New Kids on the Block
An Overview of Select 2018 FDA Drug Approvals
OACNS Pharmacology Conference: April 14, 2019

Presenters/Topics
• Kimberly Allen, DNP, APRN-CNP
  — Vraylar (cariprazine)
• Stephanie Byrd, MS, APRN-CNP
  — Xofluza (baloxavir marboxil)
• Amy Costner-Lark, DNP, APRN-CNP
  — Motegrity (prucalopride)
• Jennifer Roberts, DNP, APRN-CNP
  — Nuzyra (omadacycline)
• Diana Webber, DNP, APRN-CNP
  — Seysara (saracycline)
Objectives

By the end of this presentation, the learner will be able to:

• Discuss the clinical indications and common adverse effects of select new drugs approved by the FDA in 2018
• Outline the approved dosing guidelines and recommended dosage adjustments for select new drugs approved by the FDA in 2018
• Discuss common adverse effects of select new drugs approved by the FDA in 2018
• Compare/contrast advantages/disadvantages of select new drugs approved by the FDA in 2018 with older approved pharmacotherapeutic choices with similar clinical indications.

Vraylar (cariprazine)

“Step by Step”
Vraylar (cariprazine)

- Approved by FDA September 17, 2018
- Oral, atypical antipsychotic
- Indication
  - Treatment of bi-polar 1 and schizophrenia
  - Patients ages 18-65
  - Acute treatment of manic or mixed episodes associated with bi-polar 1 disorders
  - Treatment of schizophrenia
- Three positive, 6-week, randomized controlled trials in acute schizophrenia
  - Demonstrated superiority of cariprazine over placebo

Vraylar (cariprazine)

- Pharmacodynamics
  - Partial agonist at:
    - D2 receptors
    - D3 receptors
    - 5-HT1A receptors
  - Antagonist at:
    - 5-HT2B receptors
    - 5-HT2A receptors
  - Antagonist at (moderate to low infinity):
    - H1 receptors
    - 5-HT2C receptors
Vraylar (cariprazine)

**Dosing**
- Available as an oral capsule only
  - Capsules: 1.5mg, 3mg, 4.5mg, 6mg
- Treatment of schizophrenia
  - Starting dose: 1.5 mg/day
  - Recommended dose: 1.5 mg to 6 mg/day
- Acute treatment of manic or mixed episodes associated with bipolar disorder
  - Starting dose: 1.5 mg/day
  - Recommended dose: 3 mg – 6 mg/day

**Dose Adjustment**
- Concurrent CYP 3A4 Inducer or inhibitor
  - Inducer
    - Use is not recommended
  - Inhibitor
    - New start of inhibitor
    - Reduce cariprazine dose by 50%
  - Already on strong inhibitor
    - Max dose 3mg
Vraylar (cariprazine)

- **Dose Adjustment**
  - Renal impairment
    - CrCl ≥30ml/min
      - no dose adjustment necessary
    - CrCl ≤ 30ml/min
      - use not recommended
  - Hepatic impairment
    - Mild-moderate (Child-Pugh class A or B)
      - no dose adjustment necessary
    - Severe impairment (Child –Pugh class C)
      - use not recommended

- **Drug interactions**
  - Metabolized by CYP3A4
    - Strong CYP3A4 inhibitors: reduce dosage by half
    - CYP3A4 inducers: do not recommend use with cariprazine

- **Adverse reactions**
  - Schizophrenia trials: extrapyramidal symptoms and akathisia
  - Bipolar mania trials: extrapyramidal symptoms, akathisia, dyspepsia, somnolence, restlessness
Vraylar (cariprazine)

- Active metabolites
  - Two active metabolites
    - Desmethyl cariprazine
    - Didesmethyl cariprazine
  - Cariprazine has a half life of 2-4 days
  - Metabolites have a half life of 1-3 weeks
  - When stopping cariprazine it will takes weeks for the medication to leave the system
  - Could be a benefit for patients with compliance issues

Vraylar (cariprazine)

- Adverse Reactions
  - >10%
    - GI
      - Nausea
    - CNS
      - Akathisia
      - Parkinsonism
  - 1-10%
    - GI
      - Vomiting, constipation, decreased appetite, dry mouth
    - Weight gain
      - 2lb
    - CNS
      - Drowsiness, dizziness, anxiety, agitation
    - CV
      - HTN, tachycardia
Vraylar (cariprazine)

- Advantages
  - Once a day dosing
  - Long half life assist with non-compliant patients
  - Studies indicate superior to placebo
  - Does not affect prolactin level
  - Minimal anticholinergic side effects

- Disadvantages
  - High cost
  - EPS side effects
  - May increase metabolic syndrome
  - Clinically significant CYP3A4 drug-drug interactions
  - Has not been adequately studied in pregnant women

Vraylar (cariprazine)

- Black box warning for increased mortality in elderly patients with dementia-related psychosis
Xofluza (baloxavir marboxil) "Let’s Try it Again"

