PHARMACOLOGY UPDATE 2019: NEW DRUGS!

Kentucky Coalition of Nurse Practitioners and Nurse-Midwives
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Disclosure
Melinda C. Joyce “declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”

Objectives
1. Discuss new medications that have been recently approved by the FDA, focusing on indications for use, potential adverse reactions, and contraindications
2. Evaluate the place in therapy of new medications compared to existing therapies
3. Review safety concerns for the new medications and how these concerns may impact their use

Annual New Drug Approvals: 2009-2018

New Drugs: 2018

First-In-Class
• 32.2% of those approved in 2018 were identified as First-In-Class
  • A new and unique mechanism of action for treating a medical condition
  • Mechanism of action is different than what is currently available
• Noteworthy First-In-Class are those agents that are likely to quickly make a positive impact on care
  • Lofexidine (Lucemyra) – the first non-opioid drug product to help reduce opioid withdrawal symptoms
  • Belizumab (Frofradex) – a new type of antiretroviral for adult patients who have multi-drug resistant HIV-1 infection
### Drugs for Cancer

- 28.8% of the new drugs are for the treatment of cancer
- There were new advances in the treatment of breast, prostate, and lung cancer
- Drug therapy for other types of cancer:
  - Thyroid
  - Pheochromocytoma
  - Refractory acute myeloid leukemia
  - non-Hodgkin lymphoma
- Cancer therapy for any kind of tumor that has a specific genetic marker
- Targeted treatment based on a specific characteristic of a tumor instead of the site of origin

### Drugs for Rare Diseases

- 58% were approved to treat rare or “orphan” diseases that affect 200,000 or fewer Americans
- Burosumab (Crysvita) – first drug to treat adults and children ages one year and older with a linked hypophosphatemia (XLH), a rare, inherited form of rickets
- Cannabidiol (Epidiolex) – treatment of seizures associated with two and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome
- Pegvaliase (Palynziq) – approved for adults with a rare and serious genetic disease, phenylketonuria (PKU)

<table>
<thead>
<tr>
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<th>Trade Name</th>
<th>Brief Indication</th>
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<tr>
<td>Alacizumab **</td>
<td>Figitas</td>
<td>A prosaposin analog for Lambert-Eaton myasthenic syndrome</td>
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<td>Aplador **</td>
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<td>Avatrombopag</td>
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<td>A thrombopoietin receptor agonist for thrombocytopenia in patients with chronic liver disease scheduled for a procedure</td>
<td>Tablet</td>
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<td>Batimorex</td>
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<td>Baclofen</td>
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<td>Beligrev/Entacrinol/</td>
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<td>Baricitinib</td>
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<tr>
<td>Burosumab</td>
<td>Crysvita</td>
<td>X-linked hypophosphatemia</td>
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| ** – approved for adults with a rare and serious genetic disease, phenylketonuria (PKU) **

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<td>Calaspargase pegol</td>
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<td>Carfilzomib **</td>
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<td>Camrelizumab</td>
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<td>Dovatek **</td>
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<td>Relapsed or refractory chronic lymphocytic leukemia; small lymphocytic lymphoma; and follicular lymphoma</td>
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<td>Elagolix</td>
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<td>Gonadotropin-releasing hormone receptor antagonist for endometriosis pain</td>
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<td>Elapagademasl **</td>
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<td>Empatulimab **</td>
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<td>Primary hemophagocytic lymphohistiocytosis</td>
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<td>Community-acquired pneumonia and acute</td>
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<td>bacterial skin and skin structure infections</td>
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<td>Patirion**</td>
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<td>mediated amyloidosis</td>
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<td>Pegvaliase**</td>
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<td>Piazoncin</td>
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<td>Ravulizumab**</td>
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<td>Rifamycin</td>
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<td>Traveler's disease caused by E. coli</td>
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<td>Severe acne vulgaria</td>
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<td>Radicial cure of Plasmodium vivax malaria</td>
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<td>Tagraxofusp**</td>
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<td>metastatic breast cancer</td>
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<td>Symteko</td>
<td>Combination agent for cystic fibrosis with a</td>
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<td>Ivaclafarin**</td>
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<td>Tildrakizumab</td>
<td>Aumya</td>
<td>Interleukin-23 antagonist for moderate to severe</td>
<td>Injection</td>
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<td>plaque psoriasis</td>
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**Notable Patent Expirations in 2018**

