NEW DRUG UPDATE 2015

Leroy C. Knodel, Pharm.D.
Clinical Professor and Assistant Head, Pharmacotherapy Division,
University of Texas College of Pharmacy

Presentation Objectives

Following completion of the presentation, participants should be able to:
1. Discuss the basic pharmacology of the new drugs presented and how the pharmacologic actions relate to both therapeutic and adverse effects.
2. Discuss clinically significant adverse effects and drug interactions, and the appropriate dosing and monitoring of the new drugs presented.
3. Discuss the therapeutic role of the new drugs presented as compared to agents already marketed.

What’s Going On in the Pharmaceutical Marketplace?

• New drug development is skewed toward specialty drugs and orphan drugs
  – 50% of all new drugs approved during the past 5 years have been specialty drugs
• Specialty drugs - initiated by a specialist and typically are
  – High-cost
  – Used to treat complex, chronic conditions
  – Require
    • special handling, distribution, and/or administration
    • significant patient education and monitoring

New Drug Update 2015 is accredited by ACPE for pharmacists, ACPE 0154-0000-15-038-L01-P, and technicians, ACPE 0154-0000-15-038-L01-T for 1.5 contact hours.

Leroy Knodel has not disclosed any financial or conflicts of interest in relation to this program.

What’s Going On in the Pharmaceutical Marketplace?

• Overall drug spending increased 13% in 2014
  – Represents an increase of more than $43 billion
    • Price increases on branded drugs
    • New medications
    • ↓ patent expiration impact
    • Dramatic ↑ in expensive compounded drugs
• Specialty drug spending ↑ 31% in 2014
  – Hepatitis C medication spend ↑ 743% in 2014

What’s Going On in the Pharmaceutical Marketplace?

• Almost 75% of specialty drug sales are to physician-owned clinics
• In 2013, over half of physician visits were with specialists
• Specialty drugs account for < 1% of Rxs, but for 32% of drug spending in 2014
• Primary driver of growth in retail Rxs (2014) was Medicaid prescriptions
U.S. Specialty Drug Spending Expected to Quadruple by 2020

Source: PwC Health Research Institute, Medical cost trend: Behind the numbers 2015, June 2014, analysis based on data from CVS Caremark.

Notable Drug Patent Expirations in 2015

- Lantus® (insulin glargine) – $7.9 billion
- Abilify® (aripiprazole) – $7.8 billion
- Copaxone® (glatiramer) – $4.33 billion
- Neulasta® (pegfilgrastim) – $4.4 billion
- Namenda (memantine) – $1.5 billion
- Zyvox (linezolid) – $1.35 billion
- AndroGel (testosterone) – $1.03 billion

2013 Global Sales for each drug listed above

FDA Drug Approvals in 2014

- Total of 44 drugs approved
  – Drugs & biologics for treatment of disease
  – Infectious Disease – 12 approvals
  – bacterial, fungal, viral, and parasitic infections
- Cancer – 8 approvals
- Rare Diseases – 5 approvals

Over 60% of the new drugs approved were approved in the U.S. before receiving approval in any other country.

What’s Going On in the Pharmaceutical Marketplace?

- Growth areas for traditional drugs
  – Diabetes
  – Attention Deficit Hyperactivity Disorder
- Growth areas for specialty drugs
  – Oncology
  - Almost half of cancer drug spending is for specialty drugs that target a specific protein or genetic mutation
  – Hepatitis C
  – Inflammatory Disorders
  – Multiple Sclerosis

First Biosimilar Approved by FDA in 2015

- Biosimilar product is a biological product that is approved based on showing that it
  – Is highly similar to an already-approved biological product
  – Has no clinically meaningful differences in terms of safety and effectiveness from the reference product
- Sandoz’s Zarxio® (filgrastim-sndz) is a biosimilar to Amgen’s Neupogen® (filgrastim)

Empagliflozin (Jardiance® - Lilly/BI)

