2016 NEW DRUG UPDATE

Mark S. Johnson, Pharm.D., BCPS
Professor and Vice Chair Department of Pharmacy Practice
Director of Postgraduate Education
Bernard J. Dunn School of Pharmacy
Shenandoah University

Objectives

- Identify the new drugs approved by the FDA that are most clinically relevant to general practice in 2016/late 2015
- Discuss relevant indications, efficacy, pharmacokinetics, safety, and dosing of the new drugs
- Discuss how the new drugs differ from existing drugs on the market
- Determine how to best incorporate the new drugs into clinical practice using a case-based format

FDA Approvals

- 2015
  - 45 New Molecular Entities / New Biologics
  - 34 New Dosage Forms
- So far in 2016
  - 16 New Molecular Entities / New Biologics
  - 25 New Dosage Forms

Withdrawals

- 2015
  - Levetiracetam extended-release (Epilepsia XR™): Sun Pharma
    - FDA revoked approval due to manufacturing quality problems
- 2016
  - Niacin ER/Lovastatin (Advicor™), Niacin ER/Simvastatin (Simcor™): AbbVie
    - Withdrawn due to safety and efficacy
Clinical Case

A 70yo F with atrial fibrillation who takes dabigatran (Pradaxa™) 150mg PO Q12h for stroke prevention. She falls while walking and hits her head. CT scan reveals a large subdural hematoma. What can be given to reverse the bleeding? NKDA

Idarucizumab (Praxbind™)—Boehringer Ingelheim

• A monoclonal antibody to reverse the anticoagulant effects of dabigatran for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding
• Approved under the FDA’s accelerated approval program (drugs for serious conditions that fill an unmet medical need based on an effect on a surrogate or an intermediate clinical endpoint likely to predict a clinical benefit to patients)

Idarucizumab (Praxbind™)—Boehringer Ingelheim

• MOA
  • A humanized monoclonal antibody fragment that binds to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, and as a result neutralizing their anticoagulant effect

Idarucizumab (Praxbind™)—Boehringer Ingelheim

• Efficacy
  • Three trials involving a total of 283 healthy volunteers
  • Immediate reduction in the amount of dabigatran in blood (unbound dabigatran plasma concentration) that lasted for a period of at least 24 hours
Idarucizumab (Praxbind™)—Boehringer Ingelheim

- **Efficacy:** RE-VERSE AD Trial (ongoing)
  - 300 patients planned
  - 123 patients taking dabigatran who received idarucizumab due to uncontrolled bleeding or because they required emergency surgery
  - Anticoagulant effect of dabigatran was fully reversed in 89% of patients within four hours of receiving idarucizumab

- **ADR’s**
  - In healthy volunteers, the most frequently reported adverse reactions > 5% was headache
  - In patients, the most frequently reported adverse reactions >5% were hypokalemia, delirium, constipation, pyrexia, pneumonia

- **Warnings and Precautions:**
  - Thromboembolic Risk—resume anticoagulation as soon as possible
  - In patients with elevated coagulation parameters and reappearance of clinically relevant bleeding or requiring a second emergency surgery/urgent procedure, an additional 5 g dose may be considered
  - Hypersensitivity reactions

- **Dosing**
  - 5 g IV, provided as two separate vials each containing 2.5 g/50 mL idarucizumab
  - Given as two IV infusions no more than 15 minutes apart or by bolus injection by injecting both vials consecutively one after another via syringe
  - Limited data to support administration of an additional 5 g
  - Cost: $3500/5g

Clinical Case

- A 60yo M is currently receiving treprostinil (Orenitram) for pulmonary arterial hypertension. It is quite expensive (around $12,000 per month). Are there any new oral prostacyclin agonists that could be tried for this patient?

Selexipag (Uptravi™)—Actelion

- Prostacyclin receptor agonist for pulmonary arterial hypertension
- FDA-approved treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH

https://www.actelionpathways.com
Selexipag (Uptravi™)—Actelion

**MOA:**
- prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin
- activation of the IP receptor causes relaxation of vascular smooth muscle
- hydrolyzed by carboxylesterase 1 to yield its active metabolite (37-fold as potent as selexipag)
- selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP1-4, DP, FP and TP) and thus may have reduced GI effects (nausea and vomiting)

**Efficacy:**
- Safety and efficacy established in a long-term clinical trial of 1,156 participants with PAH (Class I-IV) x 1.4y vs. placebo (GRIPHON)
- 40% reduction of primary endpoint primarily by reducing hospitalization for PAH and reducing the risks of disease progression
- No mortality data

**ADR’s (>5%):**
- headache
- diarrhea, nausea, vomiting
- jaw pain, pain in extremity
- myalgia
- flushing

**Drug Interactions:**
- Strong CYP2C8 inhibitors (gemfibrozil): increased selexipag levels

**Dosing:**
- 200mcg PO twice daily
- May take with food to improve tolerability
- Increased in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily
- If a dose cannot be tolerated, the dose should be reduced to the previous tolerated dose
- Do not split, crush, or chew tablets

**Availability**
- 200mcg, 400mcg, 600mcg, 800mcg, 1000mcg, 1200mcg, 1400mcg, 1600mcg tablets
- Cost: $14,520/30days

**Renal Drugs**

**Clinical Case**
- A 70 F with CHF and CKD has had a steady increase in her K over the last year. It is now 5.4mEq/L. She currently is on an ACE-I and you want to continue it if possible. What are the options to lower this patient’s potassium and maintain the patient on an ACE-I?
Patiromer (Veltassa™)—Relypsa

- Oral potassium binder for hyperkalemia
- Should not be used as emergency treatment for life-threatening hyperkalemia due to its delayed onset of action


Patiromer (Veltassa™)—Relypsa

- MOA:
  - A cation exchange polymer that contains a calcium-sorbitol counterion
  - Fecal potassium excretion is increased through binding of potassium in the GI lumen, with colon the principle site of action

Patiromer (Veltassa™)—Relypsa

- Efficacy:
  - AMETHYST-DN
    - Open label trial, N=306
    - Daily administration of the potassium-binding agent safely controlled hyperkalemia over 1 year in patients with type 2 diabetes and hypertension with or without heart failure with mild to moderate hyperkalemia secondary to treatment with renin-angiotensin-aldosterone-system (RAAS)-inhibiting drugs
    - Decreased K 0.35-0.55 mEq/L in mild HK (5-5.5mEq/L) and 0.87-0.92 mEq/L in mod HK (5.5-6mEq/L)

