NEW DRUG UPDATE

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Objectives

- Identify the new drugs approved by the FDA that are most clinically relevant to general practice in 2017
- Discuss relevant indications, efficacy, pharmacokinetics, safety, and dosing of the new drugs
- Discuss how the new drugs differ from existing drugs on the market
- Describe how to best incorporate the new drugs into clinical practice using a case-based format

FDA Approvals

- 2015
  - 45 New Molecular Entities / New Biologics
  - 35 New Dosage Forms
- 2016
  - 22 New Molecular Entities / New Biologics
  - 41 New Dosage Forms
- 2017 to date
  - 20 New Molecular Entities / 14 New Biologics
  - 25 New Dosage Forms
  - 1 Withdrawal

Withdrawals

- Oxymorphone (Opana ER™)—Endo
  - Requested by FDA to be withdrawn due to concern of benefits no longer outweighing the risks
  - First time FDA has taken steps to remove a currently marketed opioid from sale due to the public health consequences of abuse
  - Post marketing data demonstrated increase in the route of abuse from nasal to injection following reformulation in 2012 (original approval in 2006), intended to make the drug resistant to physical and chemical manipulation for abuse by snorting or injecting
  - Injection abuse of reformulation associated with HIV, hepatitis C, thrombotic microangiopathy
SIGNIFICANT NEW MOLECULAR ENTITIES/BIOLOGICS

Self Assessment Questions
1. Betrixaban (Bevyxxa™) is FDA-approved for which of the following indications?
   A. Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness
   B. Treatment of venous thromboembolism in adult patients hospitalized for acute DVT or PE
   C. Prophylaxis of stroke in patients with atrial fibrillation
2. The spectrum of antimicrobial activity of delafloxacin (Baxdela™) includes which of the following:
   A. Pseudomonas aeruginosa
   B. MRSA
   C. Enterococcus faecalis
   D. All of the above

Self Assessment Questions
3. Which of the following medications is FDA approved for adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes?
   A. Safinamide (Xadago™)
   B. Edaravone (Radicava™)
   C. Valbenazine (Ingrezza™)

4. Biosimilars are considered to be interchangeable with the reference product.
   True or False

Self Assessment Questions
5. Sarilumab (Kevzara™) is a new medication for rheumatoid arthritis approved as second line therapy. What is it’s route of administration?
   A. Oral
   B. Subcutaneous
   C. Intravenous
   D. Intraarticular

6. The new drugs for plaque psoriasis (brodalumab and guselkumab) are antagonist of which of the following:
   A. IL-17 and IL-23
   B. IL-4 and IL-6
   C. Both inhibit TNF

Cardiovascular Drugs

Betrixaban (Bevyxxa™)
Portola Pharm.
- A factor Xa inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE
- First anticoagulant approved for in-hospital and extended-duration VTE prophylaxis in acutely ill medical patients
Betrixaban (Bevyxxa™)
Portola Pharm.

- Efficacy: APEX
  - \(N=7441\)
  - Prevention of VTE in high-risk acutely ill medical patients
  - Eligible patients: \(\geq 75\) years, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE (\(\geq 75\) years of age, 60-74y with D-dimer \(\geq 2\) ULN, or 40-59y with D-dimer \(\geq 2\) ULN and a history of either VTE or cancer; while the APEX Study was ongoing (after 35% enrollment), the study was amended to restrict further enrollment to patients \(\geq 75\)y or with D-dimer values > 2 x ULN)
  - Expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely immobilized for at least 24 hours
  - Causes for hospitalization: heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke

Efficacy and safety: APEX (from package insert)

<table>
<thead>
<tr>
<th></th>
<th>BEVYXXA</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Outcome</td>
<td>165 (4.4)</td>
<td>223 (6.0)</td>
<td>0.75 (0.61, 0.91)</td>
</tr>
<tr>
<td>Asymptomatic Event</td>
<td>133 (3.6)</td>
<td>176 (4.7)</td>
<td>0.71 (0.58, 0.87)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>14 (0.4)</td>
<td>22 (0.6)</td>
<td>0.64 (0.42, 0.98)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>9 (0.2)</td>
<td>18 (0.5)</td>
<td>0.44 (0.27, 0.71)</td>
</tr>
<tr>
<td>VTE-related Death</td>
<td>13 (0.3)</td>
<td>17 (0.5)</td>
<td>0.76 (0.48, 1.20)</td>
</tr>
<tr>
<td>Symptomatic Events (^2)</td>
<td>35 (0.9)</td>
<td>54 (1.5)</td>
<td>0.69 (0.46, 1.02)</td>
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</tbody>
</table>

- Major bleeding: betrixaban (0.67%) vs. enoxaparin (0.57%) (p=0.554)
- Clinically relevant nonmajor bleeding: betrixaban (2.45%) vs. enoxaparin (1.02%) (p=0.801)

Betrixaban (Bevyxxa™)
Portola Pharm.

- Boxed Warning
  - Epidural or spinal hematomas may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture.
  - Risk of these events may be increased by use of in-dwelling epidural catheters or concomitant use of medical products affecting hemostasis.
  - Hematomas may result in long-term or permanent paralysis.

- Contraindications
  - Active pathological bleeding.
  - Severe hypersensitivity reaction to betrixaban.

- Drug Interactions
  - P-glycoprotein (P-gp) inhibitors (amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) increase levels of betrixaban—need to reduce dose of betrixaban.

- Dosing
  - Initial single dose 160mg by mouth, followed by 80mg once daily by mouth, taken at the same time each day with food for 35 to 42 days.
  - Severe renal impairment (CrCl 15-29ml/min): 80mg single dose then 40mg daily.
  - Hepatic impairment: use not recommended.
  - Concomitant use of P-glycoprotein (P-gp) inhibitors: 80mg single dose then 40mg daily.
  - Safety and efficacy not established with prosthetic heart valves as has not been studied.

- Availability/Cost
  - Capsules: 40mg and 80mg.
  - Cost?
Clinical Case

A 76y M is admitted to the hospital for CHF. His past medical history is significant for CHF, HTN, type 2 diabetes, hypercholesterolemia. His home medications included enalapril, carvedilol, furosemide, metformin, aspirin, atorvastatin. NKDA BUN 16 SCr 1

- What would you recommend for VTE prophylaxis in this patient?
- What would this patient be a candidate for betrixaban?

Endocrine Drugs

Abaloparatide Injection (Tymlos™)
Radius Health, Inc.

- A synthetic peptide analog of hPTHrP (human parathyroid hormone-related protein) for the treatment of postmenopausal women with osteoporosis and high fracture risk (defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy)

Abaloparatide Injection (Tymlos™)
Radius Health, Inc.

- Warning: Risk of Osteosarcoma
  - Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma, a malignant bone tumor, in male and female rats. Unknown if will cause osteosarcoma in humans
  - Not recommended in patients at increased risk for osteosarcoma
  - Use for more than 2 years not recommended

- Precautions
  - Orthostatic Hypotension: Instruct patients to sit or lie down if symptoms develop after dose administration
  - Hypercalcemia: Avoid use in patients with pre-existing hypercalcemia and those known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism
  - Hypercalcuria and Urolithiasis: Monitor urine calcium if preexisting hypercalcuria or active urolithiasis are suspected

Abaloparatide Injection (Tymlos™)
Radius Health, Inc.