Major Summary Points

- INDICATION – adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  – Monotherapy or combination therapy
- Major competition
  – Canagliflozin (Invokana®)
  – Dapagliflozin (Farxiga®)
Empagliflozin – Major Summary Points

• Sodium-glucose co-transporter 2 (SGLT2) inhibitor
  – SGLT2 is a carrier responsible for reabsorption of glucose filter by kidneys back into the bloodstream
  – A “glucuretic”
  – Osmotic diuresis results in ↓ blood pressure

• Possible secondary effects
  – Paradoxical ↑ endogenous glucose production
  – Improved beta-cell function & insulin sensitivity

Monotherapy Results (24 weeks)

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>10 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in A1C (Adjusted Mean)</td>
<td>↓ 0.7%</td>
<td>↓ 0.9%</td>
</tr>
<tr>
<td>Change in FBS* from Baseline (Adjusted Mean)</td>
<td>↓ 19 mg/dL</td>
<td>↓ 25 mg/dL</td>
</tr>
</tbody>
</table>

* FBS – fasting blood sugar

Empagliflozin – Major Summary Points

• Weight Loss with Monotherapy (24 weeks)

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>10 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline (Adjusted Mean)</td>
<td>2.2 kg</td>
<td>2.5 kg</td>
</tr>
</tbody>
</table>

Empagliflozin – Major Summary Points

• Drug Interactions
  – Metabolized via glucuronidation by UDP-glucuronosyl transferase (UGT) enzymes
    • UGT inducers (e.g., rifampin, phenytoin, ritonavir) could ↓ AUC of dapagliflozin & empagliflozin
  – No clinically significant interactions reported

Empagliflozin – Major Summary Points

• Adverse effects
  – Hypoglycemia is unlikely with monotherapy

FDA Drug Safety Communication (May 15, 2015)

• Canagliflozin, dapagliflozin, and empagliflozin may cause ketoacidosis
• Signs of ketoacidosis - difficulty breathing, nausea, vomiting, fruity-scented breath, abdominal pain, confusion, unusual fatigue or sleepiness
• Diabetic ketoacidosis (subset of ketoacidosis/ketosis)
  – Usually occurs with low insulin levels or during prolonged fasting
  – Most commonly in type 1 diabetes
  – High blood sugar levels most commonly seen
FDA Drug Safety Communication (May 15, 2015)

- Ketoacidosis cases with “flozins”
  - Most occurred in patients with type 2 diabetes
  - Blood sugar levels (when reported) were only slightly ↑
  - Possible triggering factors - major illness, reduced food and fluid intake, and reduced insulin dose

Empagliflozin – Major Summary Points

- Pregnancy Category C
  - No well-controlled studies in pregnant women
  - Problems with renal development and maturation in rat studies
- Contraindications
  - Severe renal impairment, end-stage renal disease, patients on dialysis
  - History of serious hypersensitivity reaction

Audience Response Time

When compared to gliptins such as sitagliptin & alogliptin, empagliflozin is more likely to

A. Cause weight loss
B. Cause genital fungal infections
C. Increase serum creatinine
D. A and B only
E. A, B and C

Empagliflozin – Major Summary Points

- Warnings and Precautions
  - Symptomatic hypotension
  - Impaired renal function
  - Hypoglycemia when combined with insulin or an insulin secretagogue
  - ↑ in LDL-cholesterol
- Dapagliflozin labeling - imbalance in bladder cancers observed in clinical trials

Empagliflozin – Major Summary Points

- Empagliflozin - Dosage and Administration
  - Usual starting dose - 10 mg once daily in AM, before or after food
  - If inadequate response, ↑ dose to 25 mg
  - Do not use if eGFR is < 45 mL/min/1.73 m²
- Canagliflozin
  - Do not use if eGFR is < 45 mL/min/1.73 m²
- Dapagliflozin
  - Do not use if eGFR is < 60 mL/min/1.73 m²