Patiromer (Veltassa™)—Relypsa

- Efficacy:
  - OPAL-HK trial
    - 107 patients whose serum potassium levels had fallen below 5.1 mEq/L after 4 weeks of treatment were randomized to continue patiromer or switch to placebo
    - Median increase in K after 8 weeks was significantly greater in patients switched to placebo than in those who continued taking the active drug (0.72 vs 0 mEq/L)
    - Those who continued patiromer were less likely to have recurrent hyperkalemia than those switched to placebo (15% vs 60%) and more likely to remain on a RAAS inhibitor (94% vs 44%)

Patiromer (Veltassa™)—Relypsa

- ADR’s:
  - constipation
  - hypomagnesemia
  - diarrhea
  - nausea
  - abdominal discomfort
  - flatulence

Patiromer (Veltassa™)—Relypsa

- Drug Interactions:
  - Patiromer binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness
  - Administer other oral medications at least 6 hours before or 6 hours after patiromer
**Patiromer (Veltassa™)—Relypsa**

- **Dosing:**
  - Starting dose: 8.4gm once daily
  - May be increased or decreased to reach the desired serum potassium concentration, up to a maximum dose of 25.2gm once daily
  - Dose can be up-titrated based on serum potassium level at 1-week or longer intervals, in increments of 8.4gm

**Insulins**

- **Insulin glargine injection (Basaglar™)—Eli Lilly**
  - Long-acting human insulin analog to improve glycemic control in adult and pediatric patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus
  - First insulin product approved through an abbreviated approval pathway under the Federal Food, Drug, and Cosmetic Act
  - Not classified as a “biosimilar” by FDA since no insulin glargine products are currently licensed under the Public Health Service Act and thus no reference product—classified as “follow-on” therapy
  - Identical amino acid sequence as Lantus™

**Clinical Question**

- A DM patient wants to know if there is a cheaper alternative to Lantus™?

**Insulins**

- **Insulin glargine injection (Basaglar™)—Eli Lilly**
  - Approval based on the safety and effectiveness data for Lantus™
  - Also Basaglar™ specific data on the drug’s safety and efficacy clinical trials enrolling 534 and 744 patients with type 1 and 2 diabetes mellitus
  - Recent FDA approval follows tentative U.S. approval in August 2014, which was contingent upon patent litigation resolution—per the settlement agreement with Sanofi, Basaglar™ will be available in the U.S. starting on Dec 15, 2016

**Endocrine Drugs**

**Patiromer (Veltassa™)—Relypsa**

- **Availability:**
  - 8.4g, 16.8g, 25.2g Powder for Suspension (packets)
- **Cost:**
  - $595/30 packets
Insulins

- Insulin glargine injection (Basaglar™)—Eli Lilly
  - Available as Basaglar KwikPen™ (100u/ml)
  - Cost?

- Insulin glargine (Toujeo™)—Sanofi-Aventis
  - U-300 strength long-acting insulin for DM
  - More gradual and prolonged release from the subcutaneous depot than Lantus™, results in more even activity throughout the dosing interval and a longer duration of action, but may reduce the bioavailability
  - As effective as Lantus™ in lowering HgA1c but may cause less hypoglycemia
  - Availability: 1.5ml SoloStar pen (300IU/ml)
  - Cost: $335.50/30 days

- Insulin degludec (Tresiba™)—Novo Nordisk
  - Long-acting basal insulin analogue indicated to improve glycemic control in adults with type 1 and 2 DM
  - Long half life (25h)—once daily dosing, but does not have to be at same time each day
  - Forms multihexamers in subcutaneous tissue (delays absorption) and binds to circulating albumin (delays elimination)—results in a prolonged duration of action (>42 hours)

- Insulin degludec and Insulin aspart (Ryzodeg 70/30™)—Novo Nordisk
  - Long-acting basal insulin analogue and rapid-acting insulin analogue indicated to improve glycemic control in adults with type 1 and 2 DM
  - Availability: 3ml (100u/ml) FlexTouch pen

- Lixisenatide (Adlyxin™)—Sanofi
  - Glucagon-like peptide-1 receptor agonist approved as adjunct to diet/exercise for type 2 diabetes
  - Approved as Lyxumia™ in over 60 countries
Lixisenatide (Adlyxin™)—Sanofi

- Efficacy
  - FDA-approval based on The GetGoal clinical program of 13 clinical trials of 5,400 adults with type 2 diabetes worldwide, evaluated the safety and efficacy of lixisenatide in adults with type 2 diabetes
  - Monotherapy: significantly reduced HbA1c vs. placebo (-0.77% and -0.94% vs -0.27%; baseline HbA1c 8%); HbA1c < 7% achieved by 52.2% and 46.5% lixisenatide vs. 26.8% placebo
  - Combination Therapy: significantly reduced HbA1c vs. placebo (-0.7% to -0.9%) with lixisenatide added: with metformin with or without sulfonylureas, sulfonylureas with or without metformin, pioglitazone with or without metformin, basal insulin with or without sulfonylureas or metformin, basal insulin plus metformin with or without a thiazolidinedione

Lixisenatide (Adlyxin™)—Sanofi

- Efficacy: Comparison trials
  - Lixisenatide + metformin was noninferior to exenatide twice daily + metformin (-0.79% vs -0.96%)
  - HbA1c < 7% (48.5% vs 49.8%)
  - Lixisenatide lower rate of symptomatic hypoglycemia and less nausea
  - Lixisenatide + insulin glargine with or without metformin was noninferior to combination of insulin glargine and insulin glulisine (once or 3 times daily), with or without metformin (-0.6% vs -0.6% (insulin glulisine once daily) and -0.8% (insulin glulisine 3 times daily)

Lixisenatide (Adlyxin™)—Sanofi

- ADR’s
  - Most common: nausea, vomiting, headache, diarrhea, dizziness, hypoglycemia
  - ELIXA trial
  - CV safety trial required by FDA
    - Lixisenatide did not increase risk of CV ADR’s in over 6000 type 2 DM patients at risk for atherosclerotic CV disease
  - FDA is requiring the following post-marketing studies
    - Clinical studies to evaluate dosing, efficacy and safety in pediatric patients
    - A study evaluating the immunogenicity of lixisenatide

Lixisenatide (Adlyxin™)—Sanofi

- Drug Interactions
  - Lixisenatide delays gastric emptying
  - May delay absorption of antibiotics, acetaminophen
  - Give 1 hour before lixisenatide
  - Oral contraceptives
    - Take 1 hour before or 11 hours after lixisenatide

Lixisenatide (Adlyxin™)—Sanofi

- Dosing
  - Day 1-14: 10mcg subcut OD
  - Day 15 and further: 20mcg subcut OD
  - Once daily within 1 hour before first meal
  - Subcut in abdomen, thigh, upper arm

- Availability
  - 50mcg/ml in 3ml green prefilled pen (14 pre-set doses; 10mcg/dose)
  - 100mcg/ml in 3ml burgundy prefilled pen (14 pre-set doses; 20mcg/dose)
<table>
<thead>
<tr>
<th>ID Drugs</th>
</tr>
</thead>
</table>

## Clinical Question

- How does the new influenza vaccine compare to what’s already on the market and who would it be indicated for?
- What should a patient do to prevent cholera if traveling to an endemic area?

