New Drug Update 2018

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Disclosures

• Dr. Burton and Dr. Podoloff have no actual or potential conflict of interest associated with this presentation

• This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of Dr. Burton, Dr. Podoloff, or University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.
Objectives

• Describe indications, pharmacology, adverse effects, and dosing for recently approved medications
• Compare recently approved medications with similar products used in participant’s practice
• Explain the clinical impact and potential role in therapy of recently approved medications

Cardiology

• Betrixaban (Bevyxxa®)
Betrixaban

- **Indication:** DVT prophylaxis

- **MOA:** Factor Xa inhibition

- **Dose:** 160 mg po as a single dose on day 1, followed by 80 mg po once daily for 35 to 42 days

Betrixaban

- **Dosing Adjustments:**
  - Reduce betrixaban dose (initial and maintenance) by 50% for patients receiving or starting P-glycoprotein inhibitors
  - Renal Impairment:
    - CrCl ≥ 15 to < 30 mL/minute: initial: 80 mg single dose, followed by 40 mg once daily for 35 to 42 days. If patient is also receiving a concomitant P-gp inhibitor, avoid use of betrixaban
    - CRCL < 15ml/minute: avoid use
Betrixaban

• **Trials:** APEX
  - Inclusion Criteria: > 40 years of age or older, hospitalized for less than 96 hours for a specified acute medical illness and had reduced mobility and specific risk factors for venous thromboembolism
  - Compared the use of extended-duration betrixaban (for 35 to 42 days) with a standard enoxaparin regimen (10±4 days)

Betrixaban

• **Trials:** APEX
  - Study Conclusions: no significant difference between extended-duration betrixaban and a standard regimen of enoxaparin in primary study population but promising subgroup analysis
    - Patients ≥75 and elevated D dimer
    - Sub-analysis also highlighted potential reduction in stroke rates
Betrixaban

• Trials: APEX

<table>
<thead>
<tr>
<th></th>
<th>Primary efficacy analysis (VTE)</th>
<th>Primary safety analysis (major bleeding)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>P value</td>
</tr>
<tr>
<td>Cohort 1: Elevated D-Dimer</td>
<td>0.806</td>
<td>0.054*</td>
</tr>
<tr>
<td>Cohort 2: Elevated D-dimer or age ≥75 years</td>
<td>0.800</td>
<td>0.029</td>
</tr>
<tr>
<td>Overall study population</td>
<td>0.760</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Safety Conclusions: betrixaban was not associated with significantly more major bleeding than standard-duration enoxaparin, although there was significantly more clinically relevant non-major bleeding.
Betrixaban

- **Adverse Effects:**
  - Gastrointestinal: dyspepsia, Gl bleed, gastritis
  - Bleeding

- **Place in Therapy:**
  - Another option in crowded DOAC space; no other indications at this time

Which of the following statements is TRUE regarding Betrixaban?

A. Betrixaban is indicated for treatment of DVT/PE
B. Betrixaban is an oral direct thrombin inhibitor
C. Betrixaban was non-inferior to enoxaparin in clinical trials among patients with elevated D dimer
D. Betrixaban was associated with an increase in major bleeding in clinical trials
Which of the following statements is TRUE regarding Betrixaban?

A. Betrixaban is indicated for treatment of DVT/PE
B. Betrixaban is an oral direct thrombin inhibitor
C. **Betrixaban was non-inferior to enoxaparin in clinical trials among patients with elevated D dimer**
D. Betrixaban was associated with an increase in major bleeding in clinical trials

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**Endocrinology**

- Etelcalcetide (Parsabiv®)
Etelcalcetide

- **Indication**: Treatment of secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis
- **MOA**: Calcimimetic
- **Dose**:
  - Initial: 5 mg IV bolus 3 times per week at the end of hemodialysis
  - Titrate not more frequently than every 4 weeks to a maximum of 15 mg IV three times per week

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Etelcalcetide

- **Monitoring**:

<table>
<thead>
<tr>
<th>Serum Calcium</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to initiation</td>
<td>Prior to initiation</td>
</tr>
<tr>
<td>1 week after initiation or dose adjustment</td>
<td>4 weeks after initiation or dose adjustment</td>
</tr>
<tr>
<td>Every 4 weeks after maintenance dose established</td>
<td>Per clinical practice after maintenance dose established</td>
</tr>
</tbody>
</table>
Etelcalcetide

• Adverse Effects:
  ▫ Nausea, vomiting, diarrhea
  ▫ Decreased serum calcium
  ▫ Decreased serum phosphorous
  ▫ Muscle spasms
  ▫ Prolonged QT interval

Etelcalcetide

• Trials:
  ▫ Efficacy assessed in two 26-week, double-blind, randomized, placebo-controlled trials (n=1023)
    • Patients with SHPT were administered placebo or etelcalcetide at starting dose of 5 mg 3x per week at end of hemodialysis
  ▫ Primary endpoint achievement of a > 30% reduction from baseline in mean PTH
    • Study 1: 74% vs. 8.3%; Study 2: 75.3% vs. 9.6%
  ▫ Secondary endpoint achievement of a mean PTH ≤ 300 pg/mL
    • Study 1: 49.6% vs. 5.1%, study 2: 53.3% vs. 4.6%
Etelcalcetide

• **Trials:**
  - 26-week, randomized, double-blind, double-dummy trial comparing IV etelcalcetide vs. oral placebo and oral cinacalcet vs. IV placebo
    - Primary endpoint: noninferiority of etelcalcetide in achievement of a >30% reduction from baseline in mean PTH; \( P \) for noninferiority <.001
    - Secondary endpoint superiority in achieving >50% reduction in PTH; \( P \) for superiority .004

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Etelcalcetide

• **Place in Therapy:**
  - IV etelcalcetide vs. oral cinacalcet
    - Improved adherence
    - Decreased pill burden
  - Higher rate of ADRs than cinacalcet
  - Will risk of clinical endpoints be reduced?
What 1960’s hit plays on the radio alarm clock in *Groundhog Day*?

**Gastroenterology**

- Naldemedine (Symproic®)
- Telotristat Ethyl (Xermelo®)
Naldemedine

• **Indication**: Opioid induced constipation

• **MOA**: Peripheral acting mu-opioid receptor antagonist

• **Dose**: 0.2 mg po daily

Naldemedine

• **Adverse Effects**:
  - >10%
    - Gastrointestinal: abdominal pain (8%), diarrhea (7%)
  - 1% to 10%
    - Gastrointestinal: nausea (4%), vomiting (3%), gastroenteritis (2%)
    - Risk of opioid withdrawal in patients with compromised blood brain barrier
Naldemedine

- **Trials:** Two similar studies
  - Response = 3 SBMs per week plus change from baseline of ≥1 SBM per week FOR at least 9 out of 12 weeks INCLUDING 3 out of the last 4 weeks

- **Place in Therapy:**
  - Similar to methylnaltrexone or naloxegol

Telotristat Ethyl

- **Indication:** Carcinoid syndrome diarrhea

- **MOA:** Inhibitor of tryptophan hydroxylase (TPH)

- **Dose:** 250 mg po 3 times daily
Telotristat Ethyl

• **Adverse Effects:**
  ▫ Headache (most common 11%)
  ▫ GI: abdominal pain, constipation, flatulence
  ▫ Other: nausea, peripheral edema, depression, increased LFTs

Telotristat Ethyl

• **Trials:** Small amount of data (Telestar Trial)
  ▫ Approval based on trial of 135 patients

• **Place in Therapy:**
  ▫ For patients not adequately controlled by somatostatin analogs shown to be effective
Which of the following statements BEST describes Telotristat Ethyl place in therapy?