Xofluza (baloxavir marboxil)

- Approved by FDA October 24, 2018
- Oral, antiviral
- Indication
  - Acute uncomplicated influenza
  - Patients ages 12 years and older
  - Symptomatic no longer than 48 hours
- Approval based on two RCTs comparing it with placebo and oseltamivir for symptoms present less than 48 hours
  - Significantly reduced time of symptoms when compared with placebo
  - No difference in time of symptoms when compared with oseltamivir
Xofluza (baloxavir marboxil)

- Influenza Oct 2018-Feb 2019 (CDC)
  - 15.4-17.8 million illnesses
  - 184,000-221,000 hospitalizations
  - 11,600-19,100 deaths
- Caused by influenza virus
  - May be self-limiting
  - May develop complications
    - Sinus and ear infections most common
    - Others: pneumonia, death
- Vaccination is the best prevention

Xofluza (baloxavir marboxil)

- Influenza Symptoms
  - Fever or chills (not always)
  - Cough
  - Sore throat
  - Runny or stuffy nose
  - Muscle or body aches
  - Headaches
  - Fatigue
  - Vomiting and diarrhea (children)
Xofluza (baloxavir marboxil)

**Xofluza**
- Polymerase acidic endonuclease inhibitor
- Prevents replication of the virus
- One-time dose
  - Improve compliance
  - May lead to overprescribing
  - Not approved for all groups

**oseltamivir, zanamivir, peramivir**
- Neuraminidase inhibitor
- Inhibits spread of virus particles within the host cell
- 5-day dosing
- Oseltamivir approved for more groups
- >98% circulating flu virus in U.S. susceptible to oseltamivir

**Xofluza (baloxavir marboxil)**
- Dosing (Epocrates)
  - Adults and adolescents 12 years and older
  - Available in 20 mg and 40 mg tablets
    - 40-79.9 kg: 40 mg PO x 1
    - >80 kg: 80 mg PO x 1
  - Separate from dairy/ calcium-fortified products
- Price: about $150 (wellrx.com)
- Contraindications: hypersensitivity to drug/ingredients
- Drug interactions
  - Polyvalent cation containing laxatives, antacids or supplements
  - Includes: iron, zinc, selenium, calcium, or magnesium.
Xofluza (baloxavir marboxil)

- Side effects (<1%)
  - diarrhea
  - bronchitis
  - nasopharyngitis
  - headache
  - Nausea

- Safety/efficacy has not been established for:
  - Pregnancy/lactation (no human data)
  - Children <12 or adults >65
  - Those weighing <40 kg
  - Severe renal or hepatic impairment
  - Avoid in these populations until more data become available

Montegrity (prucalopride)

“Hangin’ Tough”
Motegrity (prucalopride)

- Indications: Chronic idiopathic constipation (CIC) for adults
- Dosage & Administration: Oral tablet
- Adults 2 mg daily
- Severe renal impairment 1 mg daily

Clinical Trial Data

- 6 double-blind, placebo controlled
- 2530 patients (half received Motegrity 2 mg and have received placebo) for 12-24 weeks
- 76% female
- 76% White, 19% Asian, 3% Black
- Mean age 47
- Mean duration of CIC 16 years with 28% having it more than 20 years
CIC defined

- Having fewer than 3 spontaneous bowel movements per week that resulted in a feeling of complete evacuation and 1 or more of the following:
  - Lumpy or hard stool
  - Sensation of incomplete evacuation
  - Straining at defecation

Results

- Primary efficacy endpoint defined as:
- Patient with an average of 3 more complete spontaneous bowel movements (CSBM) per week over the 12-24 weeks
- All studies showed improvement in CSBM/week by week 1
- Median time to first CSBM after first dosing was 1.4-4.7 days as compared to 9-20 days in placebo.
Description & Pharmacology

- Selective Serotonin Type 4 (5-HT₄) receptor agonist
- Gastrointestinal prokinetic agent that stimulates colonic peristalsis that increase bowel motility
- Mean colonic transit time was reduced by 12 hours from a baseline of 65 hours for the 2 mg group compared to an increase of 0.5 hours from a baseline of 66 hours in placebo group

Pharmacokinetics

- Steady state in 3-4 days
- Half-life 24 hours
- Peak plasma concentration in 3 hours
- Excretion – 60% unchanged in urine 5% in feces
**Side Effects**

- Headache (19%) (9%)
- Abdominal pain (16%) (11%)
- Nausea (14%) (7%)
- Diarrhea (13%) (5%)
- Abdominal distension (5%) (4%)
- 5% of patients discontinued due to side effects in the clinical trials

*Red denotes placebo side effects*

**Suicidal Ideation**

- One patient attempted 7 days after the end of trial
- No attempts in placebo group
- 2 patients completed suicide that were previously treated with Motegrity – both had been off the drug for 30 days at time of death
Use in Special Populations