### Influenza Vaccine, Adjuvanted (Fluad™)—Novartis Vaccines

- Adjuvanted influenza vaccine for patients 65yo and older
- Contains an oil-in-water emulsion of squalene oil (MF59)—this increases the immune response by recruiting antigen-presenting cells to injection site and promotes uptake of influenza virus antigens
- Is a trivalent influenza vaccine: antigens from 2 influenza A viruses and 1 influenza B virus (15mcg HA from each strain)

#### Efficacy

- **N=7082 adults ≥65 yo**
- Compared to unadjuvanted trivalent seasonal influenza vaccine (Agriflu™)
- Fluad™ was noninferior for immunogenicity vs. Agriflu™ although Fluad™ did have significantly greater antibody responses against the 3 strains 3 weeks after vaccination (but did not meet prespecified superiority)
- Injection site pain, tenderness more common with Fluad™

**SE Frey et al. Vaccine 2014; 32:5227**

- **Cost**
  - $37 per dose

### Influenza Vaccine, Adjuvanted (Fluad™)—Novartis Vaccines

- Efficacy—Other
  - Observational studies
    - Fluad™ patients less likely than unadjuvanted standard-dose trivalent vaccine patients to have symptomatic influenza or be hospitalized for influenza
  - Vs. Fluzone High Dose™
    - No comparative data

**PG Van Buynder et al. Vaccine 2013; 31:6122**

**S Mannino et al. Am J Epidemiol 2012; 176:527**

### Cholera Vaccine, Live, Oral (Vaxchora™)—PaxVax Bermuda Ltd.

- Vaccine for prevention of cholera caused by serogroup O1 in adults 18-64yo traveling to cholera affected areas who are at high risk of exposure to Vibrio cholerae 01 or high risk of poor outcomes if infected
- Not routinely recommended for most travelers
- Limitations of use
  - Effectiveness has not been established in persons living in cholera-affected areas or in persons who have preexisting immunity due to previous exposure to Vibrio cholerae or receipt of a cholera vaccine
  - Has not been shown to protect against disease caused by Vibrio cholerae serogroup O139 or other non-O1 serogroups
### Cholera Vaccine, Live, Oral (Vaxchora™) - PaxVax Bermuda Ltd.

**Efficacy**
- **N=197, double-blinded, 18-45 yo**
- No history of cholera infection or travel to cholera-endemic areas in the past 5 years
- Randomized to one dose of Cholera vaccine or placebo.
- 134 patients were challenged with wild-type V. cholerae O1 El Tor Inaba strain N16961 from 10 days or 3 months after vaccination
- **Primary Endpoint:**
  - Moderate ($\geq 3$ L) to severe ($\geq 5$ L) diarrhea in 2 of 35 (5.7%) vaccinated 10 days previously, in 4 of 33 (12.1%) vaccinated 3 months previously, in 39 of 66 (59.1%) who received placebo
- **Efficacy:** 90.3% at 10 days and 79.5% at 3 months
- Vibriocidal antibody seroconversion rate: 89.4% at 10 days after vaccination and 90.4% at 180 days after vaccination

**Efficacy: Other Seroconversion Studies**
- 18-45 yo
  - 93.5% (vaccine) vs. 4% (placebo)
- 45-64yo vs. 18-45yo (both vaccine)
  - 90.4% vs 93.5% (noninferior)

### ADR's
- Most Common: tiredness, headache, abdominal pain, nausea, vomiting, diarrhea, (all similar to placebo except diarrhea)
- Bacteria from vaccine may be shed in the stool for at least 7 days and potentially could be transmitted to close contacts (no evidence though of transmission in one study)

### Drug Interactions
- Antibiotics should not be within 14 days before vaccination (may decrease immune response to vaccine)
- Chloroquine: vaccine should be administered at least 10 days before

### Dosing
- Single oral dose at least 10 days before potential exposure to cholera
- Eating or drinking should be avoided within 60min before/after vaccine
- Reimmunization or efficacy beyond 6 months unknown

### Availability
- Single-dose cartons containing buffer and active component (lyophilized V. cholerae CVD 103-HgR) packets
- Reconstitute within 15min after removing carton from the freezer and administer in a healthcare setting within 15 min following reconstitution
- Buffer packet should be dissolved in 100ml of purified bottled water first, followed by the active component packet
- If vaccine is reconstituted in the wrong order it must be discarded.
- **Cost:** $225 per dose
Clinical Case

- A newly diagnosed adult with genotype 1 chronic hepatitis C needs to begin treatment. What would be recommended as first line therapy for this patient at this time?
- Are there any other new drugs for hepatitis C?

Elbasvir/Grazoprevir (Zepatier™)—Merck

- Oral NS5A replication complex inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir) combo for treatment of chronic hepatitis C virus (HCV) genotypes 1 and 4
- 3rd oral, interferon-free, fixed-dose combo approved for HCV genotypes 1 and 4
  - ledipasvir/sofosbuvir (Harvoni™)
  - ombitasvir/paritaprevir/ritonavir copackaged with dasabuvir (Viekira Pak™ and Viekira XR™)
  - ombitasvir/paritaprevir/ritonavir (Technivie™) coadministered with ribavirin

Elbasvir/Grazoprevir (Zepatier™)—Merck

- Efficacy
  - FDA-approval based on both treatment-naive and treatment-experienced patients infected with HCV genotype 1, 4, 6 by sustained virologic response 12 weeks after stopping treatment (SVR12)
  - Treatment naive patients: SVR12 95% (C-EDGE); SVR 12 96% co-infected with HIV (C-EDGE CO-INFECTION)
  - Treatment experience patients: SVR12 92%; SVR 96-97% with ribavirin (C-EDGE TE and C-SALVAGE)
  - With severe renal or HD: SVR12 94% (C-SURFER)

Elbasvir/Grazoprevir (Zepatier™)—Merck

- ADR’s
  - Most common: fatigue, headache, nausea (but similar to placebo)
  - Anemia (16 weeks with elbasvir/grazoprevir and ribavirin)
  - ALT increases >5 times: 1%
  - Contraindicated in moderate or severe hepatic impairment (levels increase 12x in severe hepatic impairment)
**Elbasvir/Grazoprevir (Zepatier™)—Merck**

- **Drug Interactions**
  - CYP3A4 inhibitors and inducers interact
  - OATP 1B1 and 1B3 inhibitors (cyclosporine) interact
  - Grazoprevir is weak inhibitor of CYP3A
  - Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP)