- Clinical Trials
  - The Phase 3 ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints)—randomized, double-blind, placebo-controlled, comparative, multicenter, 18 month international study in 2,463 postmenopausal women with osteoporosis designed to evaluate the efficacy and safety of abaloparatide-SC 80 mcg to reduce the risk of vertebral and nonvertebral fractures
    - Decreased the incidence of new vertebral (86%) and nonvertebral (43%) fractures (absolute risk reductions 3.6% and 2.0%)
    - Also increased bone mineral density (BMD)
  - ACTIVExtend, an extension of ACTIVE, enrolled patients who had completed 18 months of abaloparatide-SC or placebo in ACTIVE to receive up to 24 additional months of open-label alendronate
    - 186 months recently published

Abaloparatide Injection (Tymlos™)
Radius Health, Inc.

- ADR’s
  - Most common adverse reactions (incidence ≥2%): hypercalcuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, vertigo
Abaloparatide Injection (Tymlos™)  
Radius Health, Inc.  
- **Dosing**  
  - Recommended dose is 80 mcg subcutaneously once daily into periumbilical region of abdomen  
  - Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate  
  - Administer initially where the patient can sit or lie down in case symptoms of orthostatic hypotension occur  
- **Availability**  
  - Injection: 3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient-use prefilled pen  
  - Prefilled pen delivers 30 daily doses of 80 mcg abaloparatide in 40mL of sterile, clear, colorless solution  
  - Pen should be stored in the refrigerator before first use but then can be kept at room temperature for up to 30 days (different than teriparatide)  
- **Cost**  
  - $1625/prefilled pen (1month supply)

Clinical Case

- A 70yo F with osteoporosis with high fracture risk has been intolerant to bisphosphonates for osteoporosis. Her physician has prescribed abaloparatide injection (Tymlos™) for this patient. NKDA  
- The physician wants to know what contraindications and precautions he needs to consider before prescribing abaloparatide?  
- What counselling points would you make with this patient?

**Infectious Diseases Drugs**

Delafloxacin (Baxdela™)—Melinta Therapeutics

- **Spectrum of Activity**  
  - **Gram-positive organisms:**  
    - Staphylococcus aureus (MRSA and MSSA), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus), Streptococcus pyogenes, Enterococcus faecalis  
  - **Gram-negative organisms:**  
    - Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa

Delafloxacin (Baxdela™)—Melinta Therapeutics

- **Efficacy (noninferiority)**

Table 7 Clinical Response at 48–72 hours* in the ITT Population with ABSSSI in Trial 1 and Trial 2

<table>
<thead>
<tr>
<th></th>
<th>BAXDela (500 mg IV)</th>
<th>Vancomycin 15 mg/kg IV</th>
<th>Treatment Difference† (Pooled 95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Trial 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>331</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>Responded, 40%</td>
<td>259 (78.7%)</td>
<td>256 (80.9%)</td>
<td>-2.6 (-4.8, 3.6)</td>
</tr>
<tr>
<td><strong>Trial 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>423</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Responded, 40%</td>
<td>354 (83.5%)</td>
<td>354 (83.5%)</td>
<td>0.0 (-2.0, 2.0)</td>
</tr>
</tbody>
</table>

*Clinical response was defined as an 22% or greater decrease in lesion size by a blinded physician of the leading edge of any lesion at 48–72 hours after initiation of treatment without any increase in SSI.  
†Treatment difference calculated as (BAXDela - Vancomycin) * 100/
Vancomycin
Delafloxacin (Baxdela™)—Melinta Therapeutics

- **Boxed warning:**
  - Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including: tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects
  - Discontinue immediately and avoid the use of fluoroquinolones, including delafloxacin in patients who experience any of these serious adverse reactions
  - Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis—avoid with known history of myasthenia gravis
- **ADR’s**
  - Nausea (8%), diarrhea (8%), headache 3%, LFT’s elevations (3%), vomiting (2%)
**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Efficacy:**
  - Multiple clinical trials of 2,300 adults with genotype 1, 2, 3, 4, 5 or 6 HCV infection without cirrhosis or with mild cirrhosis
  - Results: 92-100% of patients had no virus detected in the blood for 8, 12 or 16 weeks duration

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Boxed warning**
  - WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV. Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Contraindications**
  - Patients with severe hepatic impairment (Child-Pugh C)
  - Coadministration with atazanavir and rifampin

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Warnings and Precautions**
  - Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment
  - Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up
  - Initiate appropriate HBV management as clinically indicated

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **ADRs**
  - Most common (>10%): headache, fatigue, nausea
  - Less common (1-10%): diarrhea, increased bilirubin

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Drug Interactions**: many possible (see package insert)
  - Metabolism/Transport Effects
    - Substrate of BCRP, CYP3A4 (minor), P-glycoprotein, SLCO1B1, SLCO1B3
    - Inhibits BCRP, CYP1A2 (weak), CYP3A4 (weak), P-glycoprotein, SLCO1B1, SLCO1B3, UGT1A1
    - Carbamazepine, efavirenz, and St. John’s wort may decrease concentrations of glecaprevir and pibrentasvir

**Glecaprevir and Pibrentasvir**
(Mavyret™)—AbbVie Inc.

- **Dosing**
  - For chronic hepatitis C (HCV monoinfected or HCV/HIV co-infected patients): Without cirrhosis or with compensated cirrhosis (Child-Pugh class A)
  - Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc
  - Treatment-naive patients:
    - Genotype 1, 2, 3, 4, 5, or 6: Three tablets once daily with food for 8 weeks (without cirrhosis) or 12 weeks (with compensated cirrhosis [Child-Pugh class A]).
  - Treatment-experienced patients:
    - Genotype 1: Prior treatment with an NS5A inhibitor containing regimen without an NS3/4A protease inhibitor: Three tablets once daily with food for 16 weeks
    - Genotype 1: Prior treatment with an NS3/4A protease inhibitor containing regimen without an NS5A inhibitor: Three tablets once daily with food for 12 weeks
    - Genotype 1, 2, 4, 5, or 6: Prior treatment with regimens containing interferon (including PEGylated formulations), ribavirin, and/or sofosbuvir, but no prior treatment with an NS3/4A protease inhibitor or NS5A inhibitor: Three tablets once daily with food for 8 weeks (without cirrhosis) or 12 weeks (with compensated cirrhosis [Child-Pugh class A]).
    - Genotype 3: Prior treatment with regimens containing interferon (including PEGylated formulations), ribavirin, and/or sofosbuvir, but no prior treatment with an NS3/4A protease inhibitor or NS5A inhibitor: Three tablets once daily with food for 16 weeks
**Glecaprevir and Pibrentasvir (Mavyret™)—AbbVie Inc.**

- **Dosing**
  - Renal Impairment
    - No dosage adjustment is required in patients with mild, moderate or severe renal impairment, including those on dialysis
  - Hepatic Impairment
    - No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh A)
    - Not recommended with moderate hepatic impairment (Child-Pugh B) as safety and efficacy have not been established
    - Contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposures of glecaprevir and pibrentasvir

**Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi™)—Gilead Sciences**

- **Availability**
  - Tablets: 100 mg glecaprevir and 40 mg pibrentasvir

- **Cost**
  - $26,400 / 8 weeks

**Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi™)—Gilead Sciences**

- An oral fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, an HCV NS3/4A protease inhibitor, and is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:
  - genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor
  - genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor
  - Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor

**Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi™)—Gilead Sciences**

- **Efficacy**
  - POLARIS-1 (N=340): 12 weeks of treatment in adults with HCV genotype 1, 2, 3, 4, 5 or 6 with or without compensated cirrhosis who had failed prior treatment with an NS5A inhibitor-containing regimen
  - POLARIS-4 (N=353): 12 weeks of treatment in adults with HCV genotypes 1a and 3 with or without compensated cirrhosis who had failed prior treatment with a sofosbuvir-containing regimen that did not include an NS5A inhibitor.
  - Results: 96% achieved the primary endpoint of SVR12, (maintaining undetectable viral load 12 weeks after completing therapy)

**Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi™)—Gilead Sciences**

- **Boxed warning**
  - WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV. Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death

- **Contraindications**
  - Coadministration with rifampin

- **Warnings and Precautions**
  - Risk of Hepatitis B virus reactivation: Test all patients for evidence of current or prior HBV before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate management for HBV infection.
  - Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur with amiodarone particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone not recommended. If no alternative, cardiac monitoring recommended.
Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi™) — Gilead Sciences

- **ADR’s**
  - Most common (>10%)
    - Central nervous system: Headache (21% to 23%), fatigue (17% to 19%)
    - Gastrointestinal: Diarrhea (13% to 14%), nausea (10% to 13%)
    - Hepatic: Increased serum bilirubin (4% to 13%)
  - Less common (1% - 10%)
    - Central nervous system: Insomnia (3% to 6%), depression (≤1%)
    - Dermatologic: Skin rash (2%)
    - Gastrointestinal: Increased serum lipase (2%)
    - Neuromuscular & skeletal: Weakness (4% to 6%)

- **Drug Interactions:** many possible (see package insert)
  - P-gp inducers and/or moderate to potent CYP (2B6, 2C8, 3A4) inducers (St. John’s wort, carbamazepine): may decrease concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir — concomitant use not recommended
  - OATP inhibitors (cyclosporine): may substantially increase exposure of voxilaprevir — use not recommended
  - Velpatasvir and voxilaprevir are inhibitors of drug transporters P-gp, BCRP, OATP1B1, OATP1B3; velpatasvir is inhibitor of OATP2B1
    - Coadministration with drugs that are substrates of these transporters may alter the exposure of such drugs — coadministration with BCRP substrates (methotrexate, Gilead Sciences 9 mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) is not recommended

- **Dosing**
  - Testing prior to the initiation of therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc
  - Chronic hepatitis C (without cirrhosis or with compensated cirrhosis [Child-Pugh class A]): Oral:
    - Genotype 1, 2, 3, 4, 5, or 6 (previously treated with a regimen containing an NS5A inhibitor): One tablet once daily with food for 12 weeks
    - Genotype 1a or 3 (previously treated with a regimen containing sofosbuvir without an NS5A inhibitor): One tablet once daily with food for 12 weeks
  - Renal Impairment
    - No dosage adjustment with mild or moderate renal impairment
    - Safety and efficacy not established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or ESRD requiring hemodialysis
  - Hepatic Impairment
    - No dosage adjustment with mild hepatic impairment (Child-Pugh A)
    - Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to the higher exposures of voxilaprevir (up to 6-fold in non-HCV infected subjects) and safety and efficacy have not been established

- **Availability**
  - Tablets: 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir

- **Cost**
  - $83,600/12 weeks

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Neurology Drugs
Edaravone (Radicava™)  
Mitsubishi Tanabe Pharma  
- A free radical scavenger that relieves the effects of oxidative stress, a likely factor in the onset and progression of amyotrophic lateral sclerosis (ALS)  
- First new treatment for ALS approved in many years  
- Orphan drug status  

Edaravone (Radicava™)  
Mitsubishi Tanabe Pharma  
- Clinical Trials  
  - Edaravone (N=69) vs. placebo (N=68), 24 weeks  
  - Primary efficacy endpoint was change in the ALSFRS-R total scores (12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency), with each item is scored from 0-4, with higher scores representing greater functional ability)  
  - Decline in ALSFRS-R scores from baseline was significantly less in the edaravone-treated patients as compared to placebo (-5.01 vs. -7.50, p=0.0013)  

Edaravone (Radicava™)  
Mitsubishi Tanabe Pharma  
- ADR's  
  - Most common adverse reactions (at least 10% and greater than placebo) are contusion, gait disturbance, and headache  
  - Sulfite sensitivity reactions  

Edaravone (Radicava™)  
Mitsubishi Tanabe Pharma  
- Dosing  
  - The recommended dosage is 60 mg administered as an intravenous infusion over 60 minutes as follows:  
    - Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period  
    - Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods  
- Availability  
  - Injection: 30 mg/100 mL in a single-dose polypropylene bag  
- Cost  
  - $146,000/year  

Clinical Case  
- A 75yo M with Parkinson’s disease is experiencing more “off” episodes. Is there anything that the patient could try?  

Safinamide (Xadago™)  
US WorldMeds  
- A monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing “off” episodes  
- Limitations of Use: Has not been shown to be effective as monotherapy for the treatment of PD
Safinamide (Xadago™)  
US WorldMeds

- Clinical Trials
  - N = 645 with PD who were also taking levodopa and were experiencing “off” time
  - Safinamide patients experienced more beneficial “on” time vs. placebo
  - Increase in “on” time was accompanied by a reduction in “off” time and better scores on a measure of motor function assessed during “on” time than before treatment

Safinamide (Xadago™)  
US WorldMeds

- N = 549 with PD
  - Adding safinamide to levodopa treatment had more “on” time without troublesome uncontrolled involuntary movement compared to those taking a placebo, and also had better scores on a measure of motor function assessed during “on” time than before treatment

<table>
<thead>
<tr>
<th>Table 2: Change in Mean Total Daily “ON” Time in Study 1</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Table 2: Change in Mean Total Daily “ON” Time in Study 1" /></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 3: Secondary Measures of Effectiveness in Study 1</th>
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<tbody>
<tr>
<td><img src="image2.png" alt="Table 3: Secondary Measures of Effectiveness in Study 1" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4: Change in Mean Total Daily “ON” Time in Study 2</th>
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</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Table 4: Change in Mean Total Daily “ON” Time in Study 2" /></td>
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</tbody>
</table>
Safinamide (Xadago™)
US WorldMeds

- Contraindications:
  - Other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (linezolid)
  - Opioid drugs (tramadol, meperidine and related derivatives); selective noradrenephrine reuptake inhibitors; tri- or tetracyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John’s wort; dextromethorphan
  - History of a hypersensitivity to safinamide
  - Severe hepatic impairment (Child-Pugh C)

- Warnings and Precautions:
  - May cause or exacerbate: hypertension; serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs; falling asleep during activities of daily living; dyskinesia; consider levodopa dose reduction; hallucinations and psychotic behavior; problems with impulse control/comulsive behaviors; withdrawal-emergent hyperpyrexia and confusion

- Dosing:
  - Start with 50 mg administered orally once daily at the same time of day; after two weeks, the dose may be increased to 100 mg once daily, based on individual need and tolerability
  - Hepatic Impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment

- Availability:
  - Tablets: 50 mg and 100 mg

- Cost:
  - $700 / 30 day supply (100mg tabs)

Valbenazine (Ingrezza™)
Neurocrine Biosciences

- A vesicular monoamine transporter 2 (VMAT2) inhibitor for treatment of tardive dyskinesia in adults
  - First drug approved in the US for tardive dyskinesia
  - Other VMAT2 inhibitors, tetrabenazine (Xenazine™) and deutetrabenazine (Austedo™) approved for treatment of chorea associated with Huntington’s disease
Valbenazine (Ingrezza™)
Neurocrine Biosciences

- **MOA**
  - Inhibits VMAT2, a transporter that regulates monoamine uptake from the neuronal cytoplasm to the synaptic vesicles for storage and release.
  - Although the exact mechanism of action in the treatment of tardive dyskinesia is not known, the inhibition of VMAT2 reduces synaptic monoamine levels.