- Budesonide/ Formoterol (Symbicort)
- Cinacalcet (Sensipar)
- Dabigatran (Pradaxa)
- Pregabalin (Lyrica)
- Solifenacin (Vescare)
- Tadalafil (Cialis)
- Tiotropium (Spiriva)

**Notable Withdrawals in 2018**

- Daclizumab (Zinbryta)
  - A monoclonal antibody indicated for the treatment of relapsing multiple sclerosis
  - Was removed by the manufacturer from the worldwide market in March, 2018
  - Removed due to safety concerns, including reports of severe liver damage and immune-related conditions

**ANTIMICROBIAL AGENTS**
Antimicrobial Agents

- **Baloxavir**
  - An oral antiviral for treatment of uncomplicated influenza

- **Eravacycline**
  - A tetracycline antibiotic for complicated intra-abdominal infections

- **Omadacycline**
  - An oral/parenteral tetracycline for community-acquired pneumonia and skin infections

- **Plazomicin**
  - An aminoglycoside for complicated urinary tract infections including pyelonephritis

- **Rifamycin**
  - An antibacterial for travelers' diarrhea caused by non-invasive strains of *E. coli*

- **Sarecycline**
  - An oral tetracycline for moderate to severe acne

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**Baloxavir (Xofluza)**

- **Indication:**
  - Single dose oral treatment of acute uncomplicated influenza in patients > 12 years who have been symptomatic for no more than 48 hours

- **Mechanism of Action:**
  - Baloxavir marboxil is an oral prodrug that is converted to baloxavir
  - Inhibitor of the endonuclease activity, which is required for viral gene transcription, thus inhibiting viral replication
  - Has shown activity against both influenza A and B, including strains resistant to current antiviral agents
  - As compared to placebo, baloxavir was found to significantly shorten time to alleviation of symptoms

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**Baloxavir**

- **Cautions:**
  - Has not been studied in pediatric patients or in pregnant patients
  - Has not been evaluated for prophylaxis

- **Adverse Effects:**
  - Most common side effects are GI, especially diarrhea
  - Nasopharyngitis has also been reported

- **Drug Interactions:**
  - Concomitant administration with antacids and vitamins and minerals, such as iron, calcium, or magnesium should be avoided

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**Omadacycline (Nuzyra)**

- **Indication:**
  - Once daily oral or injectable tetracycline antibiotic indicated for:
    - Community-acquired bacterial pneumonia
    - Susceptible strains include: *Streptococcus pneumoniae; Staphylococcus aureus; Haemophilus influenzae; Klebsiella pneumoniae; Legionella pneumophila; Mycoplasma and Chlamydia*
  - Acute bacterial skin and skin structure infections (ABSSSI)
    - Susceptible strains include: *Staphylococcus aureus; Staphylococcus lugdunensis; Streptococcus pyogenes; Enterococcus faecalis; Enterobacter cloacae; and Klebsiella pneumonia*

- **Mechanism of Action:**
  - Omadacycline is a tetracycline that binds to the 3OS ribosomal subunit and blocks protein synthesis

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**Omadacycline**

- **Cautions:**
  - Tetracycline Allergy
  - Pregnancy: In the second and third trimesters, may cause permanent discoloration of the teeth or reversible inhibition of bone growth
  - Nursing: Not recommended for administration during breast feeding or for four days after the last dose
  - Pediatric: Not recommended for children < 8 years of age and not studied in patients < 18 years
  - Mortality rate was higher in older patients (> 65 years) with multiple comorbidities treated with omadacycline for community-acquired bacterial pneumonia compared to patients treated with moxifloxacin
  - Should not be mixed with other drugs or added to solutions of other drugs
Omadacycline