- **Availability/Dosing**
  - Tablets 50 mg elbasvir and 100 mg grazoprevir
  - One tablet once daily for 12 weeks
  - Genotype 1a infection with high-level NS5A resistance-associated polymorphisms at baseline should also receive ribavirin and treated 16 weeks
  - Genotype 1a or 1b infection previously treated with peginterferon, ribavirin, protease inhibitor should also receive ribavirin and treated 12 weeks
  - Genotype 4 previously treated with peginterferon and ribavirin: add ribavirin and treated x 16 weeks

- **Cost**
  - $54,600 x 12 weeks
  - Other oral combos range from $80,000 to $150,000 x 12 weeks

**Sofosbuvir/Velpatasvir (Epclusa™)—Gilead Sciences, Inc.**

- **MOA**
  - Sofosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication
  - Velpatasvir inhibits viral replication by binding to the NS5A protein

- **Efficacy**
  - Four randomized trials in treatment-naïve and experienced patients with HCV infection
  - ASTRAL-1 (Genotypes 1, 2, 4, 5, 6): SVR 12 99% vs. 0% placebo
  - ASTRAL-2 (Genotype 2): SVR 12 99% vs. 94% (sofosbuvir/ribavirin)
  - ASTRAL-3 (Genotype 3): SVR 12 95% vs. 80% (sofosbuvir/ribavirin 24 weeks)
  - ASTRAL-4 enrolled only patients with moderate (Child-Pugh B) decompensated cirrhosis (Genotypes 1, 2, 3, 4, 5, 6): 83% vs. 94% (+ ribavirin) vs. 86% (24 weeks)
Sofosbuvir/Velpatasvir (Epclusa™) - Gilead Sciences, Inc.

- ADR’s
  - Most common (>10%): headache, fatigue
  - Most common (>10%) when combined with ribavirin (12 weeks): fatigue, anemia, nausea, headache, insomnia, diarrhea

- Drug Interactions
  - Many
  - Amiodarone (serious symptomatic bradycardia)
  - Sofosbuvir and velpatasvir: substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP): increase topotecan
  - Velpatasvir is minimally metabolized by CYP3A4
  - Inducers (rifampin, carbamazepine, rifabutin) may decrease Epclusa™
  - Velpatasvir is an inhibitor of P-gp, BCRP, and organic anion transporting polypeptide (OATP) 1B1, 1B3, and 2B1
  - May increase intestinal absorption of drugs that are substrates of these transporters
  - Epclusa™ can increase levels of digoxin, rosuvastatin, atorvastatin, tenofovir
  - Acid reducing drugs:
    - Absorption of velpatasvir decreases as gastric pH increases
    - PPI not recommended (studied only with omeprazole). If necessary, give Epclusa™ with food and 4 hours before omeprazole 20mg
    - Antacids should be taken 4 hours before or after Epclusa™
    - H2-receptor antagonists and Epclusa™ can be taken at the same time or 12 hours apart

- Dosing
  - One tablet (400mg sofosbuvir/100mg velpatasvir) orally once daily for 12 weeks
  - With decompensated cirrhosis (Child-Pugh B or C): should also take ribavirin
  - Cost
    - $74,760/12 weeks

Respiratory Drugs

Mepolizumab (Nucala™) — GSK

- A humanized interleukin-5 (IL-5) antagonist monoclonal antibody, for maintenance treatment of severe asthma in patients ≥ 12 years old as add-on maintenance treatment who have an eosinophilic phenotype
- MOA: binds to IL-5 receptors which reduces the production and survival of eosinophils and decreases airway inflammation

Clinical Case

- A 14yo M was recently hospitalized for a severe asthma exacerbation, his 3rd in the past year. He has a history of eosinophilic asthma and is on systemic prednisone therapy. The family wants to know if there is anything to help the patient decrease the patient's prednisone use.
Mepolizumab (Nucala™)—
GSK

- **Efficacy**
  - N=621 with ≥2 asthma exacerbations requiring systemic glucocorticoids and eosinophilic airway inflammation
  - IV mepolizumab 75, 250, or 750 mg vs. placebo every 4 weeks x 13 doses
  - Clinically significant asthma exacerbations were significantly lower with mepolizumab vs. placebo (1.24, 1.46, and 1.15 per patient-year, vs 2.40)

  Pavord et al. Lancet 2012; 380:651

- **Efficacy**
  - N=576 with severe asthma and ≥2 exacerbations requiring systemic glucocorticoids and eosinophilic inflammation
  - Mepolizumab 75 mg IV or 100 mg SC vs. placebo every 4 weeks x 32 weeks
  - Annualized frequency of clinically significant exacerbations was stat sig reduced 47% with IV mepolizumab and 53% with SC mepolizumab vs. placebo (also 74% and 80% greater reduction with serum eosinophils ≥ 500 cells/mL)


- **Efficacy**
  - N=135 with a ≥6-month history of maintenance treatment with systemic glucocorticoid and eosinophilic inflammation
  - Mepolizumab 100 mg SC every 4 weeks vs. placebo x 20 weeks
  - Mepolizumab more likely (2.39 times) vs. placebo to have their glucocorticoid dose reduced
  - Median reduction in glucocorticoid dose from baseline of 50% vs. 0% with placebo


- **ADR’s**:
  - Common (≥5%): injection-site reactions, headache, back pain, fatigue
  - Hypersensitivity reactions: can occur within hours or days of therapy
  - Rare: herpes zoster infections

Mepolizumab (Nucala™)—
GSK

- **Dosing/Administration**:
  - 100mg injected subcutaneously into the upper arm, thigh, or abdomen every 4 weeks
  - Optimal duration of treatment unknown

- **Availability/Cost**:
  - 100mg single dose vials
  - $2500/100mg dose

Reslizumab (Cinqair™)—
Teva Pharmaceutical

- An interleukin-5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype

- Limitation of Use: not indicated for treatment of other eosinophilic conditions; not indicated for the relief of acute bronchospasm or status asthmaticus

https://www.besse.com/PublishingImages/Cinqair/46418_w6.png
**Reslizumab (Cinqair™)—Teva Pharmaceutical**

- **Efficacy**
  - Four double-blind, randomized, placebo-controlled trials in patients with severe asthma on currently available therapies
  - Vs. Placebo:
    - fewer asthma attacks, and a longer time to the first attack.
    - significant improvement in lung function, as measured FEV₁

- **Warnings and Precautions**
  - Malignancy: Malignancies were observed
  - Reduction in corticosteroid dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy. Decrease corticosteroids gradually, if appropriate
  - Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before starting. If patients become infected on reslizumab, and do not respond to anti-helminth tx, discontinue reslizumab until the parasitic infection resolves

- **Boxed Warning**
  - Anaphylaxis 0.3%
  - Patients should be observed for an appropriate period of time after infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening
  - Discontinue immediately if the patient experiences anaphylaxis

### Table 3: Mean Change (95% CI) from Baseline in FEV₁ in mL Over 16 Weeks (Difference from CINQAIR and Placebo) in Patients with Severe Asthma with an Eosinophilic Phenotype

<table>
<thead>
<tr>
<th>Study</th>
<th>FEV₁ change in mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>137 (76, 198)</td>
</tr>
<tr>
<td>Study II</td>
<td>93 (31, 155)</td>
</tr>
<tr>
<td>Study III</td>
<td>130 (80, 259)</td>
</tr>
<tr>
<td>Study IV*</td>
<td>76 (-6, 158)</td>
</tr>
</tbody>
</table>

*Study IV ended as patient monostated to blood eosinophil.