- **Clinical Trials:** KINECT 3
  - N = 225 patients with schizophrenia, schizoaffective disorder or a mood disorder, and with moderate or severe tardive dyskinesia, randomized to valbenazine 40 or 80 mg, or placebo once daily, double blind.
  - Primary endpoint was the mean change from baseline to week 6 in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia score.
  - Baseline AIMS dyskinesia score (scale of 0-28): 10.4 in patients randomized to valbenazine 80 mg and 9.9 randomized to placebo.

- **After 6 weeks,** mean change from baseline in AIMS dyskinesia score was significantly greater for valbenazine 80 mg/day (−3.2 vs −0.1); the score was also reduced but not significant for valbenazine 40 mg/day (−1.9).

- **Placebo patients re-randomized after 6 weeks to receive valbenazine 40 or 80 mg once daily for 42 weeks.** After valbenazine was stopped at 48 weeks, AIMS dyskinesia scores returned toward baseline and most patients had a recurrence of symptoms at 52 weeks.

- **ADR’s**
  - Most common ADR: somnolence.
  - QT interval prolongation—should not be used in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval.
  - Active metabolite of valbenazine is the (+)-α-isomer of tetrabenazine (Valbenazine has not been associated with an increased risk of suicidal thoughts and behavior but patients at risk for suicide or violent behavior or with unstable psychiatric symptoms were excluded from clinical trials).

- **Drug Interactions**
  - Valbenazine is metabolized by CYP3A4/5 and its active metabolite by CYP2D6.
  - Concurrent administration of strong CYP3A4 inducers can reduce valbenazine serum concentrations and is not recommended.
  - Coadministration of strong CYP3A4 inhibitors can increase serum concentrations of valbenazine and its active metabolite, and the risk of QT interval prolongation; the dosage of valbenazine should be reduced to 40 mg/day if it is taken concurrently with a strong CYP3A4 inhibitor.
  - CYP2D6 poor metabolizers taking a CYP2D6 inhibitor may need a lower dose of valbenazine.
  - Concurrent administration of monoamine oxidase inhibitors (MAOIs) and valbenazine can increase the risk of serotonin syndrome and should be avoided.

- **Dosing**
  - Recommended dosage of valbenazine is 40 mg once daily orally for 7 days, followed by 80 mg once daily.
  - Patients with moderate or severe hepatic impairment should take 40 mg once daily.
  - Patients at risk of QT interval prolongation should have their QT interval assessed before increasing the dosage of valbenazine.
  - Should not be used in patients with severe renal impairment or in those taking strong CYP3A4 inhibitors or MAOIs.

- **Availability/Cost**
  - Will only be available at select specialty pharmacies.
  - One-year supply of the drug costs $126,600.
Clinical Case

- A 45 year old male with a past medical history of schizophrenia. The patient has been taking quetiapine now for several years but has developed tardive dyskinesia. His past medical history is significant for hypertension for which he takes hydrochlorothiazide. His labs are all WNL.
  - The medical team wants to know what options exist for treating this patient’s tardive dyskinesia?
  - The team wants to begin valbenazine. What considerations should be taken into account for this patient before prescribing?

Clinical Question

- A patient wants to know if there is a less expensive alternative to Remicade™ or Humira™ for his rheumatoid arthritis?

Rheumatology Drugs

Biosimilars

- Biological products are derived from a living organism and can come from many sources, including humans, animals, microorganisms or yeast
  - A biosimilar drug is “highly similar” to an already-approved biological drug and no “clinically meaningful difference” in safety and effectiveness from the original drug, and the newer product has only “minor differences in clinically inactive components” from the original, but not considered “interchangeable” like generics

Infliximab-abda (Renflexis™)
Samsung Bioepis Co. / Merck

- A tumor necrosis factor blocker biosimilar to Remicade™
- 2nd biosimilar to Remicade™ approved in U.S. (infliximab-dyyb [Inflectra™] was first approved in 2016)
- Approved for the treatment of:
  - adult and pediatric Crohn’s disease
  - adult ulcerative colitis
  - rheumatoid arthritis
  - ankylosing spondylitis
  - psoriatic arthritis
  - adult plaque psoriasis
- Cost: $753/100mg (vs. $753/100mg Inflectra™ vs. $1113/100mg Remicade™)

Adalimumab-adbm (Cyltezo™)
Boehringer Ingelheim

- A tumor necrosis factor blocker biosimilar to adalimumab (Humira™)
- Second FDA-approved biosimilar to Humira™ (adalimumab-atto [Amjevita™] was the first approved in 2016)
- Approved for the treatment of adults with:
  - moderately to severely active rheumatoid arthritis
  - active psoriatic arthritis
  - active ankylosing spondylitis
  - moderately to severely active Crohn’s disease
  - moderately to severely active ulcerative colitis
  - moderate-to-severe plaque psoriasis.
- Approved for children aged 4 years or older with:
  - moderately to severely active polyarticular juvenile idiopathic arthritis
  - ?Cost
Sarilumab (Kevzara™) Sanofi-Aventis
- An IL-6 receptor antagonist for second-line treatment of adults with moderate to severe rheumatoid arthritis
- Another IL-6 inhibitor tocilizumab (Actemra™) was approved earlier
- MOA: IL-6 is a pro-inflammatory cytokine that is overproduced in patients with RA and contributes to joint destruction

Efficacy:
- N=1197 moderate to severe RA not responded to methotrexate
- Sarilumab 150 vs. 200mg vs. placebo
- Sarilumab was significantly more effective than placebo in change from baseline in physical function at week 16, rate of ACR20 (66.4%, 58% vs. 33.34%) response at week 24, change in radiologic damage from baseline at week 52

Efficacy: MOBILITY trial
- N=546 DMARD-treated patients with moderately to severely active RA that had not responded to a TNF inhibitor
- Sarilumab 150mg vs. 200 mg vs. placebo added to DMARD therapy
- Sarilumab was significantly more effective than placebo in change from baseline in physical function at week 12, rate of ACR20 (55.8%, 60.9% vs. 33.7%) response at week 24

Efficacy: MONARCH
- N=369 with active RA with inadequate response or intolerance to methotrexate
- Sarilumab 200mg vs. adalimumab 40mg every 2 weeks
- Improvement from baseline on DAS28-ESR disease activity score significantly greater with sarilumab vs. adalimumab (-3.28 vs -2.20) at 24 weeks
- ACR20/50/70 response rates significantly higher with sarilumab (71.7%/45.7%/23.4%) vs. adalimumab (58.4%/29.7%/11.9%) at 24 weeks