- **Adverse Effects:**
  - GI side effects
  - Nausea (2-22%)
  - Vomiting (3-11%)
  - Cardiovascular, especially hypertension (3%)
  - Central nervous system
    - Headache (3%)
    - Insomnia (3%)
    - Vertigo
  - Infusion site reactions
  - Abnormal liver function tests
  - Clostridium difficile-associated diarrhea
  - Oral and vulvovaginal candidiasis
  - Anaphylactic reactions have been reported

- **Drug Interactions:**
  - May enhance the anticoagulant effects of vitamin K antagonists
  - Avoid dairy, antacids, iron preparations, and multivitamins for at least 4 hours after the oral dose
  - The injectable product should be administered through a dedicated line

- **Availability/ Cost:**
  - 150 mg tablets
    - $237.00 each
  - 100 mg single dose vials for reconstitution
    - $414.00/ 100 mg

- **Dose:**
  - **Pneumonia**
    - **IV:**
      - 200 mg IV as a single dose on day 1 or 100 mg IV twice daily on day 1 followed by 100 mg IV once daily for 7 to 14 days
    - **Oral:**
      - 300 mg once daily for 7 to 14 days
  - **ABSSSI**
    - **IV:**
      - 200 mg IV as a single dose on day 1 or 100 mg IV twice daily on day 1 followed by 100 mg IV once daily for 7 to 14 days
    - **Oral:**
      - 450 mg orally on days 1 and 2, followed by 300 mg once daily for 7 to 14 days
      - 200 mg dose should be infused over at least 60 minutes and 100 mg dose over 30 minutes
      - Reconstituted solution should be a clear, yellowish-orange color

Rifamycin (Aemcolo)

- **Indication:**
  - Treatment of travelers’ diarrhea caused by non-invasive strains of *E. coli* in adults
  - Is not indicated for patients with diarrhea complicated by fever or bloody stool or due to pathogens other than non-invasive *E. coli*

- **Mechanism of Action:**
  - Rifamycin inhibits bacterial synthesis by inhibiting the beta-subunit of the bacterial DNA-dependent RNA polymerase

- **Cautions:**
  - Effectiveness has not been demonstrated for other pathogens
  - Discontinue treatment and consider alternative antibacterial therapy if diarrhea worsens or persists for longer than 48 hours
  - Medication should not be crushed, broken, or chewed and should be taken with at least 6 to 8 ounces of liquid (preferably water)

- **Adverse Effects:**
  - Constipation (4%) and abdominal pain
  - Headache (3%)

- **Drug Interactions:**
  - None identified at this time due to low systemic absorption

- **Availability/ Cost:**
  - 194 mg tablets
    - $14.40 each

- **Dose:**
  - 388 mg twice daily for 3 days
Sarecycline

- **Indications:**
  - A tetracycline-derived antibiotic for moderate to severe non-nodular acne in patients aged 9 and older

- **Mechanism of Action:**
  - Tetracyclines inhibit protein synthesis by binding to the 30S and possibly the 50S ribosomal subunit of susceptible bacteria
  - The full mechanism of action for the treatment of acne is not fully understood

- **Efficacy:**
  - Has been shown to significantly reduce lesions as early as 3 weeks after start of treatment

- **Cautions:**
  - Efficacy beyond 12 weeks and safety beyond 12 months has not been established
  - Has not been studied in the treatment of any other infections
  - Pregnancy: Teratogenic effects are possible, especially during the second and third trimesters
    - May cause permanent discoloration of the teeth or reversible inhibition of bone growth
  - Breast Feeding: Not recommended
  - Pediatric: Not recommended for children < 9 years of age
  - Intracranial hypertension:
    - Has been associated with the tetracyclines
    - Headache, blurred vision, and/or papilledema may occur
    - Women of child-bearing age who are overweight are at greater risk
    - Permanent visual loss is possible