### Table 2: Frequency of Asthma Exacerbations during the 52-Week Treatment Period in Patients with Severe Asthma with an Eosinophilic Phenotype (Studies I and II)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Asthma Exacerbation Rate</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINQAIR 3 mg/kg (n=245)</td>
<td>0.90</td>
<td>0.5</td>
</tr>
<tr>
<td>Placebo (n=244)</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Study II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINQAIR 3 mg/kg (n=234)</td>
<td>0.80</td>
<td>0.41</td>
</tr>
<tr>
<td>Placebo (n=232)</td>
<td>2.11</td>
<td></td>
</tr>
</tbody>
</table>

### Exacerbations requiring systemic corticosteroid use

| Study I       |                          |                     |
| CINQAIR 3 mg/kg (n=245) | 0.72 | 0.45 | (0.33, 0.67) |
| Placebo (n=244) | 1.60 |     | (0.93, 1.06) |
| Study II      |                          |                     |
| CINQAIR 3 mg/kg (n=254) | 0.85 | 0.59 | (0.37, 0.84) |
| Placebo (n=252) | 1.66 |     | (0.96, 2.03) |

### Exacerbations resulting in a hospitalization AND/OR emergency room visit

| Study I       |                          |                     |
| CINQAIR 3 mg/kg (n=245) | 0.14 | 0.97 | (0.32, 1.36) |
| Placebo (n=244) | 0.21 |     | (0.95, 1.09) |
| Study II      |                          |                     |
| CINQAIR 3 mg/kg (n=252) | 0.03 | 0.69 | (0.26, 1.15) |
| Placebo (n=252) | 0.09 |     | (0.49, 1.09) |

*Randomized patients

### ADR’s

- most common (≥2%): oropharyngeal pain
- CPK elevations/myalgias
Reslizumab (Cinqair™)—
Teva Pharmaceutical

- Dosing and Availability
  - Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials
  - Should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis
  - Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes
  - Cost: $2505

Psychiatry Drugs

Clinical Question

- Are there any newly approved antipsychotics available and how do they compare to those already on the market?

Cariprazine (Vraylar™)—
Actavis

- Atypical antipsychotic for treatment of schizophrenia and treatment of manic or mixed episodes associated with bipolar I disorder
- MOA:
  - Combination of partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors
  - 10-fold affinity for D3 receptors than D2 receptors

Cariprazine (Vraylar™)—
Actavis

- Efficacy
  - Schizophrenia:
    - 1733 total patients in trials
    - Improved efficacy vs. placebo
    - 6 weeks
  - Bipolar I Disorder:
    - 1025 total patients in trials
    - Improved efficacy vs. placebo
    - 3 weeks

Cariprazine (Vraylar™)—
Actavis

- ADR’s:
  - Extrapyramidal symptoms
  - Akathisia
  - Dyspepsia
  - Vomiting
  - Somnolence
  - Restlessness

www.vraylar.com
**Cariprazine (Vraylar™)—Actavis**

- Drug Interactions:
  - Strong CYP3A4 inhibitors: Decrease cariprazine dose by ½
  - CYP3A4 inducers: Not recommended

- Dosing:
  - Dose Range:
    - Schizophrenia: 1.5mg to 6mg once daily
    - Bipolar disorder: 3mg to 6mg once daily
  - Starting dose 1.5mg, can be increased to 3mg on Day 2
  - Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5mg or 3mg increments

- Availability
  - Capsules: 1.5, 3, 4.5, 6mg
  - Cost: $1006.10/30 days

---

**Long-Acting Injectable Second Generation Antipsychotics for Schizophrenia**

- Aripiprazole lauroxil (Aristada™)—Alkermes
  - Available in 441, 662, 882 mg prefilled syringes
  - Dosing: 441-882mg IM once/month or 882mg IM q 6 weeks
  - Cost: $2186.00/1 syringe

- Paliperidone palmitate (Invega Trinza™)—Janssen
  - Available in 273, 410, 546, 819mg prefilled syringes
  - Dosing: 410mg IM Q 3 months
  - Cost: $3014.20/3 months

---

**Clinical Case**

A 75yo female with Parkinson’s disease has been experiencing hallucinations and delusions due to Parkinson’s disease psychosis. You are asked to give a recommendation to help treat this.

---

**Pimavanserin (Nuplazid™)**

Acadia Pharmaceuticals Inc.

- A non-dopaminergic, selective serotonin inverse agonist (SSIA), an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis

---

![Image](image_url)
Pimavanserin (Nuplazid™)  
Acadia Pharmaceuticals Inc.  
- Boxed warning: Increased mortality in elderly patients with dementia-related psychosis  
  - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death  
  - Not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson’s disease psychosis

Pimavanserin (Nuplazid™)  
Acadia Pharmaceuticals Inc.  
- Warnings and Precautions:  
  - QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval  
- ADR’s:  
  - Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state

Pimavanserin (Nuplazid™)  
Acadia Pharmaceuticals Inc.  
- Drug Interactions:  
  - Strong CYP3A4 Inhibitors: Reduce pimavanserin dose by one-half  
  - Strong CYP3A4 Inducers: Monitor for reduced efficacy—increase in pimavanserin dosage may be needed

Pimavanserin (Nuplazid™)  
Acadia Pharmaceuticals Inc.  
- Dosing and Availability:  
  - Tablets: 17 mg  
  - 34 mg PO as two 17 mg tablets once daily, without titration  
  - Can be taken with or without food  
  - Cost: $1950/30days
Neurology Drugs

Clinical Question

- How does the antiepileptic brivaracetam compare to levetiracetam?