ADR’s
- Most common: infection (7%), neutropenia (7%), increased LFT’s (5%), injection site erythema (5%)
- Increased serum lipids possible
- Warnings and Precautions
- Serious Infections: Avoid use during an active infection
- Neutropenia, thrombocytopenia, elevated LFT’s, lipid abnormalities: monitor labs
- Gastrointestinal perforation: risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids
- Hypersensitivity reactions
- Live vaccines: avoid use with due to the risk of infection

Drug Interactions
- Caution when co-administered with CYP substrates with a narrow therapeutic index (e.g. warfarin or theophylline), or with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure and reduced activity of the substrate drug
Sarilumab (Kevzara™)
Sanofi-Aventis
- **Dosing**
  - 200 mg injected subcutaneously every two weeks, with or without methotrexate or another nonbiologic DMARD
  - Reduce dose to 150 mg in patients with neutropenia, thrombocytopenia, and/or increased LFT’s
  - Not recommended in patients with ANC < 2000/mm³, platelets < 150,000/mm³, LFT’s >1.5 times normal
- **Availability/Cost**
  - Syringe: 150mg/1.14ml, 200mg/1.14ml
  - $3000/30days

Clinical Case
- A 50y M with rheumatoid arthritis is no longer responding to methotrexate or Humira™. His past medical history is significant for atrial fibrillation for which he takes warfarin. His labs are otherwise normal. NKDA
- The physician wants to begin sarilumab. What considerations should be taken into account for this patient before prescribing?

Gastrointestinal Drugs

Clinical Case
- A 55yo M with opioid-induced constipation due to MS Contin™ for chronic back pain wants to know if there is anything to help relieve his constipation?

Naldemedine (Symproic™)
Shionogi
- An opioid antagonist for opioid-induced constipation in adult patients with chronic non-cancer pain

Clinical Trials
- COMPOSE program, a global comprehensive development program comprised of clinical studies conducted in adult patients with opioid induced constipation and chronic non-cancer pain
  - Comprised of three studies: COMPOSE I, COMPOSE II and COMPOSE III. COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, while COMPOSE III was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study
### Naldemedine (Symproic™)

**Shionogi**

- **Contraindications/Warnings/Precautions**
  - Patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction
  - Patients with a history of a hypersensitivity reaction to naldemedine
  - Gastrointestinal perforation: Consider the overall risk-benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if development of symptoms
  - Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor symptoms of opioid withdrawal

- **ADR’s**
  - Most common adverse reactions (≥2%) are: abdominal pain, diarrhea, and nausea

- **Drug Interactions**
  - Strong CYP3A inducers (e.g., rifampin): Decreased naldemedine concentrations; avoid concomitant use
  - Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use
  - Moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A4 inhibitors: Increased naldemedine concentrations; monitor for adverse reactions
  - P-gp inhibitors (e.g., cyclosporine): Monitor for adverse reactions

- **Dosing**
  - In adults, the recommended dosage is 0.2 mg once daily orally with or without food
  - Alteration of analgesic dosing regimen prior to initiating naldemedine is not required
  - Patients receiving opioids for less than 4 weeks may be less responsive to naldemedine
  - Discontinue naldemedine if treatment with the opioid pain medication is also discontinued

- **Availability**
  - Tablets: 0.2 mg naldemedine

- **Cost**
  - ?

### Plecanatide (Trulance™)

**Synergy Pharm**

- **Mechanism of Action**
  - A guanylate cyclase-C agonist for chronic idiopathic constipation (CIC)
  - Other drugs for CIC: linaclotide (Linzess™), guanylate cyclase-C receptor agonist and lubiprostone (Amitiza™), a chloride channel activator

- **Table 4: Efficacy Responder Rates in Studies 1 and 2 in Patients with IBS-C and Chronic Non-Cancer Pain**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NALDMEGENE 0.2 mg once daily (N=277)</td>
<td>Placebo (N=277)</td>
<td>Treatment Difference [95% CI]</td>
</tr>
<tr>
<td>Responders (%)</td>
<td>150 (54%)</td>
<td>94 (32%)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.0037</td>
<td>-0.8000</td>
</tr>
</tbody>
</table>

*The primary endpoint was defined as a patient who had at least 3 BM’s per week and a change from baseline of at least 1 BM per week for at least 1 of the 12 study weeks and 3 of the last 4 weeks.

CI = Confidence interval

- **www.trulance.com**

### Plecanatide (Trulance™)

**Synergy Pharm**

- **Mechanism of Action**
  - A synthetic analog of uroguanylin, which is an endogenous guanylate cyclase-C receptor agonist
  - Both plecanatide and its active metabolite bind to guanylate cyclase-C on the luminal surface of the intestinal epithelium, increasing concentrations of cyclic guanosine monophosphate (cGMP)
  - Elevation of intracellular cGMP activates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, which stimulates secretion of chloride and bicarbonate into the intestinal lumen, increasing intraluminal fluid and accelerating intestinal transit
Plecanatide (Trulance™)
Synergy Pharm

- Clinical Trials
  - Over 2500 adults in two 12-week, randomized, double-blind trials of plecanatide 3 mg once daily vs. placebo (one published, one in abstract)
  - A durable overall response, the primary efficacy endpoint, was defined as ≥3 complete spontaneous bowel movements (CSBMs) and at least 1 more CSBM than at baseline for 9 of the 12 treatment weeks and for at least 3 of the last 4 weeks
  - Response rate 21% and 29% with plecanatide vs. 10% and 13% with placebo (stat sig)
  - Plecanatide had an average of about 1 additional CSBM per week compared to those taking placebo (stat sig)
  - Improvements in CSBM frequency occurred within the first week of treatment
  - Plecanatide showed sig greater improvements from baseline in stool consistency and straining during bowel movements than those taking placebo
  - After study period, patients were followed for an additional 2 weeks; those who had taken plecanatide and stopped generally reported a return to baseline of their bowel movement frequency and CIC symptoms

-ADR’s
  - Most common adverse effect: diarrhea (5%) vs. placebo (1%)
  - Severe diarrhea occurred in 0.6% of plecanatide-treated patients and in 0.3% of those taking placebo
  - Dehydration could occur in pediatric patients (seen in young mice studies; plecanatide is contraindicated for use in patients <6 years old and should be avoided in those 6-18 years old
  - Other adverse effects that occurred in <2% of plecanatide-treated patients and at a higher rate than with placebo included abdominal distension, flatulence, abdominal tenderness, and liver enzyme elevations

- Dosing
  - The recommended dosage of plecanatide is one 3-mg tablet once daily taken with or without food orally
  - Tablets can be crushed and mixed with applesauce or water for oral administration or mixed with water and given via nasogastric or gastric tube.
  - Cost
    - $353.50 / 30 days

Brodalumab (Siliq™)
Valeant

- A human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies
- Available only through a restricted program called the Siliq™ REMS Program (due to suicide risk)