Empagliflozin – Major Summary Points

- FDA requiring studies to assess:
  - Risk of serious adverse effects (e.g., cardiovascular)
  - Pediatric studies
  - Juvenile toxicity (e.g., renal development, bone development, and growth in animal models)
**Dulaglutide (Trulicity® - Lilly)**

**Major Summary Points**

- **INDICATION** – adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Monotherapy or combination therapy
  - Not first-line therapy for patients inadequately controlled on diet and exercise

---

**Dulaglutide versus Liraglutide**

- 52-week monotherapy study in type 2 diabetics
  - Dulaglutide 0.75 mg once weekly vs liraglutide 0.9 mg*
  - Dulaglutide was superior to liraglutide
  - HbA1C decreased by 1.39% (D) vs. 1.19% (L)
  - GI adverse effects similar in both groups
    - Nausea – 6.1% (D) vs. 8% (L)
    - Diarrhea – 7.1% (D) vs. 4.4% (L)
    - Constipation – 7.1% (D) vs. 4.4% (L)
  - Decreased appetite – 0.7% (D) vs. 5.1% (L); p<0.05

*Highest approved dose in Japan

75th American Diabetes Association (ADA) Scientific Sessions in Boston

---

**Dulaglutide – Major Summary Points**

- Glucagon-like peptide -1 (GLP-1) receptor agonist
  - Stimulates endogenous insulin production
  - Inhibits release of postprandial glucagons
  - Slows gastric emptying
  - Increases satiety
- **Competition**
  - Liraglutide (Victoza®) – daily injection
  - Exenatide extended-release (Bydureon®) – weekly injection
  - Albiglutide (Tanzeum®) – weekly injection

---

**Dulaglutide versus Liraglutide**

- 26-week study as add-on therapy in type 2 diabetics inadequately controlled on metformin
  - Dulaglutide was non-inferior
  - HbA1C decreased by 1.42% (D) vs. 1.36% (L)
  - Adverse effects and drug discontinuation rates similar in both groups
    - Adverse GI events overall – 36% (D) vs. 36% (L)
    - Nausea – 20% (D) vs. 18% (L)
    - Vomiting – 7% (D) vs. 8% (L)

---

**Dulaglutide – Major Summary Points**

- Warnings and precautions
  - Pancreatitis reported with all GLP-1 agonists
  - Hypoglycemia - can occur with insulin secretagogues (e.g., sulfonylureas) or insulin
  - Hypersensitivity reactions
    - Especially important in patients experiencing GI adverse effects
  - Drug interactions – delay gastric emptying
**Dulaglutide – Major Summary Points**

- Dulaglutide*
  - Initial dosage – 0.75 mg SC in abdomen, thigh or upper arm once weekly
  - ↑ dose to 1.5 mg as needed and tolerated
  - If dose is missed, administer within 3 days
  
* Available as single-dose pen

---

**Audience Response Time**

Which of the following is/are established advantages of dulaglutide (Trulicity®) over liraglutide (Victoza®)?

A. Less frequent dosing  
B. Associated with greater weight loss  
C. More effective at lowering HbA1c  
D. A and B only  
E. A, B and C

---

**Vorapaxar (Zontivity® - MSK)**

- **Major Summary Points**
  - INDICATION – reduction of thrombotic cardiovascular events in patients (1) with a history of MI or (2) with peripheral arterial disease
  - Not approved as monotherapy
  - Use in combination with aspirin or clopidogrel (Plavix®)

---

**Vorapaxar – Major Summary Points**

- Protease-activated receptor-1 (PAR-1) reversible antagonist
  - Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation
  - Does NOT inhibit ADP-, collagen- or thromboxane mimetic-induced platelet aggregation
  - Metabolized by CYP3A4 and CYP2J2; primary route of elimination is feces