A. Telotristat Ethyl should be considered first line therapy for patients with carcinoid syndrome diarrhea
B. Telotristat Ethyl should be used as monotherapy for patients inadequately controlled by other therapies
C. Telotristat Ethyl should be used in combination with somatostatin analog therapy
Musculoskeletal

- Abaloparatide (Tymlos®)

Abaloparatide

- **Indication**: Treatment of postmenopausal women with osteoporosis at high risk for fracture

- **MOA**: Parathyroid hormone analog

- **Dose**: 80 mcg SQ once daily
Abaloparatide

• Adverse Effects:
  ▫ Orthostatic hypotension
  ▫ Palpitations
  ▫ Injection site reactions
  ▫ Hypercalcemia
  ▫ Hypercalciuria
  ▫ Hyperuricemia

• Monitoring Parameters:
  ▫ Uric acid
  ▫ Calcium

Boxed Warning:
Increased incidence of osteosarcoma

Abaloparatide

• Trials: ACTIVE
  ▫ Efficacy evaluated in a single, randomized, double-blind, placebo-controlled trial in 1645 postmenopausal women with osteoporosis
  ▫ Received placebo or abaloparatide 80 mcg SQ daily for 18 months
  ▫ Primary endpoint incidence of new vertebral fractures
    • RRR 86%, ARR 3.6%
Abaloparatide

• **Place in Therapy:**
  - Similar to teriparatide
  - Treatment duration > 2 years is not recommended
  - Follow up abaloparatide therapy with bisphosphonates for several years to maintain bone density gains
  - Supplement calcium and vitamin D if dietary intake inadequate

What is the 5 letter stage name of Gordon Matthew Thomas Sumner?
Hepatology

• Glecaprevir and pibrentasvir (Mavyret®)
• Sofosbuvir, velpatasvir, and voxilaprevir (Vosevi®)

Glecaprevir and pibrentasvir

• **Indication:**
  - Chronic Hepatitis C patients without cirrhosis or with compensated cirrhosis

• **MOA:**
  - **Glecaprevir** is an inhibitor of hepatitis C virus (HCV) NS3/4A protease, essential for viral replication
  - **Pibrentasvir** is an inhibitor of HCV NS5A, essential for viral RNA replication and virion assembly
Glecaprevir and pibrentasvir

- **Dose**: 3 tablets po daily (glecaprevir 100 mg and pibrentasvir 40 mg)
  - Duration dependent on genotype and treatment naive vs. treatment experienced patients
  - 8 to 16 week duration

Glecaprevir and pibrentasvir

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>&gt; 10% Headache</td>
</tr>
<tr>
<td>P-gp Inhibitors</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>1-10 % Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Increased serum bilirubin (2X UNL)</td>
</tr>
</tbody>
</table>
Glecaprevir and pibrentasvir

- **Trials:**
  - Nine trials divided by Genotype 1-6
  - Two compared glecaprevir/pibrentasvir to sofosbuvir/velpatasvir with similar efficacy

- **Place in Therapy:**
  - Should be considered first choice in most treatment naïve patients

Sofosbuvir, velpatasvir, and voxilaprevir

- **Indication:** Chronic Hepatitis C patients without cirrhosis or with compensated cirrhosis AND WHO HAVE BEEN PREVIOUSLY TREATED

- **Dose:** One tablet (sofosbuvir 400 mg, velpatasvir 100 mg, and voxilaprevir 100 mg) daily for 12 weeks
Sofosbuvir, velpatasvir, and voxilaprevir

- **MOA:**
  - **Sofosbuvir** is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication and acts as a chain terminator.
  - **Velpatasvir** is an inhibitor of the HCV NS5A protein, which is also required for viral replication.
  - **Voxilaprevir** is a noncovalent, reversible inhibitor of the NS3/4A protease, which is essential for viral replication.

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Sofosbuvir, velpatasvir, and voxilaprevir

**Adverse Effects**

- Headache
- Fatigue/weakness
- Diarrhea
- Increased bilirubin
- Insomnia
- Skin rash

**Drug Interactions**

- Statins
- P-gp Inhibitors
Sofosbuvir, velpatasvir, and voxilaprevir

• Trials:
  ▫ Varied studies by genotype with strong SVR > 90% in all

• Place in Therapy:
  ▫ Salvage therapy

Which of the following agents is approved for treatment naïve Hepatitis C patients?