Brivaracetam (Briviact™)—UCB

- Selective, high-affinity synaptic vesicle protein 2A ligand and analog of levetiracetam indicated as adjunctive treatment of partial-onset seizures in patients with epilepsy ≥ 16yo

MOA

- Binds selectively to synaptic vesicle protein 2A (SV2A) in the brain, modulating neurotransmitter release into the synapse
- Has a 10- to 30-fold higher affinity for SV2A than levetiracetam
- Also a partial antagonist on neuronal voltage-gated sodium channels
- In animal models, had higher brain permeability and a more rapid onset of action than levetiracetam

Efficacy

- Demonstrated in three clinical trials involving 1,550 subjects and when taken with other meds for seizure
- Randomized, double-blind, placebo-controlled 12-week trials of adjunctive brivaracetam in patients ≥16 yo with uncontrolled partial-onset seizures
- Most patients were already taking 1 or 2 other antiepileptic drugs
- Mean reduction in seizure frequency 9.5% - 25.7%
- Adding brivaracetam was not beneficial for the 20% of patients in 2 of the studies with concomitant levetiracetam treatment, but adjunctive brivaracetam significantly reduced seizure frequency among the patients in another study who had previously tried and discontinued levetiracetam

ADR’s

- Common: somnolence and sedation (16%), dizziness (12%), fatigue (9%), and nausea and vomiting (5%)
- Psychiatric ADR’s 13%: anxiety, depression, aggression, psychosis
- Chronic interstitial nephritis (1 patient)
- Hypersensitivity reactions: bronchospasm, angioedema
- Schedule V controlled substance
Brivaracetam (Briviact™)—UCB

- Drug Interactions
  - Rifampin: decreases brivaracetam (thus increase dose 100%)
  - Brivaracetam increased active metabolite of carbamazepine (thus reduce carbamazepine dose)
  - Brivaracetam increased phenytoin 20% (monitor)
  - CYP2C19 interactions possible

Dosing

- Recommended starting dosage: 50 mg twice daily
- Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily or up to 100 mg twice daily
- Dose modify for hepatic impairment
- Injection may be used when oral administration is temporarily not feasible

Availability

- Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg; Oral solution: 10 mg/mL; Injection: 50 mg/5 mL single-dose vial
- Cost: $910 / 30 days

Clinical Question

- Is there anything new to treat multiple sclerosis?

Daclizumab (Zinbryta™)—AbbVie, Inc. and Biogen

- Efficacy
  - 2 randomized trials in adults with relapsing multiple sclerosis
  - Daclizumab high-yield process significantly decreased the annualized relapse rate vs. placebo in 52-week SELECT trial (N=621; 21% (150 mg) and 23% (300 mg) vs 46%) and compared with interferon beta-1a in 144-week DECIDE trial (N=1841; (150 mg) 22% vs 39%)
  - Daclizumab significantly reduced the mean number of new or newly-enlarging T2 hyperintense lesions at week 52 in SELECT (2.4 (150 mg) and 1.7 (300 mg) vs 8.1 with placebo), and at week 96 in DECIDE (4.3 (150 mg) vs 9.4 with interferon beta 1-a)
  - Daclizumab had higher incidences of infection, rash, liver events
  - Post-hoc analysis of SELECT: more daclizumab-treated patients where free of disease activity at 1 year (36% (150 mg) and 41% (300 mg) vs 11% placebo)

- Efficacy
  - Boxed Warning
    - Hepatic Injury Including Autoimmune Hepatitis
    - Obtain transaminase and bilirubin levels before initiation
    - Monitor and evaluate transaminase and bilirubin levels monthly and up to 6 months after the last dose
    - Contraindicated in patients with pre-existing hepatic disease or hepatic impairment
    - Other Immune-Mediated Disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur and may require treatment with systemic corticosteroids or immunosuppressive medication
Daclizumab (Zinbryta™)—AbbVie, Inc. and Biogen

- **ADR’s**
  - Most common (≥5% and ≥2% higher incidence than comparator Avonex™): nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, lymphadenopathy
  - Most common vs. placebo: upper respiratory tract infection, depression, rash, pharyngitis, increased alanine aminotransferase (ALT)
- **Drug Interactions**
  - Other heptatotoxic medications

Rheumatology Drugs

Clinical Question

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

Infliximab-dyyb (Inflectra™)—Celltrion

- A tumor necrosis factor (TNF) blocker biosimilar to infliximab (Remicade™) for the treatment of Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
- 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

Etanercept-szzs (Erelzi™)—Sandoz

- A tumor necrosis factor (TNF) blocker biosimilar to etanercept (Enbrel™)
- Approved for the treatment of:
  - moderate to severe rheumatoid arthritis, either as a standalone therapy or in combination with methotrexate
  - moderate to severe polyarticular juvenile idiopathic arthritis in patients ages two and older
  - active psoriatic arthritis, including use in combination with methotrexate in psoriatic arthritis patients who do not respond adequately to methotrexate alone
  - active ankylosing spondylitis
  - chronic moderate to severe plaque psoriasis in adult patients (18 years or older) who are candidates for systemic therapy or phototherapy

Daclizumab (Zinbryta™)—AbbVie, Inc. and Biogen

- **Dosing**
  - Recommended dose 150 mg subcutaneously once monthly
  - Instruct patients to inject a missed dose as soon as possible but no more than two weeks late. After two weeks, skip the missed dose and take the next dose on schedule.
  - Administer only one dose at a time.
- **Availability**
  - Injection: 150 mg/mL solution in a single-dose prefilled syringe
  - Available only through a restricted distribution program called the ZINBRYTA REMS Program
Clinical Case

- A 65yo M is newly diagnosed with gout for which he has not required therapy to this point. Would he be a good candidate to try the new drug lesinurad (Zurampic™)?

Lesinurad (Zurampic™)—AstraZeneca

- A URAT1 inhibitor FDA-approved for the adjunct treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone
  - Has boxed warning due to risk of acute renal failure, which is more common when administered as monotherapy and with higher than approved doses—should always be used in combination with a xanthine oxidase inhibitor

Lesinurad (Zurampic™)—AstraZeneca

- MOA: inhibits function of 2 transporter proteins involved in uric acid reabsorption in the kidney
  - uric acid transporter 1 (URAT1), (responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen)
  - organic anion transporter 4 (OAT4) (protein associated with diuretic-induced hyperuricemia)

Lesinurad (Zurampic™)—AstraZeneca

- Efficacy
  - CLEAR 1 and CLEAR 2
    - Lesinurad + allopurinol vs. allopurinol
    - More patients achieved serum uric acid levels < 6mg/dl by month 6 with combo vs. allopurinol
  - CRYSTAL
    - Lesinurad + febuxostat vs. febuxostat in gout with tophi
    - Combo showed greater uric acid lowering <5mg/dl vs. febuxostat at all months except month 6

Lesinurad (Zurampic™)—AstraZeneca

- ADR’s (>2%):
  - headache
  - influenza
  - blood creatinine increased
  - gastroesophageal reflux disease
- Drug Interactions:
  - CYP2C9 Inhibitors: Use with caution
  - CYP3A4 Substrates: Monitor for efficacy of the 3A4 substrate