---

**Vorapaxar – Major Summary Points**

- Effective half-life of 3-4 days; apparent terminal elimination half-life of 8 days
  - No known treatment to reverse antiplatelet effects
- Drug interactions
  - Avoid strong CYP3A4 inhibitors (e.g., ketoconazole) and inducers (e.g., rifampin)
  - Avoid use with anticoagulants
- Contraindications
  - History of stroke, TIA, intracranial hemorrhage
  - Active pathological bleeding

---

**Vorapaxar Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of CV death, MI &amp; stroke (secondary endpoint)</td>
<td>7.9%</td>
<td>9.5%*</td>
</tr>
<tr>
<td>Composite of CV death, MI, stroke, &amp; UCR (primary endpoint)</td>
<td>10.1%</td>
<td>11.8%*</td>
</tr>
</tbody>
</table>

*P < .001  
UCR – urgent coronary revascularization
**Vorapaxar – Major Summary Points**

- **Bleeding in TRA 2°P - TIMI 50 trial**
<table>
<thead>
<tr>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>1.0%</td>
</tr>
<tr>
<td>Moderate or Severe</td>
<td>2.4%</td>
</tr>
<tr>
<td>Any Bleeding (Severe/Moderate/Mild)</td>
<td>19.8%</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.2%</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.4%</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
  * p<.05

- **Dosage** – one tablet once daily

---

**Audience Response Time**

Which of the following is true regarding the antiplatelet effects of vorapaxar?

A. Significant effects persist for 4 weeks or longer after discontinuation
B. Can be enhanced by taking concomitant CYP3A4 inhibitors such as ketoconazole
C. Can be reversed with hemodialysis
D. A and B only
E. A, B and C

---

**Edoxaban (Savaysa® - Daiichi Sankyo)**

**Major Summary Points**

- **INDICATIONS**
  - To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)
  - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant
- **Should NOT be used in patients with creatinine clearance (CrCL) > 95 mL/min because of ↑ risk of ischemic stroke compared to warfarin**

---

**Edoxaban – Major Summary Points**

- **MOA** - direct factor Xa inhibitor similar to rivaroxaban and apixaban; taken once daily
- **NOAC Competition**
  - Dabigatran (Pradaxa®) - taken twice daily
  - Rivaroxaban (Xarelto®) - taken once daily
  - Apixaban (Eliquis®) - taken twice daily
- **All NOACs appear to be safe and effective alternatives to warfarin in the treatment of NVAF and acute venous thromboembolism**

---

**Atrial Fibrillation**

- Most common cardiac arrhythmia
- Frequently becomes chronic and associated with small ↑ in risk of death
- Depending on 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 of 65
  - Seen in 10% of persons over age of 75
- Frequently asymptomatic, but can cause dizziness, fainting, chest pain, and CHF

---

**Edoxaban – Major Summary Points**

- High renal clearance with 50% eliminated unchanged in urine
  - Drug exposure >70% higher in patients with a CrCl ≤ 50 mL/min than in those with a CrCl ≥ 80 mL/min
- Absorption not affected by food; half-life – 10-14 hrs
- Ischemic stroke significantly higher with edoxaban (0.9%) than with warfarin (0.4%) in patients with CrCl >95 mL/min
**ENGAGE AF-TMI 48 Study**

- Double-blind, noninferiority trial of over 21,000 patients; patients randomized to received either edoxaban 30 mg, edoxaban 60 mg or warfarin (titrated to INR 2-3)

<table>
<thead>
<tr>
<th>First Stroke or Systemic Embolic Event</th>
<th>Edoxaban 60 mg (%/year)</th>
<th>Warfarin (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* Noninferiority established, but superiority of edoxaban was not shown.