- Clinical Trials
  - Safety and efficacy were established in three randomized, placebo-controlled clinical trials with a total of 4,373 adults with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy
  - More patients treated with brodalumab compared to placebo and ustekinumab (Stelara™) had reduction of symptoms and skin that was clear or almost clear, as assessed by scoring of the extent, nature and severity of psoriatic changes of the skin
    - PASI 100 37-44% (B) vs. 19-22% (U) vs. 1% (P)
    - sPGA clear 37-45% (B) vs. 19-21% (U) vs. 1% (P)
**Brodalumab (Siliq™)**
**Valeant**
- **Warnings**
  - Suicidal ideation and behavior
- **Contraindications**
  - Crohn’s disease
- **Warnings and Precautions**
  - Infections: Serious infections have occurred
  - Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment
  - Crohn’s Disease: Crohn’s disease occurred during clinical trials
  - Immunizations: Avoid using live vaccines

**Dosing**
- Administer 210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks

**Availability**
- Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe

**Cost**
- $2400/1 month (2 syringes)

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**Guselkumab (Tremfya™)**
**Janssen Biotech**
- **Efficacy**
  - VOYAGE 1
    - N=837
    - Evaluated the efficacy and safety of guselkumab vs. adalimumab and placebo in adult patients with moderate to severe plaque psoriasis
    - Week 16, 85.1% receiving guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks achieved cleared (IGA 0) or minimal disease (IGA 1) vs. 6.9% placebo (p < 0.001)
    - 73.3% receiving guselkumab achieved a PASI 90 response, or near complete skin clearance, vs. 2.9% of patients receiving placebo (p < 0.001)
    - Week 16, more patients receiving guselkumab achieved IGA 0/1 and PASI 90 (85.1% and 73.3%) compared with adalimumab (65.9% and 49.7%)
    - Week 24, more patients achieved PASI 90 with guselkumab vs. adalimumab (80.2% vs. 53.9%)
    - Higher levels of skin clearance with guselkumab continued through weeks 24 and 48, with significantly more patients receiving guselkumab achieving IGA 0/1 and PASI 90, as well as measures of full skin clearance

  - VOYAGE 2
    - N=992
    - Evaluated the safety and efficacy of guselkumab vs. placebo and adalimumab and of guselkumab maintenance therapy compared with withdrawal of therapy in adult patients with moderate to severe plaque psoriasis
    - At week 16, 84.1% receiving guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks achieved an Investigator’s Global Assessment (IGA) score of cleared (0) or minimal (1) disease vs. 8.5% of those receiving placebo (P < 0.001)
    - 70.0% of patients receiving guselkumab achieved a Psoriasis Area Severity Index (PASI) 90 score (near complete skin clearance) compared with 2.4% of patients receiving placebo (P < 0.001)

  - NAVIGATE
    - N=268
    - Evaluated guselkumab in patients who had an inadequate response to treatment with ustekinumab (Stelara™) for 24 weeks
    - More patients on guselkumab compared to ustekinumab achieved an IGA score of 0 or 1 (considered cleared or almost cleared) with a ≥2 grade improvement at Week 28 (31% vs 14%, respectively; 12 weeks after randomization)
**Guselkumab (Tremfya™)**

**Janssen Biotech**

- **Warnings and Precautions:**
  - Infections: May increase the risk of infection. If a serious infection develops, discontinue.
  - Tuberculosis (TB): Evaluate for TB prior to initiating treatment
- **ADR’s**
  - Most common (≥1%): upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, herpes simplex infections
- **Drug Interactions**
  - Avoid use of live vaccines

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**Dupilumab (Dupixent™)**

**Regeneron**

- **An IL-4RA antagonist for moderate to severe eczema (atopic dermatitis) that has not responded to topical therapies**
  - Can be used with or without topical corticosteroids

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**Clinical Trials**

- Randomized, double-blind, 12-week trial: N = 109 adults with moderate to severe atopic dermatitis poorly controlled with topical agents
- Weekly subcutaneous injections of dupilumab 300 mg showed significantly greater improvements in scores on the Eczema Area and Severity Index (EASI) than those given placebo injections
- Complete or almost complete clearing of skin lesions occurred in 40% of patients treated with dupilumab versus 7% of those who received placebo
- Pruritus scores decreased by 56% with dupilumab compared to 15% with placebo

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**Clinical Trials**

- 2 randomized, double-blind, 16-week trials (SOLO 1 and SOLO 2) in a total of 1379 adults with moderate to severe atopic dermatitis inadequately controlled on topical therapy
- Dupilumab monotherapy was significantly more effective than placebo primary endpoint of a score of 0 or 1 (clear or almost clear) on the Investigator’s Global Assessment (IGA) and a reduction of ≥2 points on that score from baseline
- Primary endpoint occurred in 37% and 36% of patients who received dupilumab weekly in the two trials and in 38% and 36% of those who received the drug every other week, compared to 10% and 8% with placebo
- Dupilumab associated with significantly more frequent improvement of at least 75% on the EASI score (EASI-75), reduced pruritus (a significant reduction in itching was apparent by the second week of treatment), and improved quality of life vs. placebo
Dupilumab (Dupixent™) Regeneron

- ADR's
  - Injection site reactions (mostly mild or moderate)
  - Conjunctivitis (10%)
  - Keratitis and blepharitis
  - Oral herpes (4%) and other herpes simplex virus infections (2%)
- Drug Interactions
  - Increased levels of cytokines such as IL-4 and IL-13 can alter CYP enzyme formation
  - Antagonism of these cytokines by dupilumab could, therefore, affect CYP enzyme activity
  - Dose adjustments may be required for CYP substrates taken concomitantly with dupilumab

Self Assessment Questions

1. Betrixaban (Bevyxxa™) is FDA-approved for which of the following indications?
   A. Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness
   B. Treatment of venous thromboembolism in adult patients hospitalized for acute DVT or PE
   C. Prophylaxis of stroke in patients with atrial fibrillation

2. The spectrum of antimicrobial activity of delafloxacin (Baxdela™) includes which of the following:
   A. Pseudomonas aeruginosa
   B. MRSA
   C. Enterococcus faecalis
   D. All of the above

3. Which of the following medications is FDA approved for adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes?
   A. Safinamide (Xadago™)
   B. Edaravone (Radicava™)
   C. Valbenazine (Ingrezza™)

4. Biosimilars are considered to be interchangeable with the reference product.
   True or False

5. Sarilumab (Kevzara™) is a new medication for rheumatoid arthritis approved as second line therapy. What is its route of administration?
   A. Oral
   B. Subcutaneous
   C. Intravenous
   D. Intraarticular

6. The new drugs for plaque psoriasis (brodalumab and guselkumab) are antagonist of which of the following:
   A. IL-17 and IL-23
   B. IL-4 and IL-6
   C. Both inhibit TNF

Informational Slides

- These medications will not be discussed in detail during the lecture based on time limitations
- The use of these medications will be more in specialty areas of practice and less use in general practice but are provided to the audience as a reference
Hematology/Oncology

- Ribociclib (Kisqali™)—Novartis
  - Selective cyclin-dependent kinase inhibitor indicated for the combination treatment of postmenopausal women with HR+/HER2-negative metastatic breast cancer

- Midostaurin (Rydapt™)—Novartis
  - Oral, multi-targeted kinase inhibitor for treatment of acute myeloid leukemia (AML) in newly-diagnosed adults with an FMS-like tyrosine kinase-3 (FLT3) mutation, and for treatment of advanced systemic mastocytosis (SM), which includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) and mast cell leukemia