Lesinurad (Zurampic™)—AstraZeneca

- Dosing:
  - 200 mg PO once daily in the morning, at the same time as the morning dose of xanthine oxidase inhibitor (allopurinol or febuxostat)
  - Do not use if CrCl < 45ml/min
  - If treatment with the xanthine oxidase inhibitor is interrupted, lesinurad should also be interrupted
  - Not recommended for asymptomatic hyperuricemia
  - Stay well hydrated (2 liters of liquid per day)
- Availability: 200mg tablets
- Cost?
**Miscellaneous Drugs**

**Lifitegrast Ophthalmic Solution (Xiidra™)**
Shire US Inc.

- **MOA**
  - LFA-1 is a protein expressed on leukocyte surfaces that binds to intracellular adhesion molecule-1 (ICAM-1) (may be overexpressed in the corneal and conjunctival tissue of patients with dry eye disease)—resulting interaction stimulates T-cell activation and migration, leading to propagation of pro-inflammatory factors and inflammation of the ocular surface
  - Lifitegrast reduces ocular surface inflammation by binding to LFA-1, preventing its interaction with ICAM-1

- **Efficacy**
  - Demonstrated in 4 x 12 week randomized, double-blinded, vehicle controlled trial in 2133 adults
  - Other ophthalmic meds not allowed (Artificial Tears)
  - Results
    - Change in Inferior Corneal Fluorescein Staining Score (scale 0 to 4 with higher scores more disease) at Day 84 improved with lifitegrast: +0.04 to -0.8 (lifitegrast) vs. +0.38 to -0.71 (vehicle)
    - Eye Dryness Score (scale 0-100 with higher scores more dry eyes) at Day 84 improved with lifitegrast: -14.4 to -37.7 (lifitegrast) vs. -7.2 to -30.5 (vehicle)

- **ADR’s**
  - Most common (5-25% of patients): eye irritation, dysgeusia, reduced visual acuity
  - Most reactions mild to moderate in severity
  - One-year safety study (SONATA): no serious treatment-related adverse events occurred among 220 patients who used lifitegrast

- **Administration**
  - One drop of solution instilled in each eye twice daily
  - Contact lenses should be removed before instilling the drops, but may be replaced 15 minutes after administration

- **Availability**
  - 5% ophthalmic solution
  - Cartons of 60 single-use containers

- **Cost**
  - $426.70 5% single use container (compared to $426.70 Restasis™ and $398.10 Lacrisert™)
Informational Slides

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

CNS Drugs

Sugammadex (Bridion™)—Merck

- A modified gamma cyclodextrin
- FDA-approved for the reversal of neuromuscular blockade induced by rocuronium and vecuronium in adults undergoing surgery
- Not approved by FDA several times since 2007 due to cardiac arrhythmias, hypersensitivity reactions, anaphylaxis—updated safety information recently presented for approval

Sugammadex (Bridion™)—Merck

- MOA: Forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction
- Results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium

Sugammadex (Bridion™)—Merck

- Efficacy:
  - Safety and efficacy evaluated in three Phase 3 clinical trials of 456 participants
  - Return to recovery time was faster overall for the sugammadex treatment groups compared to the comparator groups (neostigmine) with most participants recovering within 5 minutes of use

Sugammadex (Bridion™)—Merck

- Efficacy:
  - Due to concerns about the nature and frequency of anaphylaxis (severe, potentially life-threatening allergic reaction) and hypersensitivity reactions reported in the clinical trials, sugammadex was further evaluated in a randomized, double-blind, parallel-group, repeat-dose trial
  - Of the 299 participants, 1 had an anaphylactic reaction
**Sugammadex (Bridion™)—Merck**

- **ADR’s:**
  - Most common (>10%)
    - vomiting
    - pain
    - nausea
    - hypotension
    - headache
  - Other
    - anaphylaxis (0.3%)
    - bradycardia

- **Dosing:**
  - For rocuronium and vecuronium:
    - 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation
    - 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation
  - For rocuronium only:
    - 16 mg/kg is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium.

- **Availability**
  - 200 mg/2 mL and 500 mg/5 mL single-dose vials

- **Cost**
  - 200mg vial $95
  - 500mg vial $174.8

---

**Elvitegravir, Cobicistat, Emtricitabine, Tenofovir alafenamide (Genvoya™)—Gilead Sciences**

- Genvoya is a four-drug combination of:
  - elvitegravir (HIV-1 integrase strand transfer inhibitor (INSTI))
  - cobicistat (CYP3A inhibitor)
  - emtricitabine and tenofovir alafenamide (HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs))

- Indicated as a complete regimen for the treatment of HIV-1 infection in adults and peds patients ≥ 12 yo who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya™
**Elvitegravir, Cobicistat, Emtricitabine, Tenofovir alafenamide (Genvoya™)— Gilead Sciences**

**Efficacy:**
- Treatment-naïve patients
- Non-inferior compared to Stribild™ (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) as 92.4% of Genvoya™ patients and 90.4% of Stribild™ patients had HIV-1 RNA levels < 50 copies/mL at Week 48
- Tests of certain renal and bone laboratory parameters also favored Genvoya™

- Also studied in virologically suppressed patients who switched from tenofovir-based regimens
- Genvoya™ was found to be statistically non-inferior to the tenofovir-based regimens based on the percentages of patients with HIV-1 RNA levels less than 50 copies/mL at Week 48
- Genvoya™ patients also demonstrated improvements in certain bone and renal lab parameters compared to tenofovir-based regimens

**ADR’s:**
- Most common (>10%): nausea
- Black box warning:
  - Lactic acidosis and severe hepatomegaly with steatosis, including fatalities (nucleoside analogs)
  - Not approved for chronic hepatitis B virus (HBV) infection
  - Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV and have discontinued emtricitabine and/or tenofovir disoproxil fumarate—monitor hepatic function

**Drug Interactions:**
- Should not be administered with other antiretroviral medications for treatment of HIV-1 infection
- CYP3A or CYP2D6 drugs potential for interactions

**Availability:**
- Tablets: 150mg elvitegravir, 150mg cobicistat, 200mg emtricitabine, 10mg tenofovir alafenamide

**Dosing:**
- Testing: Prior to initiation, test for hepatitis B
- Recommended dosage: One tablet taken orally once daily with food
- Not recommended in patients with est CrCl < 30 mL/min
- Not recommended in severe hepatic impairment

---

**Dermatology Drugs**
### Ixekizumab (Taltz™)—Eli Lilly

- **Humanized interleukin-17A antagonist indicated for**
  the **treatment of adults with moderate-to-severe plaque psoriasis**
- **Second IL-17A antagonist approved for plaque psoriasis in US**
  (secukinumab (Cosentyx™))
- **MOA:** IL-17A is a naturally occurring pro-inflammatory cytokine that’s inhibited by ixekizumab