A. Naldemedine
B. Glecaprevir and pibrentasvir
C. Sofosbuvir, velpatasvir, and voxilaprevir
D. Glycopyrrolate
Which of the following agents is approved for treatment naïve Hepatitis C patients?

A. Naldemedine  
B. **Glecaprevir and pibrentasvir**  
C. Sofosbuvir, velpatasvir, and voxilaprevir  
D. Glycopyrrolate

What is the “pink panther” in the movie **The Pink Panther** starring Peter Sellers?
Neurology

• Safinamide (Xadago®)
• Pimavanserin (Nuplazid®)

Safinamide

• **Indication:** Adjunctive treatment to levodopa-carbidopa therapy in patients with Parkinson's disease experiencing "off " episodes

• **MOA:** Selective monoamine oxidase (MAO) type B inhibitor

• **Dose:** 50 mg po once daily, may increase to 100 mg po once daily after 2 weeks
Safinamide

• **Dose Adjustments:**
  ▫ Renal impairment: no adjustment
  ▫ Hepatic impairment:
    • Mild: no adjustment
    • Moderate: maximum dose 50 mg once daily
    • Severe: use is contraindicated

• **Drug Contraindications**
  ▫ Linezolid
  ▫ Opioids
    • Methadone, meperidine, tramadol
  ▫ Amphetamines
  ▫ Dextromethorphan
  ▫ Cyclobenzaprine
  ▫ Antidepressants

• **Dietary Considerations**
  ▫ Interaction with tyramine containing foods unlikely at doses ≤100 mg/day
  ▫ Patients should avoid foods with very high (>150 mg) tyramine concentrations
Safinamide

Adverse Effects:

<table>
<thead>
<tr>
<th>Dyskinesia (~20%)</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Increased LFTs</td>
</tr>
<tr>
<td>Nausea</td>
<td>Impulse control problems</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>

Trials:

- Compared to placebo in 2 double-blind, 24 week trials in PD patients experiencing “off” time during treatment with carbidopa/levodopa and other PD medications
  - Randomized to either safinamide 50 mg, safinamide 100 mg, or placebo
- Primary measure of effectiveness change from baseline in total daily “on” time
  - Safinamide 50 mg and 100 mg increased “on” time compared to placebo (about 60 minutes)
Safinamide

- **Place in Therapy:**
  - No evidence safinamide works better than selegiline or rasagiline
    - Consider in patients who don’t tolerate other therapy
  - Cannot be used as monotherapy; adjunctive therapy with carbidopa/levodopa only
  - No evidence of neuroprotection

What does Uma Thurman wear on her feet for most of *Pulp Fiction*?
Pimavanserin

- **Indication:** Treatment of hallucinations and delusions associated with Parkinson’s disease psychosis
- **MOA:** Atypical antipsychotic
  - Inverse agonist and antagonist with high affinity for 5-HT$_{2A}$ receptors
  - Low affinity for 5-HT$_{2C}$ receptors
  - No affinity for 5-HT$_{2B}$, dopaminergic, histaminergic, muscarinic, or adrenergic receptors
- **Dose:** 34 mg po once daily

Pimavanserin

- **Dose Adjustments:**
  - Hepatic impairment: not recommended
  - Renal impairment:
    - CrCL $>$ 30 ml/minute: no adjustment
    - CrCL $<$ 30 ml/minute: not recommended
- **Drug Interactions:**
  - Concomitant therapy with strong CYP3A4 inhibitors
    - Reduce pimavanserin to 17 mg once daily
  - Concomitant therapy with strong CYP3A4 inducers
    - Monitor for reduced efficacy of pimavanserin
Pimavanserin

• **Adverse Effects:**
  - Peripheral edema
  - Confusion
  - Hallucinations
  - Nausea