Hematology/Oncology

- Durvalumab (Imfinzi™)—AstraZeneca
  - An anti-PD-L1 (programmed death ligand-1) human monoclonal antibody for the treatment of patients with locally advanced or metastatic urothelial carcinoma

- Brigatinib (Alunbrig™)—Ariad Pharm
  - A kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Hematology/Oncology

- Avelumab (Bavencio™)—EMD Serono
  - A monoclonal antibody for metastatic Merkel cell carcinoma and urothelial carcinoma

- Neratinib (Nerlynx™)—Puma Biotechnology
  - A tyrosine kinase inhibitor for the extended adjuvant treatment of early-stage HER2-positive breast cancer

- Niraparib (Zejula™)—Tesaro
  - An oral, poly ADP-ribose polymerase (PARP) inhibitor for the maintenance treatment of patients with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer

- Telotristat (Xermelo™)—Lexicon Pharm
  - An oral tryptophan hydroxylase inhibitor indicated for use in combination with somatostatin analog (SSA) therapy for the treatment of carcinoid syndrome diarrhea in patients with metastatic neuroendocrine tumors
**Hematology/Oncology**

- **Factor IX, glycopegylated (Rebinyn™)**—Novo Nordisk
  - An extended-half-life recombinant DNA-derived coagulation factor IX concentrate for the treatment and control of bleeding episodes in patients with hemophilia B

- **Rituximab/Hyaluronidase (Rituxan Hycela™)**—Genentech
  - New formulation in adults for: follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL)
  - Hyaluronidase human is an enzyme that helps to deliver rituximab subcutaneously, allowing the drug to be infused in minutes instead of hours IV

**Endocrine Drugs**

**Etelcalcetide (Parsabiv™)** Amgen
- A calcium-sensing receptor agonist for secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis

https://www.multivu.com/players/English/8004551-amgen-parsabiv-fda-approval/

**Etelcalcetide (Parsabiv™)** Amgen
- **Limitations of Use:**
  - Has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations

**Etelcalcetide (Parsabiv™)** Amgen
- **Warnings and Precautions**
  - Hypocalcemia (sometimes severe)
  - Worsening Heart Failure
  - Upper Gastrointestinal (GI) Bleeding
  - Adynamic Bone (if PTH levels are chronically suppressed)

**Etelcalcetide (Parsabiv™)** Amgen
- **Clinical Trials**
  - Two 26-week, randomized, double-blind, placebo-controlled trials, total of 1,023 patients with moderate-to-severe secondary HPT (PTH greater than 400 pg/mL) on hemodialysis randomized to IV etelcalcetide or placebo 3 times a week, at end of dialysis and standard care of vitamin D and/or phosphate binders
  - Primary endpoint: proportion of patients achieving greater than 30% reduction from baseline in PTH during Efficacy Assessment Phase (EAP) (weeks 20 - 27)
  - Secondary endpoints included the proportion of patients with PTH less than or equal to 300 pg/mL during the EAP, and % reductions in PTH, albumin-adjusted calcium (cCa), phosphate (P) and cCa x P during the EAP
  - Both studies showed significantly more etelcalcetide vs. placebo patients:
  - Greater than 30% reduction from baseline in PTH during the EAP: 77% vs. 11% in Study 1, and 79% vs. 11% in Study 2
  - PTH levels 300 pg/mL or less during EAP: 52% vs. 6% Study 1, 56% vs. 5% Study 2
  - Also, greater percent reduction from baseline achieved with etelcalcetide than placebo during the EAP, for PTH, corrected calcium and phosphate
**Etelcalcetide (Parsabiv™)**
Amgen

- **Most common adverse reactions (≥ 5%)** were muscle spasms (12%), diarrhea (11%), nausea (11%), vomiting (9%), headache (8%), hypocalcemia, paresthesia (6%)

**Dosing**
- Recommended starting dose is 5 mg by intravenous bolus injection three times per week at the end of hemodialysis treatment (into venous line of dialysis circuit)
- Maintenance dose is individualized and determined by titration based on parathyroid hormone (PTH) and corrected serum calcium response. The dose range is 2.5 to 15 mg three times per week
- Dose may be increased in 2.5 mg or 5 mg increments no more than every 4 weeks
- Measure serum calcium 1 week after initiation or dose adjustment and every 4 weeks for maintenance and measure PTH 4 weeks from initiation or dose change
- Decrease or temporarily discontinue if PTH levels below the target range; decrease or temporarily discontinue or use concomitant therapies to increase corrected serum calcium with a corrected serum calcium below the lower limit of normal but at or above 7.5 mg/dL without symptoms of hypocalcemia; stop and treat hypocalcemia if the corrected serum calcium falls below 7.5 mg/dL or symptoms of hypocalcemia

**Availability**
- Injection: 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL solution in a single-dose vial

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**Deflazacort (Emflaza™)**
Marathon Pharm

- An oral corticosteroid for Duchenne muscular dystrophy patients 5 years of age and older

**Clinical Trials**
- N = 196 male patients who were 5-15 years old at the beginning of the trial with documented mutation of the dystrophin gene and onset of weakness before age 5
  - At week 12, patients taking deflazacort had improvements in a clinical assessment of muscle strength across a number of muscles vs. placebo
  - An overall stability in average muscle strength was maintained through the end of study at week 52 in the deflazacort-treated patients
- N = 29 male patients of 104 weeks
  - Deflazacort had greater assessment of average muscle strength
  - Deflazacort patient appeared to lose the ability to walk later than those treated with placebo

**Warnings/Precautions**
- **Alterations in Endocrine Function**
- **Immunosuppression and Increased Risk of Infection**
- **Alterations in Cardiovascular/Renal Function**
- **Gastrointestinal Perforation**
- **Behavioral and Mood Disturbances**
- **Effects on Bones**
- **Ophthalmic Effects**
- **Vaccination**: Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids
- **Serious Skin Rashes**
### Deflazacort (Emflaza™)
**Marathon Pharm**
- **ADR's**
  - The most common adverse reactions (≥ 10%): Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiauria, hirsutism, central obesity, nasopharyngitis
- **Drug Interactions**
  - Moderate or strong CYP3A4 inhibitors: Give one third of the recommended dosage of deflazacort
  - Avoid use of moderate or strong CYP3A4 inducers with deflazacort as they may reduce efficacy

### Dosing
- The recommended once-daily dosage is approximately 0.9 mg/kg/day administered orally
- Discontinue gradually when administered for more than a few days

### Availability
- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg
- Oral Suspension: 22.75 mg/mL

### Cost
- Depends on patient's weight/dose
- 18mg tabs: $4100/30 tabs
- 30mg tabs: $6900/30 tabs
- 36mg tabs: $7700/30 tabs

### Ocrelizumab (Ocrevus™)
**Genentech**
- A humanized monoclonal antibody designed to selectively target CD20-positive B cells (a specific type of immune cell thought to be a key contributor to myelin and axonal nerve cell damage)
- Indicated as a treatment for both relapsing (RMS) and primary progressive (PPMS) forms of multiple sclerosis