**Bleeding Rates for NVAF Patients (CrCl ≤ 95 mL/min)**

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban 60 mg (%/year)</th>
<th>Warfarin (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>3.1*</td>
<td>3.7*</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.5*</td>
<td>1.0*</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.8*</td>
<td>1.3*</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.2*</td>
<td>0.4*</td>
</tr>
</tbody>
</table>

* All comparisons are statistically significant (p < 0.05)

- Absence of specific antidote
  - Hemodialysis, vitamin K, and other approaches are NOT effective
  - Prothrombin complex concentrate used with some success
  - Anticoagulant effect persists ~24 hours after last dose

**Edoxaban – Major Summary Points**

- Warnings and precautions
  - Bleeding - avoid drugs that can ↑ risk of bleeding
  - Mechanical heart valves or moderate to severe mitral stenosis
- Most common adverse effects
  - Bleeding
  - Anemia
- Not recommended in moderate or severe hepatic impairment
- Pregnancy category C

**Edoxaban – Dosage and Administration**

**Nonvalvular Atrial Fibrillation**

- Assess CrCL before initiating therapy
- Dosage
  - 60 mg once daily (CrCL >50 to ≤ 95 mL/min)
  - 30 mg once daily (CrCL 15-50 mL/min)
- Missed dose – take same day (don’t double dose the next day)

**Deep Vein Thrombosis & Pulmonary Embolism**

- Assess CrCL before initiating therapy
- Dosage
  - 60 mg once daily (CrCL > 50 to ≤ 95 mL/min)
  - 30 mg once daily if
    - CrCL 15-50 mL/min, or
    - Body weight ≤ 60 kg, or
    - Patients on certain P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, oral ketoconazole)
- Missed dose – take same day (don’t double dose the next day)

**Edoxaban – Major Summary Points**

- Drug Interactions
  - Anticoagulants, antiplatelet drugs, and thrombolitics
  - Can ↑ risk of bleeding (including low-dose ASA)
  - P-gp Inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, oral ketoconazole)
  - NVAF – no dosage adjustment recommended
  - VTE – reduce dosage to 30 mg once daily
  - P-gp inducer (rifampin) – avoid concomitant use in NVAF and VTE

**Edoxaban – Major Summary Points**

- Absence of specific antidote
  - Hemodialysis, vitamin K, and other approaches are NOT effective
  - Prothrombin complex concentrate used with some success
  - Anticoagulant effect persists ~24 hours after last dose
NOACs vs. Warfarin
Safety & Efficacy Comparison in NVAF

<table>
<thead>
<tr>
<th>NOACs</th>
<th>Efficacy</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Similar</td>
<td>Less</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>Superior</td>
<td>Less†</td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>Superior</td>
<td>Less</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>Similar</td>
<td>Less</td>
</tr>
</tbody>
</table>

* Efficacy endpoints differ among trials (e.g., stroke, stroke or systemic embolism)
**Bleeding endpoints differ among trials (e.g., intracranial bleeding, fatal bleeding, major bleeding, major GI bleeding)
† Major GI bleeding was higher

Comparison of NOACs and Warfarin

• NOACs - Potential Advantages
  – Predictable pharmacokinetics
  – Routine monitoring not required
  – Rapid onset /offset
  – No dietary restrictions
  – Fewer drug interactions

• NOACs - Potential Disadvantages
  – Higher drug costs
  – No established method to assess anticoagulant effect
  – Rapid offset - ↑ risk of thrombosis with missed doses
  – Not recommended in end-stage renal disease
  – Absence of specific antidotes – prothrombin complex concentrate used with some success

Audience Response Time
Newer oral anticoagulants such as edoxaban
A. Do not require INR monitoring
B. Do not require dietary restrictions
C. Have longer half-lives than warfarin
D. A and B only
E. A, B and C

Comparison of NOACs and Warfarin

• Warfarin
  – Advantages
    • Lower drug costs
    • Antidote available for bleeding episodes
  – Disadvantages
    • Requires frequent monitoring
    • Requires dietary restrictions
    • Drug interactions

Eluxadoline (Viberzi® - Actavis)

Major Summary Points
• INDICATION – treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults

• Categorization of IBS
  – Diarrhea-predominant (IBS-D) – approximately 33%
  – Constipation-predominant (IBS-C) – approximately 33%
  – Mixed diarrhea and constipation – approximately 33%
**Epidemiology of IBS**

