inhibiting the enzyme (DPP-4) that is responsible for inactivation of incretins
  - DPP-4 = Dipeptidyl peptidase-4
- Beneficial agents as there is a neutral effect on weight
- Beneficial effects on blood pressure and lipid levels have not been shown consistently but more intense trials for cardiovascular benefit are on-going
- Some agents may be associated with heart failure risk
  - More likely to see an increase in hospitalizations

DPP-4 Inhibitors Safety Warnings

- Pancreatitis
  - Rare, but necessary to monitor
  - Any new or unexplained abdominal pain or radiating back pain
  - Generally resolves once the medication is discontinued
  - Usually starts within the first 30 days of therapy
  - Patients often have other risk factors for the development of pancreatitis
- Joint Pain
  - New warning and precaution added to labels of all DPP-4 Inhibitors
  - Can be severe and potentially debilitating
  - 10 cases that were reported to the FDA required hospitalization for disabling joint pain
  - Symptoms appeared within 1 day to years after starting the DPP-4

SGLT2 Inhibitors “Flozins”

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Blocks glucose reabsorption in kidney; increases glycosuria
  - Sodium Glucose Co-Transporter 2 (SGLT 2) is expressed in the proximal renal tubules and is responsible for the reabsorption of the majority of glucose filtered by the kidney
- Lowers A1c 0.5 -1%
- Not likely to be a first-line agent but should be an adjunct agent to metformin after trying sulfonylureas or gliptins
SGLT-2 Inhibitors Adverse Effects

- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - Urinary tract infections
  - Frequent urination
  - Increased thirst
  - Possible dehydration
  - GI problems, especially when combined with metformin
  - Hyperkalemia
    - More of a concern when used with other agents that can cause hyperkalemia
  - Hypotension

- More of a concern when used with other agents that can cause hyperkalemia

- Hypotension
  - More of a concern when used with other agents that can cause hypotension

Safety Warnings/Concerns

- Canagliflozin and Bone Fractures
  - Increased bone fracture associated with canagliflozin
  - Fractures seen as early as 12 weeks of therapy initiation
  - Mostly due to trauma
  - Falls from standing height
  - Upper extremities most likely affected

- Dapagliflozin and Bladder Cancer

GLP-1 Agonists

- Exenatide
- Liraglutide
- Albiglutide
- Dulaglutide
- Stimulation of glucagon-like peptide (GLP-1) receptors results in increase insulin secretion in response to elevated blood glucose, decreased glucagon secretion, slowed gastric emptying, and increased satiety
- A1c reduction depends on the agent
  - 0.9% to 1.9% reduction
- Low risk of hypoglycemia
- Decreases appetite, so most patients do see weight loss
- Reduces post-prandial glucose values
- Modest improvements in some cardiovascular risk factors (blood pressure; lipids)
GLP-1 Agonist Warnings
Renal Impairment
• All of the agents have the potential to cause renal impairment
• Between April 2005 and October 2008, 62 cases of acute renal failure and 17 cases of renal insufficiency were noted
• Most cases were with pre-existing renal disease or at least one risk factor for kidney disease
• Agents are not recommended for use in patients with severe renal impairment
• Should monitor renal function

GLP-1 Agonist Warnings
Pancreatitis
• All agents have the potential to cause rare fatal and non-fatal hemorrhagic or necrotizing pancreatitis
• The characteristics and complications of pancreatitis cases are consistent with pancreatitis in the general population
• Most patients that have developed pancreatitis had other risk factors
  – Alcohol
  – Tobacco
  – High triglycerides
  – Obesity
• Should not be used in patients with confirmed pancreatitis or a strong history of the disorder
• Patients should be observed for signs and symptoms of pancreatitis
  – Abdominal pain that may radiate to the back
  – Swollen, tender abdomen
  – Nausea/vomiting
  – Fever
  – Increased heart rate
  – Constipation or diarrhea (with a high fat meal)

GLP-1 Agonist Warnings
Thyroid C Cell Tumors
• Black-Box Warning for all agents except exenatide
  – Thyroid C-cell tumors in rats
  – Doses much higher than what would be used in humans
  – This type of cancer is extremely rare
  – A few reports of thyroid cancer have been reported
  – Use cautiously in patients with a family history of medullary thyroid cancer or in patients with a history of multiple endocrine neoplasia syndrome type 2
Insulin Glargine (Toujeo)

- U300 – higher concentration of insulin glargine, a basal, long-acting insulin
  - 300 units of insulin per one ml
  - Need to be careful to avoid potential medication errors
- Onset develops over 6 hours with no significant peak
- Should be administered subcutaneously daily, at the same time each day
- Make take at least five days to see maximum effect of the selected dose
  - Initial dose is unlikely to have sufficient coverage
- Similar efficacy and side effect profile of other long-acting insulin
  - lowers A1C about 0.73% from baseline
- May see less weight gain than with other insulin products
- Less hypoglycemia
  - Especially nocturnal hypoglycemic events
- Not exactly sure of the place in treatment guidelines

Conclusions

- We have covered LOTS of material today!!!
- Medications, guidelines, and the world of pharmacy is continually changing
- Necessary to stay as updated as possible
- Safety concerns may limit the usefulness of some medications in particular patients
- The proliferation of new medications is wonderful, but must always question whether or not a medication is truly "new and improved"

Questions?

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Thank You!