- **Adverse Effects:**
  - GI: Nausea (3%)
  - CNS Effects: Lightheadedness, dizziness, and vertigo may occur
  - Photosensitivity
  - Superinfection, including potential Clostridium difficile-associated diarrhea

- **Drug Interactions:**
  - Avoid concomitant administration of oral isotretinoin (may increase the chance of the intracranial hypertension)
  - Separate dosing from antacids containing aluminum, calcium, magnesium, bismuth subsalicylate, and iron-containing products by at least 2 hours
  - May need to reduce anticoagulant doses of warfarin
  - Monitor digoxin for possible toxicity and adjust dose as needed

- **Availability/ Cost:**
  - 60 mg tablets
  - 100 mg tablets
  - 150 mg tablets
  - All doses are priced the same at $34.40 per tablet

- **Dose:**
  - 33-54 kg: 60 mg once daily
  - 55-84 kg: 100 mg once daily
  - 85-136 kg: 150 mg one daily
  - Should be taken with 8 oz of water
  - Avoid calcium-containing products, medications or foods for at least 2 hours

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**CENTRAL NERVOUS SYSTEM AGENTS**

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**Migraine**

- 25% of women and 6% of men in the United States have had a migraine headache
  - Prevalence is highest between age 25 – 55 years
  - Headache lasting from 4 to 72 hours
  - At least two of the following:
    - Unilateral location
    - Pulsating quality
    - Moderate or severe intensity
    - Aggravation by routine physical activity
  - At least one of the following:
    - Nausea and/or vomiting
    - Photophobia and phonophobia
  - At least five attacks fulfilling these criteria
  - No evidence of organic disease
Etiology of Migraine Headache

- May be due to both vascular changes and neuronal etiology
- Vascular component - constriction of blood vessels followed by reflex dilation – the dilation is what leads to the headache
- Neuronal component - depressed neuronal activity spreads across the brain and the headache occurs due to an inflammatory response due to compensatory over-activity in certain nerves leading to release of substance P and other vasoactive substances
- Genetic component - familial tendencies

Triggers
- Food triggers – cheese; wine; alcohol; chocolate; caffeine
- Behavior triggers – stress; sleep deprivation or excess; skipped meals; hormonal changes
- Environmental triggers – glare or flickering lights; noise; odors; weather changes

Treatment can be behavioral, abortive, or preventive

Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists

- Erenumab-aooe (Aimovig)
- Fremanezumab-vfrm (Ajovy)
- Galcanezumab-gnlm (Emgality)

Indications:
- Indicated for the preventive treatment of migraine in adults
- May be best for those patients with adherence issues, side effects, poor response, or drug interaction concerns with oral preventive agents

Mechanism of Action:
- Human immunoglobulin G2 monoclonal antibody that has high affinity binding to the calcitonin gene-related peptide receptor (CGRP)
- CGRP receptor is believed to be released during a migraine and transmits signals that can cause incapacitating pain
- Produced through recombinant DNA technology

CGRP Antagonists

<table>
<thead>
<tr>
<th>Erenumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
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<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Selectively targets and blocks the CGRP receptor</td>
<td>Binds to the CGRP ligand and blocks its binding to the receptor</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Decrease in monthly migraine days as compared to placebo: 70 mg: Decreased by 3.2 days Placebo: Decreased by 1.8 days</td>
<td>Decrease in monthly migraine days as compared to placebo: 225 mg: Decreased by 4.2 days Placebo: Decreased by 1.9 days</td>
</tr>
<tr>
<td>Dosage/Administration</td>
<td>70 mg subcutaneously once monthly</td>
<td>225 mg subcutaneously once monthly or 675 mg every 3 months</td>
</tr>
<tr>
<td>Availability/Cost</td>
<td>70 mg auto-injector: $575.00</td>
<td>225 mg pre-filled pen: $575.00</td>
</tr>
<tr>
<td>Notes</td>
<td>The needle shield and cap of the pen contain natural rubber, which could be of concern for those that are sensitive to latex</td>
<td>The 675 mg dose is given by three consecutive injections of 225 mg</td>
</tr>
</tbody>
</table>