  **Boxed Warning:**
  Increased mortality in elderly patients with dementia-related psychosis

Pimavanserin

• **Trials:**
  - Efficacy evaluated in a single 6-week, randomized, placebo-controlled, parallel-group trial (n=199)
    - Primary endpoint change from baseline to week 6 in Scale for Assessment of Positive Symptoms- Parkinson’s Disease (SAPS-PD)
    - A decrease in SAPS-PD score by at least 2.33 points considered clinically significant
    - This reduction was shown in 65.3% of pimavanserin-treated patients vs. 42.2% of placebo-receiving patients
Pimavanserin

• Safety Concerns:
  ▫ Increased reports of adverse reactions
  ▫ Reports of ineffectiveness
  ▫ Inappropriate combination therapy with other antipsychotics

<table>
<thead>
<tr>
<th>Table 1. Most frequently reported adverse event terms for pimavanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
</tr>
<tr>
<td>All Reports</td>
</tr>
<tr>
<td>Hallucinations</td>
</tr>
<tr>
<td>Drug ineffective</td>
</tr>
<tr>
<td>Confusional state</td>
</tr>
<tr>
<td>Death**</td>
</tr>
</tbody>
</table>

*One report can include multiple terms
**Includes event term and outcomes of death

www.ismp.org/QuarterWatch/pdfs/2017Q1pdf

Pimavanserin

• Place in Therapy:
  ▫ First drug FDA approved to treat hallucinations and delusions associated with Parkinson’s disease psychosis
  ▫ Does not appear to negatively impact motor function
  ▫ More trials needed to assess safety and efficacy
What comedy series’ theme tune was Liberty Bell by John Phillip Sousa?

Ophthalmology

- Latanoprostene bunod (Vyzulta®)
Latanoprostene bunod

- **Indication**: Elevated intraocular pressure (glaucoma)
- **MOA**: prodrug with dual mechanism of action
  1. rapidly metabolized in the eye to latanoprost
  2. rapidly metabolized to NO
- **Dose**: Instill 1 drop into affected eye(s) once daily in the evening

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Latanoprostene bunod

- **Adverse Effects**:
  - Eye irritation
  - Conjunctival hyperemia
  - Lash growth
  - Iris color changes
Latanoprostene bunod

• **Trials:**
  ▫ 70% of those taking latanoprost bunod achieved an average IOP of 18mmHg or less whereas less than 50% of those taking latanoprost achieved the same average IOP

• **Place in Therapy:**
  ▫ Try latanoprost first

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**Infectious Disease**

• Zoster vaccine (recombinant) (Shingrix®)
• Meropenem and vaborbactam (Vabomere®)
Zoster vaccine (recombinant)

- **Indication**: Prevention of herpes zoster (shingles) in patients ≥ 50 years of age
- **MOA**: Stimulates active immunity to disease caused by the varicella-zoster virus
- **Dose**: Adults ≥ 50 years: IM: 0.5 mL administered as a 2-dose series at 0 and 2 to 6 months

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### Adverse Reactions:

<table>
<thead>
<tr>
<th>Injection Site Reactions</th>
<th>Systemic Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (80%)</td>
<td>Muscle pain (46%)</td>
</tr>
<tr>
<td>Redness</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Swelling</td>
<td>Headache</td>
</tr>
</tbody>
</table>
Zoster vaccine (recombinant)

• **Trials:** ZOE-50
  ▫ Efficacy evaluated in randomized, placebo-controlled study of 15,411 adults ≥ 50 years of age
  ▫ Primary objective to assess efficacy of vaccine in reducing risk of herpes zoster in older adults
  ▫ Overall vaccine efficacy was 97.2%

Zoster vaccine (recombinant)

• **Trials:** ZOE-70
  ▫ Efficacy evaluated
  ▫ Primary objective to assess efficacy of vaccine in reducing risk of herpes zoster in adults ≥ 70 years
  ▫ Overall vaccine efficacy was 89.8%
Zoster vaccine (recombinant)