### Clinical Trials
- **OPERA I and OPERA II**: Phase III, randomized, double-blind, double-dummy, global multi-center studies evaluating the efficacy and safety of ocrelizumab (600 mg administered by intravenous infusion every six months) compared with interferon beta-1a (44 mcg administered by subcutaneous injection three times per week) in 1,656 people with relapsing forms of MS (relapsing MS (RMS) was defined as relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) with relapses)
- **ORATORIO**: Phase III, randomized, double-blind, global multi-center study evaluating the efficacy and safety of ocrelizumab (600 mg administered by intravenous infusion every six months; given as two 300 mg infusions two weeks apart) compared with placebo in 732 people with PPMS. The blinded treatment period of the ORATORIO study continued until all patients had received at least 120 weeks of either ocrelizumab or placebo and a predefined number of confirmed disability progression (CDP) events was reached overall in the study

### Clinical Trials: Ocrevus
- **A 24% relative risk reduction in CDP sustained for at least 12 weeks compared with placebo, as measured by the EDSS (p=0.0321)**
- **-0.39 cm³ mean change in volume of brain hyperintense T2 lesions compared with a 0.79 cm³ mean change in volume of placebo-treated patients over 120 weeks (p < 0.0001)**
- **25% relative risk reduction in the proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks**

- **46% and 47% relative reduction in the annualized relapse rate (ARR) compared with interferon beta-1a over the two-year period in OPERA I and OPERA II, respectively (p < 0.0001 and p < 0.0001)***
- **40% relative risk reduction in confirmed disability progression (CDP) sustained for 12 weeks compared with interferon beta-1a in a pooled analysis of OPERA I and OPERA II, as measured by the Expanded Disability Status Scale (EDSS) (p=0.0006)**
- **94% and 95% relative reduction in the total number of T1-gadolinium-enhancing lesions compared with interferon beta-1a in OPERA I and OPERA II, respectively (p < 0.0001 and p < 0.0001)***
- **77% and 83% relative reduction in the total number of new and/or enlarging T2 lesions compared with interferon beta-1a in OPERA I and OPERA II, respectively (p < 0.0001 and p < 0.0001)***
Ocrelizumab (Ocrevus™) Genentech

- **Contraindications**
  - Active hepatitis B virus infection
  - History of life-threatening infusion reaction to ocrelizumab
- **Warnings and Precautions**
  - Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue if a life-threatening or disabling infusion reaction occurs.
  - Infections: Delay administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.
  - Malignancies: Increased risk of malignancy, including breast cancer.
- **ADR’s**
  - The most common adverse reactions were:
    - RMS (incidence ≥10% and > REBIF): upper respiratory tract infections and infusion reactions.
    - PPMS (incidence ≥10% and > placebo): upper respiratory tract infections, skin infections, and lower respiratory tract infections.
- **Dosing**
  - Hepatitis B virus screening is required before the first dose.
  - Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (diphenhydramine) prior to each infusion.
  - Administer by intravenous infusion: Start dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion. Subsequent doses: 600 mg intravenous infusion every 6 months.
  - Must be diluted prior to administration.
  - Monitor patients closely during and for at least one hour after infusion.
- **Availability**
  - Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial.
  - Cost: $65,000/year.

Deutetrabenazine (Austedo™) Teva

- **Clinical Trials**
  - Randomized, double-blind, placebo-controlled, multi-center trial.
  - N = 90 ambulatory patients with manifest chorea associated with Huntington’s disease.
  - Total Maximal Chorea Scores for patients improved by approximately 4.4 units from baseline to the maintenance period (average of Week 9 and Week 12), compared to approximately 1.9 units in the placebo group.
  - Treatment effect of -2.5 units was statistically significant (p<0.0001).
  - The Maintenance Endpoint is the mean of the Total Maximal Chorea Scores for the Week 9 and Week 12 visits—actual the Week 13 follow-up visit (1 week after discontinuation of the study medication), the Total Maximal Chorea Scores of patients who had received deutetrabenazine returned to baseline.

- **Warnings/Contraindications/Precautions**
  - Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington’s disease.
  - Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation.
  - Contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.
  - Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs.
  - Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs.
  - Sedation/somnolence: May impair the patient’s ability to drive or operate complex machinery.
Deutetrabenazine (Austedo™)  
Teva
- ADR’s
  - Most common adverse reactions (>8% of AUSTEDO-treated patients and greater than placebo) were: somnolence, diarrhea, dry mouth, and fatigue
- Drug Interactions
  - Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose is 36 mg per day (18 mg twice daily)
  - Alcohol or other sedating drugs: May have additive sedation and somnolence

Deutetrabenazine (Austedo™)  
Teva
- Dosing
  - Starting dose is 6 mg once daily orally with food
  - Titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum recommended daily dosage of 48 mg (24 mg twice daily)
  - Swallow tablets whole; do not chew, crush, or break
  - If switching patients from tetrabenazine, discontinue tetrabenazine and initiate deutetrabenazine the following day
  - Maximum recommended dosage in poor CYP2D6 metabolizers is 36 mg per day (18 mg twice daily)
- Availability
  - Tablets: 6 mg, 9 mg, and 12 mg

Miscellaneous

House Dust Mite Allergen Extract (Odactra™)  
Merck
- A sublingual tablet allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to Dermatophagoides farinae or Dermatophagoides pteronyssinus house dust mites, or skin testing to licensed house dust mite allergen extracts
- Approved for use in adults 18 through 65 years

House Dust Mite Allergen Extract (Odactra™)  
Merck
- Clinical Trials
  - Studies conducted in the United States, Canada and Europe, involving approximately 2,500 participants
  - Participants reported their symptoms and the need to use symptom-relieving allergy medications
  - During treatment, participants taking house dust mite allergen extract experienced a 16%-18% reduction in symptoms and the need for additional medications vs. placebo

House Dust Mite Allergen Extract (Odactra™)  
Merck
- Warning: Severe Allergic Reactions
  - Can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction
  - Do not administer to patients with severe, unstable or uncontrolled asthma
  - Also caution with severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy, history of eosinophilic esophagitis
  - Observe patients in the office for at least 30min following initial dose
  - Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use
  - May not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction
  - May not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators such as those taking beta-blockers
House Dust Mite Allergen Extract (Odactra™)
Merck

- ADR's
  - The most common adverse reactions reported in ≥10%: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, tongue swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore in the mouth, and taste alteration/food tastes different

Dosing
- For sublingual use only
- One tablet daily
- Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute.
- Administer the first dose of ODACTRA under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose

Availability
- Tablet, 12 SQ-HDM

Cost
- ?

Miscellaneous

- C1 Esterase Inhibitor (Haegarda™)—CSL Behring
  - A low-volume subcutaneous C1-esterase inhibitor replacement therapy to prevent Hereditary Angioedema (HAE) attacks

- Cerliponase Alfa (Brineura™)—BioMarin
  - An enzyme replacement therapy for the restoration of tripeptidyl peptidase-1 (TPP1) enzyme activity in patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), or TPP1 deficiency, a form of Batten disease

Selected References
- Various online references, databases, and review/primary literature were used in preparation of this lecture that were accessed August 2017. These included but were not limited to: The Medical Letter, Pharmacist’s Letter, Clinical Pharmacology, Lexicomp, Micromedex, FDA.gov website, Drugs.com, primary literature.