#### Efficacy (UNCOVER-1)
- **Randomized, double-blind trial; N=1296 adults with moderate to severe plaque psoriasis;**
  ixekizumab every 2 or 4 weeks vs placebo
- **Results:** Significantly more patients 12 weeks with ixekizumab (83%-89%) achieved ≥75% reduction in the Psoriasis Area and Severity Index score (PASI 75) and a score of 0 (clear) or 1 (minimal) with at least a 2-point reduction from baseline on the static Physician Global Assessment (sPGA) scale (76%-82%) vs. placebo (3-4%)

#### Efficacy (UNCOVER-2 and UNCOVER-3)
- **Double-blind, placebo- and active-controlled trials N=2570 total adults with moderate to severe plaque psoriasis;**
  ixekizumab every 2 or 4 weeks, the TNF inhibitor etanercept, or placebo
- **Significantly more patients 12 weeks with ixekizumab (73%-90%) achieved PASI 75 and sPGA score of 0 or 1 vs. etanercept (36-53%) vs. placebo (8%-7%)**

#### Efficacy: Continued Treatment
- **UNCOVER-1 and UNCOVER-2 patients for additional 48 weeks**
  ixekizumab every 4 weeks
- **75% maintained an sPGA score of 0 or 1 at week 60 vs. 7% placebo**
- **Median time to relapse of 5 months in the placebo group**

### ADR’s
- Mild to moderate injection-site reactions (10-15%)
- Vaginal and oral candidiasis possible
- Crohn’s disease and ulcerative colitis and exacerbations possible

### Drug Interactions
- **Avoid live vaccines during treatment**
- **Dosing**
  - Recommended dose of ixekizumab is two injections (160 mg) administered subcutaneously at week 0, followed by one injection (80 mg) at weeks 2, 4, 6, 8, 10, and 12, and then every 4 weeks
Ixekizumab (Taltz™)—Eli Lilly

- **Cost and Availability**
  - Cartons containing prefilled, single-use autoinjectors or syringes of single 80-mg dose
  - $12,300 for 12 weeks
    - Compared to secukinumab (Cosentyx™) $11,724.70 for 12 weeks

Hematology/Oncology Drugs

Oncology Drugs

- Nivolumab (Opdivo™)—Bristol-Myers Squibb
  - Treatment of metastatic squamous non-small cell lung cancer
- Alectinib (Alecensa™)—Genentech
  - Oral kinase inhibitor for certain types of advanced non-small cell lung cancer
- Cobimetinib (Cotellic™)—Genentech
  - Oral kinase inhibitor for advanced melanoma
- Ixazomib (Ninlaro™)—Takeda
  - Oral proteasome inhibitor for multiple myeloma

- Osimertinib (Tagrisso™)—AstraZeneca
  - Oral kinase inhibitor for metastatic non-small cell lung cancer
- Trabectedin (Yondelis™)—Janssen Biotech
  - Alkylating agent for certain advanced soft tissue sarcomas
- Daratumumab (Darzalex™)—Janssen Biotech
  - Monoclonal antibody for multiple myeloma
- Elotuzumab (Empliciti™)—BMS
  - Immune system activator for multiple myeloma

Oncology Drugs

- Necitumumab (Portrazza™)—Lilly
  - Epidermal growth factor receptor antagonist for metastatic squamous non-small cell lung cancer
- Atezolizumab (Tecentriq™)—Genentech
  - Programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with advanced urothelial carcinoma
- Cabozantinib (Cabometyx™)—Exelixis
  - Tyrosine kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

Oncology Drugs

- Venetoclax (Venclexta™)—AbbVie Inc.
  - Oral B-cell lymphoma-2 (BCL-2) inhibitor for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion
- Atezolizumab (Tecentriq™)—Genentech
  - A programmed death-ligand 1 blocking antibody for advanced urothelial carcinoma.
Hematology Drugs

- Antihemophilic factor PEGylated (Adynovate™)—Baxalta
  - PEGylated formulation for prophylaxis and treatment/control of bleeding episodes in patients with hemophilia A
- Coagulation factor X (Coagadex™)—BPL
  - Human blood coagulation factor for patients with hereditary Factor X deficiency
- Coagulation factor IX (recombinant), albumin fusion protein (Idelvion™)—CSL Behring
  - Long-acting recombinant human blood coagulation factor indicated for the control and prevention of bleeding episodes in patients with hemophilia B

Hematology Drugs

- von Willebrand factor (Vonvendi™)—Baxalta US
  - Recombinant von Willebrand factor for control of bleeding episodes in patients with von Willebrand disease
- Antihemophilic factor (recombinant) (Kovaltry™)—Bayer HealthCare Pharm
  - Human DNA sequence derived, full length Factor VIII concentrate indicated for the control and prevention of bleeding episodes in adults and children with hemophilia A

Miscellaneous Drugs

- Uridine triacetate (Xuriden™)—Wellstat Therapeutics
  - Pyrimidine analog for uridine replacement for hereditary orotic aciduria
- Crotalidae Immune F(ab)’2 (Anavip™)—Rare Disease Therapeutics
  - Equine-derived antivenin for management of North American rattlesnake bite
- Obeticholic acid (Ocaliva™)— Intercept Pharmaceuticals
  - Farnesoid X receptor agonist for treatment of primary biliary cholangitis in combination with ursodeoxycholic acid if inadequate response or as monotherapy if intolerant to ursodeoxycholic acid
- Aminolevulinic acid (Ameluz Gel™)—Biofrontera AG
  - A porphyrin precursor used in combination with the BF-RhodoLED lamp for photodynamic therapy (PDT) treatment of actinic keratoses on the face and scalp

Miscellaneous Drugs

- Sebelipase alfa (Kanuma™)—Alexion
  - Enzyme replacement for lysosomal acid lipase deficiency
- Asfotase alfa (Strensiq™)—Alexion
  - Tissue nonspecific alkaline phosphatase for perinatal/infantile and juvenile onset hypophosphatasia
- Defibrotide (Defitelio™)—Jazz Pharmaceuticals
  - Deoxyribonucleic acid derivative anticoagulant for the treatment of patients with hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT)
- Obiltoxaximab (Anthim™)—Elusys Therapeutics
  - Monoclonal antibody (mAb) anthrax antitoxin for the treatment and prevention of inhalational anthrax

Selected References

- Various online references, databases, and review/primary literature were used in preparation of this lecture that were accessed Nov 2015 to August 2016. These included but were not limited to: The Medical Letter, Pharmacist’s Letter, Clinical Pharmacology, Lexicomp, Micromedex, FDA.gov website, Drugs.com, primary literature.

New Drug Update