CGRP Antagonists

- Cautions:
  - Theoretical concern for cardiac side effects as these agents antagonize calcitonin gene-related peptide, which is a vasodilator
  - Unknown as to what kind of effects could be seen when used in pregnancy

- Adverse Effects:
  - Injection site reactions, including injection site erythema, pain, and pruritus
  - Contraindication (3.6%)
  - May be more common with erenumab
  - Muscle cramps and/or spasms (2%)
  - Hypersensitivity reactions requiring discontinuation and/or corticosteroid treatment have been reported within hours to one month after administration of fremanezumab and galcanezumab
Endometriosis

- Chronic, estrogen-dependent, inflammatory disorder affecting up to 10% of women during their reproductive years
- Commonly associated with dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and infertility
- Cause of endometriosis is not fully understood, but involves endometrial cells growing outside of the uterus
- Endometrial tissue outside of the uterus leads to chronic inflammation
- Medications and surgical therapies (ablation, hysterectomy) are treatment options

Elagolix (Orlissa)

- **Indication:**
  - Management of moderate-to-severe pain associated with endometriosis

- **Mechanism of Action:**
  - Short-acting gonadotropin-releasing hormone antagonist that suppresses pituitary and ovarian hormone function
  - Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are suppressed leading to decreased blood concentrations of estradiol and progesterone
  - Gonadotropin-releasing hormone antagonists do not cause a symptom flare like gonadotropin-releasing agonists, such as leuprolide or nafarelin as down regulation is not required

Elagolix

- **Efficacy:**
  - Studies showed a higher proportion of women treated with elagolix were responders for dysmenorrhea and non-menstrual pelvic pain as compared to placebo at month 3 of treatment
  - Statistically significant reduction from baseline for endometriosis pain at month 3
  - Statistically significant reduction from baseline for dysmenorrhea and non-menstrual pelvic pain scores at month 6

- **Cautions:**
  - Pregnancy
    - Contraindicated as early exposure in pregnancy may increase risk of early pregnancy loss
  - Risk of decrease in bone mineral density
  - Consider bone density assessment if history of low-trauma fracture or other risk factors for osteoporosis or bone loss
  - Supplementation with calcium and vitamin D may be beneficial
  - Duration of treatment should be limited
  - Severe liver dysfunction - contraindicated

Elagolix

- **Adverse Effects:**
  - Night sweats (45%)
  - Hot flushes (45%)
  - Amenorrhea (45%)
  - Decreased bone mineral density (21%)
  - Headache (20%)
  - Nausea (16%)
  - Arthralgias (5%)
  - Increased liver function tests
  - Decreased libido
  - Mood changes
  - Watch for depression and suicidal ideation

Elagolix

- **Drug Interactions:**
  - Estrogen-containing contraceptives may reduce the effectiveness of elagolix
  - Strong CYP3A inhibitors
    - Duration of treatment may need to be reduced
  - Strong CYP3A inducers
    - Plasma concentrations may be decreased
    - May potentiate p-gp substrates (such as dabigatran and digoxin) leading to an increased concentration and activity of those agents

Elagolix

- **Availability/ Cost:**
  - 150 mg tablets
    - $36.21/ each
  - 200 mg tablets
    - $18.10/ each
**Elagolix**

- **Dose:**
  - Endometriosis
    - 150 mg daily with a maximum treatment duration of 24 months
  - Endometriosis with dyspareunia
    - 200 mg twice daily with a maximum treatment duration of 6 months
  - A non-hormonal contraceptive should be used during elagolix treatment and for one week after stopping elagolix, as estrogen-containing contraceptives may reduce the effectiveness of elagolix.