- Pregnancy - Available data from case reports with use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes
- Lactation – is present in milk – assess risk vs benefit
- Geriatric – No overall differences in safety or efficacy
- Renal impairment – dose adjustment to 1 mg daily

Drug Interactions

- Erythromycin concentrations increased 40%
- No interaction with warfarin, digoxin, paxil, OCP’s
- No impact on fertility
Nuzyra (Omadacyine)

“You Got It”

• Approved by FDA October 2, 2018
• Modernized tetracycline
• Oral IV and Oral antibiotic
• Indications:
  • Antibacterial for Community Acquired Bacterial pneumonia (CABP)
  • Acute Bacterial Skin and Skin Structure Infections (ABSSI)
Most common leading infection leading to infection in all age groups
Economic effect is approximately $17 billion in the United States
CABP population 18 years older:
Symptoms 3 or more of the following: cough, purulent sputum production, dyspnea, or pleuritic chest pain
And at least 2 abnormal vital signs
Laboratory confirmed pneumonia

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**Nuzyra (Omadacycline)**

<table>
<thead>
<tr>
<th>CABP</th>
<th>ABSSSI</th>
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<tbody>
<tr>
<td><strong>GRAM-POSITIVE BACTERIA</strong></td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td>Enterococcus faecalis</td>
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<tr>
<td>Staphylococcus aureus (methicillin-susceptible isolates)</td>
<td>S. aureus (methicillin-susceptible and-resistant isolates)</td>
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<tr>
<td><strong>GRAM-NEGATIVE BACTERIA</strong></td>
<td>Staphylococcus lugdunensis</td>
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<td>Haemophilus influenzae</td>
<td>Streptococcus anginosus grp. (includes S. anginosus, Streptococcus intermedius, and Streptococcus constellatus)</td>
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<td>Haemophilus parainfluenza</td>
<td>Streptococcus pyogenes</td>
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<td>Klebsiella pneumonia</td>
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<td><strong>OTHER MICROORGANISMS</strong></td>
<td><strong>GRAM-NEGATIVE BACTERIA</strong></td>
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<td>Chlamyphila pneumoniae</td>
<td>Enterobacter cloacae</td>
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<td>Legionella pneumophila</td>
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<td>Mycoplasma pneumoniae</td>
<td>K. pneumoniae</td>
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Nuzyra (Omadacyine)

- Approval by several multinational double-blind, double-dummy, randomized, non-inferiority trials
- Compared omadacycline with moxifloxacin
- Primary end point was early clinical response
- Conclusions of study: omadacyline was noninferior to moxifloxacin

**Dosing**
- Once per day oral & IV

**Adverse Reactions**
- Most common nausea, vomiting, diarrhea
- IV infusion site reaction

**Contraindications**
- Known hypersensitivity to omadacycline or tetracycline class antibacterial drugs

**Drug interactions**
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage while taking NUZYRA.
- Absorption of tetracyclines, including NUZYRA is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron containing preparations.
Seysara (sarecycline)

“I’ll Be Loving You Forever”

- Approved by FDA October 2018
- Oral, narrow-spectrum, tetracycline-derived antibiotic
  - Targets *P. acnes*; *S. aureus*
  - Anti-inflammatory properties
- Indication
  - Moderate to severe acne vulgaris
  - Patients ages 9 years and older
- Approval based on two large Phase III RCTs
  - Significantly reduced inflammatory lesion count at 12 weeks compared to placebo (*p*<0.004)
Seysara (sarecycline)

• Acne overview
  – Affects ~90% of world’s population
  – Chronic inflammation of pilosebaceous glands
  – Onset typically during puberty

• Four major factors produce acne lesions
  – Elevated sebum secretion
  – Abnormal keratinization
  – Bacterial colonization by *Propionibacterium acnes*
  – Inflammation

Seysara (sarecycline)

• Current anti-acne drugs (topical and oral)
  – Retinoids
  – Anti-androgens
  – Antibiotics
  – Benzoyl peroxide

• Advantages of sarecycline
  – Effective if resistance to clindamycin or erythromycin
  – Once-daily vs 2-4x daily improves adherence
  – Fewer adverse effects compared to retinoids, anti-androgens
  – More effective than benzoyl peroxide
Seysara (sarecycline)

- Cautions/possible adverse effects
  - GI irritation ("pill esophagitis")
  - Photosensitivity
  - Risk for *C-diff* associated diarrhea
  - Possible CNS effects
  - Overgrowth non-susceptible organisms
- Can cause fetal harm in pregnancy
- Use in children up to age 8 yrs may cause tooth discoloration

Seysara (sarecycline)

- Patient education
  - Dosing: tablets 60, 100, 150 mg
    - Weight-based from 33 kg-136 kg
  - Price: GoodRx $850 for 30 tablets
  - Evaluate efficacy at 12 weeks; safety beyond 12 mos not established
  - Take with or without food; not with milk
  - Take with enough fluids to reduce esophageal irritation
  - Drug interactions
    - Beta-lactams
    - Tretinoins/oral retinoids
    - Oral iron products