- 15%-20% prevalence in North America; female to male ratio is 2:1
- Most common in young adults (<45); usual age at first presentation of symptoms is 30-50 years and prevalence ↓ after age 60
- Synonyms: spastic colon
- Functional disorder
- Chronic or recurrent abdominal complaints without a structural or biochemical cause

**General Management of IBS**

- Focus on comfort, not cure
- Dietary Modifications
- Medications
  - Fiber & bulking agents
  - Antidiarrheals
  - Alosetron (Lotronex®)
  - Laxatives
  - Antispasmodics/anticholinergics
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Probiotics and antibiotics

**Symptoms of IBS**

- Abdominal discomfort and pain
  - Intermittent crampy pain relieved with bowel movements
- Bloating, diarrhea, constipation, or alternating diarrhea and constipation
- Depression, anxiety or stress
- IBS symptoms may be exacerbated by stress, alcohol, or food

**Eluxadoline – Clinical Efficacy**

- FDA approval based on results from 2 randomized, double-blind, placebo controlled trials in over 2,400 patients with IBS-D
- Efficacy evaluated based on both abdominal pain and stool consistency scores

**Eluxadoline – Major Summary Points**

- Mechanism of action – mu opioid receptor agonist; lesser effects on delta and kappa opioid receptors
- Will not be available until the DEA has made a final scheduling decision

**Eluxadoline – Clinical Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>E 75 mg BID</th>
<th>E 100 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (Composite Response over 12 weeks)</td>
<td>16-24%</td>
<td>24-29%</td>
<td>25-30%</td>
</tr>
<tr>
<td>Responders (Composite Response over 26 weeks)</td>
<td>20-23%</td>
<td>23-30%</td>
<td>29-33%</td>
</tr>
<tr>
<td>Responders (Abdominal pain improvement ≥ 30% over 12 weeks)</td>
<td>40-45%</td>
<td>42-48%</td>
<td>43-51%</td>
</tr>
<tr>
<td>Responders (Stool Scale Improvement over 12 weeks)</td>
<td>21-22%</td>
<td>30-37%</td>
<td>34-36%</td>
</tr>
</tbody>
</table>
Eluxadoline – Major Summary Points

**Contraindications**
- Biliary duct obstruction or sphincter of Oddi disease or dysfunction
- Alcoholism, alcohol abuse, alcohol addiction, or drink more than 3 alcoholic beverages/day
- History of pancreatitis or structural diseases of the pancreas
- Severe hepatic impairment
- Severe constipation or known or suspected mechanical gastrointestinal obstruction

**Warnings and Precautions**
- sphincter of Oddi spasm and pancreatitis
  - Monitor patients without a gallbladder for
    - New or worsening abdominal pain, with or without nausea and vomiting, or
    - Acute biliary pain with liver or pancreatic enzyme elevations
  - Discontinue eluxadoline and seek medical attention if symptoms develop
  - Occurs in < 1% of patients, usually within first week of treatment

Eluxadoline – Drug Interactions

**OATP1B1 Inhibitors**
- Examples - cyclosporine, gemfibrozil, rifampin, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), eltrombopag
  - Possible impact - ↑ eluxadoline exposure

**Strong CYP Inhibitors***
- Examples - ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine, bupropion
  - Possible impact - ↑ eluxadoline exposure

*Precautionary measure until all metabolic pathways of eluxadoline are determined.