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**Menopausal Symptoms**

- About half of peri-menopausal and post-menopausal women experience vaginal symptoms due to the loss of estrogen.
- Symptoms include:
  - Genital: irritation, dryness, burning, and itching
  - Sexual: dyspareunia, discomfort
  - Urinary: urgency, frequency, recurrent urinary tract infections
- Vaginal lubricants and moisturizers provide symptom relief but generally do not have an effect on vaginal atrophy.
- Vaginal estrogens can improve vaginal symptoms by:
  - Decreasing vaginal pH
  - Improving elasticity and thickness of vulvovaginal tissues
  - Increasing vaginal secretions and decreasing vaginal dryness
  - Restoring vaginal blood flow
  - Reducing the risk of recurrent urinary tract infections

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**Estradiol (Imvexxy)**

- **Indication:**
  - Estradiol softgel capsule (vaginal insert) indicated for moderate-to-severe dyspareunia due to menopause

- **Mechanism of Action:**
  - Local estrogens have been shown to reduce vaginal pH levels and mature the vaginal and urethral mucosa after 12 weeks of therapy, improving vaginal dryness and mucosal atrophy.

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- **Efficacy:**
  - Women were assigned to placebo, estradiol 4 mcg, or estradiol 10 mcg for 12 weeks with the following assessments:
    - Most bothersome moderate to severe symptoms of dyspareunia
    - Percentage of vaginal superficial and percentage of vaginal parabasal cells on vaginal smear
    - Vaginal pH
  - For dyspareunia, both strengths of estradiol were found to be statistically superior as compared to placebo.
  - A statistically significant increase in the percentage of superficial cells and a corresponding decrease in parabasal cells was noted in both strengths of estradiol as compared to placebo.
  - The mean reduction in vaginal pH was also statistically significant for both strengths as compared to placebo.

- **Contraindications:**
  - Undiagnosed abnormal genital bleeding
  - Known, suspected, or history of breast cancer or other estrogen-dependent neoplasia
  - Active deep vein thrombosis (DVT), pulmonary embolism (PE) or history of these conditions
  - Active or history of thromboembolic disease
  - Hepatic impairment or disease
  - Hereditary angioedema
  - Estrogens with or without progestin should not be used to prevent cardiovascular disease

- **Cautions:**
  - Increased risk of endometrial carcinoma or hyperplasia when used with an intact uterus
  - Adding progestin is recommended
  - Increased risk of thromboembolic disorders
  - Monitor and manage risk factors
  - Increase risk of gallbladder diseases

- **Adverse Effects:**
  - Headache (13%)
  - Insomnia
  - Hot flash
  - Breast tenderness or discomfort
  - Diarrhea
  - Back pain
  - Vaginitis/ Vaginal discomfort/ Vaginal pain
  - Urinary tract infection
Estradiol

- Drug Interactions:
  - May be antagonized by strong CYP3A4 inducers
  - May be potentiated by strong CYP3A4 inhibitors
  - May need to increase the thyroid dose with concomitant thyroid replacement

- Availability/ Cost:
  - 4 mcg vaginal insert
    - $180/ month supply
  - 10 mcg vaginal insert
    - $180/ month supply

Segesterone/ Ethinyl Estradiol (Annovera)

- Indications:
  - Contraceptive vaginal ring, which provides an entire year of protection against unintended pregnancy while under a woman's control

- Mechanism of Action:
  - A vaginal ring that releases a combination of two hormones, segesterone, a progestin and ethinyl estradiol, an estrogen to suppress ovulation