- **Trials:**
  - Pooled analysis of ZOE-50 and ZOE-70
  - Primary objective to assess efficacy of vaccine in reducing risk of herpes zoster and the risk of postherpetic neuralgia in participants > 70 years
  - Overall vaccine efficacy was 91.3%
  - Prevention of postherpetic neuralgia 88.8%

<table>
<thead>
<tr>
<th>Shingrix®</th>
<th>Zostavax®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-live, recombinant</td>
<td>Live, attenuated</td>
</tr>
<tr>
<td>Contains boosting adjuvant</td>
<td>No boosting adjuvant</td>
</tr>
<tr>
<td>Two dose series</td>
<td>Single dose</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Store in refrigerator</td>
<td>Store in freezer</td>
</tr>
<tr>
<td>Recommended age &gt; 50 years</td>
<td>Recommended age &gt; 60 years</td>
</tr>
<tr>
<td>More effective</td>
<td>Less effective</td>
</tr>
</tbody>
</table>
Zoster vaccine (recombinant)

- **Place in Therapy:**
  - Zoster vaccine (recombinant) is preferred shingles vaccine per CDC
  - 2 dose series beginning at age 50 years
  - Administer regardless of past episodes of herpes zoster or receipt of zoster vaccine (live/attenuated)
    - Separate doses by minimum 8 weeks
  - Contraindicated in pregnancy and immunocompromised patients

Which of the following statements is TRUE regarding zoster vaccine (recombinant)?

A. It is administered as a single intramuscular dose
B. It is indicated for patients > 60 years of age
C. It is considered equally efficacious to zoster vaccine (live/attenuated)
D. It is recommended even if a patient has already received zoster vaccine (live/attenuated)
Which of the following statements is TRUE regarding zoster vaccine (recombinant)?

A. It is administered as a single intramuscular dose  
B. It is indicated for patients $\geq 60$ years of age  
C. It is considered equally efficacious to zoster vaccine (live/attenuated)  
D. It is recommended even if a patient has already received zoster vaccine (live/attenuated)

What is the name of Spider-Man’s childhood sweetheart?
Meropenem-vaborbactam

- **Indication**: Antibiotic for treatment of complicated UTI, including pyelonephritis
- **MOA**:
  - **Meropenem**: Interferes with bacterial cell wall synthesis
  - **Vaborbactam**: Beta-lactamase inhibitor

Meropenem-vaborbactam

- **Spectrum of Activity**:
  - Broad spectrum gram negative coverage, including multi-drug resistant organisms
  - Vaborbactam extends coverage to include some carbapenem-resistant organisms
  - Highly active against many carbapenem-resistant Enterobacteriaceae (CRE)
Meropenem-vaborbactam

• **Dose:** 4 grams IV every 8 hours as a 3-hour infusion
  ▫ Short stability once mixed; 4 hours at room temperature

• **Dose Adjustments:**
  ▫ Hepatic: no dose adjustment
  ▫ Renal: adjust dose based on renal function
  ▫ Hemodialysis: administer dose after hemodialysis

Meropenem-vaborbactam

• **Drug Interactions:**
  ▫ Carbapenems decrease valproic acid levels
  ▫ Concomitant use is not recommended
  ▫ Consider supplemental anticonvulsant therapy if meropenem-vaborbactam is necessary
Meropenem-vaborbactam

• Adverse Effects:
  ▫ Infusion site reactions
  ▫ Headache
  ▫ Diarrhea
  ▫ Potential to cause serious side effects such as seizure or anaphylaxis

Meropenem-vaborbactam

• Trials: TANGO-1
  ▫ Evaluated in randomized, double-blind, double-dummy trial in 545 patients with cUTI
  ▫ Compared meropenem-vaborbactam to piperacillin-tazobactam
  ▫ Primary endpoint was clinical cure and microbial eradication at end of IV therapy: 98.4% of M-V patients and 94% P-T patients
Meropenem-vaborbactam

- **Trials**: TANGO-2
  - Randomized open-label trial of M-V versus “best available therapy” in patients with serious infections caused by CRE
  - Randomization to BAT arm stopped early
    - M-V associated with higher overall cure and lower mortality
    - M-V associated with better safety and better overall risk-benefit

Meropenem-vaborbactam

- **Place in Therapy**:
  - First carbapenem-betalactamase inhibitor combination approved in the United States
  - Reserve for carbapenem-resistant Enterobacteriaceae (CRE)
What is the name of the ten-year-old boy who finds E.T.?