Eluxadoline – Abuse Potential

**Unknown – limited data**
- Euphoria and “feeling drunk” reported in ≤ 0.2% of clinical trial patients
- In recreational opioid-experienced individuals
  - Supratherapeutic doses produced euphoria in up to 28% of subjects (compared to 76% with oxycodone)

Eluxadoline – Most Common Adverse effects

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Eluxadoline 75 mg</th>
<th>Eluxadoline 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Eluxadoline – Drug Causes Constipation
- Examples - opioids, anticholinergics
- Possible impact - ↑ risk of constipation

**OATP1B1 and BCRP Substrates**
- Examples - rosuvastatin
- Possible impact - ↑ substrate exposure

**CYP3A Substrates with Narrow Therapeutic Index**
- Examples - cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
- Possible impact - ↑ substrate exposure
Eluxadoline – Dosage and Administration

- Usual adult dosage – 100 mg BID with food
  - High fat meals may ↓ bioavailability
- Loperamide can be used occasionally for the ACUTE management of severe diarrhea

Audience Response Time

Which of the following are true regarding Sphincter of Oddi spasm and pancreatitis with eluxadoline?

A. Characterized by new or worsening abdominal pain, with or without nausea & vomiting
B. Most likely to occur during the first week or weeks of therapy
C. More likely to occur in persons without a gallbladder
D. All of the above

Suvorexant (Belsomra® - Merck)

Major Summary Points

- INDICATION –treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
- Reviewed by FDA in 2013 – not approved due to safety concerns
  - Doses used at the time – 30 and 40 mg
  - Current doses – 10 and 20 mg

Lightning Rounds

Eluxadoline – Dosage and Administration

- 75 mg BID with food in patients who
  - Do NOT have a gallbladder
  - Are unable to tolerate the 100 mg dose
  - Are receiving concomitant OATP1B1 inhibitors
  - Have mild/moderate hepatic impairment
- Discontinue in patients who develop severe constipation for more than 4 days
- Missed dose – take next dose at regular time

Suvorexant – Major Summary Points

- MOA - orexin receptor antagonist
- Metabolism – primarily by CYP3A
- Elimination – primarily in feces
- Efficacy* in 2 studies (>600 patients)
  - Onset of sleep shortened by 5-8 minutes
  - Duration of sleep increased by 11-31 minutes

*Efficacy results are based on the DIFFERENCE between the mean placebo response and the mean suvorexant response
Suvorexant – Major Summary Points

• Typical hypnotic warnings
  – Next day somnolence/impairment
  – Avoid alcohol and other CNS depressants
  – Caution in depressed or suicidal patients, or patients with compromised respiratory function
  – Monitor for behavioral changes
    • Nighttime “sleep-driving”
    • Sex and other activities while sleeping
  – Others – sleep paralysis, hallucinations, cataplexy-like symptoms

Suvorexant – Dosage and Administration

• Recommended
  – 10 mg ONCE per night; take 30 minutes before HS
  – If 10 mg dose ineffective, but well tolerated, dose can be increased to 20 mg ONCE daily
  – Onset can be delayed if taken with or soon after a meal
• Obese females demonstrate a greater “exposure” to recommended doses

Suvorexant – CYP3A Drug Interactions

• CYP3A Inhibitors
  – Strong Inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nefinvir, indinavir, boceprevir, telaprevir, telithromycin & convivaptan)
    • Concomitant use of suvorexant is NOT recommended
  – Moderate Inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, imatinib, fosamprenavir, grapefruit juice, verapamil)
    • Recommended dose of suvorexant is 5 mg; can be increased to 10 mg based on tolerability
• CYP3A Inducers
  – Strong Inducers (e.g., rifampin, carbamazepine and phenytoin)
    • Decreased suvorexant efficacy possible

Audience Response Time

Which of the following is/are advantages of suvorexant over currently available hypnotics?

A. Faster onset of effect
B. Fewer adverse effects
C. Fewer drug interactions
D. None of the above

New Cholesterol Drugs: PCSK9 Inhibitors

• Alirocumab (Praluent® - Sanofi/Regeneron)
  – Final FDA decision expected by July 24, 2015
• Evolocumab (Repatha® - Amgen)
  – Final FDA decision expected by August 27, 2015
Evolocumab & Alirocumab

- Proprotein convertase subtilisin/kexin 9 (PCSK9) enzyme inhibitors
  - Monoclonal antibodies that inactivate PCSK9
  - PCSK9 inactivates/degrades hepatic LDL receptors
  - LDL receptors transport circulating LDL into the liver for metabolism

Evolocumab & Alirocumab: Clinical Considerations

- Dramatically lower LDL cholesterol
  - After 1 year of treatment, LDL ↓ 50-60%
- Meta-analysis of short term trials have shown reduced all-cause mortality rates and MIs
- Long-term, prospective trials to be completed in 2017

Evolocumab & Alirocumab: Clinical Considerations

- FDA Report
  “The possibility that LDL reduction isn’t always a surrogate for ↓ risk of heart disease is ‘particularly relevant’ now that statins are the go-to cholesterol treatment and have proven a heart benefit”

Evolocumab & Alirocumab: Dosing

- Alirocumab (Praluent®)
  - 75 mg SQ once very 2 weeks
  - Patients requiring greater LDL reduction can be started on 150 mg SQ every 2 weeks
- Evolocumab (Repatha®)
  - Familial homozygous hyperlipidemia
    - 420 mg every 2 weeks or monthly
  - Primary hyperlipidemia and mixed dyslipidemia
    - 140 mg every 2 weeks or 420 mg monthly

Recent FDA Advisory Panel Recommendations

June 4, 2015

“Female Viagra”
“gender equity”
26 drugs marketed for the treatment of male sexual dysfunctions, but none for women
Members of the FDA advisory committee “were emotionally blackmailed”…. ‘something was better than nothing’
FDA has not approved flibanserin - evidence of their discomfort with women taking control over their sexuality. “…The implication is that men can be trusted to make a rational decision of risk versus reward and women can’t.”

Flibanserin – Brief History
• Originally created by Boehringer Ingelheim as an antidepressant
  – ↑ sexual interest & sexual satisfaction reported by a number of women
• Sprout Pharmaceutical purchased rights to flibanserin to pursue a HSDD indication
• Reviewed by FDA in 2010 and not approved
  – Lack of compelling efficacy data versus adverse effects (e.g., dizziness, nausea, headaches)

Flibanserin – Major Summary Points
• Proposed labeling
  – If clinical response not achieve in 12 weeks, D/C
  – Only take at bedtime and do NOT double dose
  – Moderate to strong CYP3A4 inhibitors are contraindicated
  – Avoid driving until the following morning
  – Dose-related increase in the incidence of mammary tumors in female mice
  – No direct-to-consumer advertising for at least 18 months after start of marketing

Flibanserin - Sprout Pharmaceuticals
Major Summary Points
• INDICATION – treatment of premenopausal women with hypoactive sexual desire disorder (HSDD)
• Estimated that 10-33% of women have HSDD
• Clinical trials show 43-60% of women exceeded established criteria to demonstrate meaningful efficacy
• Unlike most male agents which are taken when needed, flibanserin is taken every day

Flibanserin – Major Summary Points
• Postsynaptic 5-HT1A agonist 5-HT2A antagonist
• Most common AEs (FDA Briefing Document)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Flibanserin 100 mg qhs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3.1%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Efinaconazole (Jublia® - Valeant) Tavaborole (Kerydin® - Anacor/Sandoz)
Major Summary Points
• INDICATION – the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*
Efinaconazole & Tavaborole

• Once daily application to top and under the tip of affected nail
• Complete course of therapy – 48 weeks
• Efficacy – YOU BE THE JUDGE!

<table>
<thead>
<tr>
<th></th>
<th>Jublia®</th>
<th>Kerydin®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Cure</td>
<td>15-18%</td>
<td>7-9%</td>
</tr>
<tr>
<td>Complete or Almost</td>
<td>23-26%</td>
<td>15-18%</td>
</tr>
<tr>
<td>Complete Cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycologic Cure</td>
<td>53-55%</td>
<td>31-36%</td>
</tr>
</tbody>
</table>

Audience Challenge

Will you be able to use the information included in this presentation to improve the care you provide to your patients?

• Yes
• No

Your Questions