Respiratory

- Glycopyrrolate (Lonhala Magnair®)
Glycopyrrolate

• **Indication:** COPD

• **MOA:** Long-acting anticholinergic

• **Dose:** One vial (25 mcg) inhaled twice daily

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Glycopyrrolate

• **Adverse Effects:**
  - Edema
  - Fatigue
  - UTI

• **Place in Therapy:**
  - First LAMA in nebulizer formulation
  - Performed similarly to tiotropium handihaler in trials
Hematology

- Neratinib (Nerlynx®)

Neratinib

- **Indication**: For the extended adjuvant treatment of early stage HER2-positive breast cancer, following adjuvant trastuzumab-based therapy

- **MOA**: Irreversible tyrosine kinase inhibitor that binds to epidermal growth factor receptor (EGFR), human epidermal receptor type 2 (HER2), and HER4
Neratinib

• Dose:
  ▫ 240 mg (6 x 40 mg) orally once daily with food for 1 year
  ▫ Hepatic impairment:
    • Mild/moderate: no dose adjustment
    • Severe: reduce dose to 80 mg once daily
• Drug Interactions:
  ▫ Avoid concomitant use with proton pump inhibitors and $H_2$-receptor antagonists
  ▫ Administer neratinib 3 hours after antacids

Neratinib

• Adverse Effects:
  ▫ Diarrhea, nausea, abdominal pain
  ▫ Fatigue
  ▫ Skin rash
  ▫ Muscle spasms
  ▫ Elevated LFTs

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>95</td>
</tr>
<tr>
<td>Grade 3</td>
<td>40</td>
</tr>
</tbody>
</table>
Neratinib

- **Antidiarrheal Prophylaxis:**
  - Initiate loperamide with first dose of neratinib and continue through first 2 cycles

<table>
<thead>
<tr>
<th>Time on Neratinib</th>
<th>Loperamide Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2 (days 1-14)</td>
<td>4 mg</td>
<td>TID</td>
</tr>
<tr>
<td>Weeks 3-8 (days 15-56)</td>
<td>4 mg</td>
<td>BID</td>
</tr>
<tr>
<td>Weeks 9-52 (days 57-365)</td>
<td>4 mg</td>
<td>PRN (not to exceed 16 mg/day)</td>
</tr>
</tbody>
</table>

**GI Toxicity**
- Diarrhea
- Dehydration
- Antidiarrheal prophylaxis lowers risk
- May require dose adjustment

**Hepatotoxicity**
- LFTs prior to treatment start
- Monthly for 3 months, then every 3 months
- May require dose adjustment

**Pregnancy**
- Pregnancy test prior to treatment
- Females use contraception until 1 month after last dose
- Males use contraception until 3 months after last dose
Neratinib

- **Trials:** ExteNET
  - Compared to placebo in randomized, double blind study over 12 months
    - Women with stage 1-3 HER2-positive breast cancer who had been treated with trastuzumab (n=2840)
    - Primary outcome invasive disease-free survival at 2 years
      - Neratinib group 93.9% vs. placebo group 91.6%
  - Follow-up analysis: invasive disease-free survival at 5 years
    - Neratinib group 90.2% vs. placebo group 87.7%

Neratinib

- **Place in Therapy:**
  - Extended adjuvant treatment of early-stage, HER2-positive breast cancer in patients previously treated with trastuzumab
  - First extended adjuvant therapy; appears to lower risk of cancer relapse
  - Which patients should receive this therapy?
References


References

• Efficacy and Tolerability (n.d) www.symproic.com/hcp/study-design/primary-endpoint
References


References