- Efficacy:
  - Based on two clinical studies that last for 12 months, about 2-4 women out of 100 may get pregnant during the first year
  - This efficacy is similar to contraceptive skin patches but not as effective as intrauterine devices or injections

Segesterone/ Ethinyl Estradiol

- Contraindications:
  - Undiagnosed abnormal genital bleeding
  - Known, suspected, or history of breast cancer or other estrogen-dependent neoplasia
  - Active deep vein thrombosis (DVT), pulmonary embolism (PE) or history of these conditions
  - Active or history of thromboembolic disease
  - Hepatic impairment or disease
  - Should not be used in patients over the age of 35 who smoke
  - Discontinue if pregnancy should occur

- Cautions:
  - Increased risk of thromboembolic disorders
  - Monitor and manage risk factors
  - Use cautiously if uncontrolled hypertension
  - Use cautiously if uncontrolled dyslipidemia
  - Increase risk of gallbladder disease
  - Significant changes in headaches
  - Not adequately evaluated in patients with a body mass index > 29
  - Combination hormonal contraceptives do not protect against HIV infection or other sexually transmitted diseases

- Adverse Effects:
  - Headache, including migraine (35%)
  - Nausea (25%)
  - Vomiting (25%)
  - Abdominal pain (13%)
  - Vaginal discharge (12%)
  - Breast tenderness (10%)
  - Toxic shock syndrome
  - Heavy menstrual bleeding
  - Breakthrough bleeding
  - Pruritus

- Dose:
  - One vaginal insert daily for 2 weeks, followed by one insert twice weekly
  - Should begin with the 4 mcg dose, increasing to the 10 mcg dose if needed
  - Manually inserted by patient without an applicator
  - Can be used at any time of the day
  - The use of a progestin is recommended by the manufacturer
Segesterone/ Ethinyl Estradiol

- **Drug Interactions:**
  - May be antagonized by strong CYP3A4 inducers
  - May decrease effectiveness or increase breakthrough bleeding
  - May need a back-up or alternative method of contraception
  - May need to increase the thyroid dose with concomitant thyroid replacement

- **Availability/ Cost:**
  - Silicone elastomer vaginal system containing 103 mg segesterone and 17.4 mg ethinyl estradiol
  - Not yet marketed or priced

Segesterone/ Ethinyl Estradiol

- **Dose:**
  - The vaginal system is inserted and left in place for 21 days
  - The day that the system is inserted is considered to be day 1
  - If patient has not taken a hormonal contraceptive, insert between days 2 and 5 of the menstrual cycle
  - The vaginal system is removed on day 22 and is left out for 7 full days
  - Bleeding should occur during the 7 days that the vaginal system is out
  - The system should be cleaned with warm water and mild soap, dried with a clean cloth and stored in the provided case, away from children, pets, and extreme temperatures
  - The vaginal system is then replaced for another 4 week cycle and this can be repeated for 13 cycles
  - After 13 cycles, a new prescription will need to be obtained as the system will no longer contain sufficient amount of hormones

Segesterone/ Ethinyl Estradiol

- **Notes:**
  - For the first cycle, a back-up barrier contraceptive should be used for the first 7 days
  - Any deviation from the recommended dosing cycle that results in the ring being out of the vagina for more than 7 days requires back-up contraception
  - If the ring is accidentally expelled during the 21 days of vaginal use and replaced within 2 hours, back-up contraception is not required
  - If the ring is accidentally expelled and out of the vagina for more than 2 hours, back-up contraception should be used until the ring has been in place for 7 consecutive days
  - Do not insert in less than 4 weeks following childbirth

Hyperhidrosis

- Hyperhidrosis or excessive sweating is a common disorder, affecting approximately 2-3% of Americans.
- Can be axillary or palmar/planter hyperhidrosis
- Often begins in adolescence and continues through life
- Although hyperhidrosis can be caused by certain neurologic and endocrine disease, most cases are in otherwise healthy patients
- Heat and emotions may trigger hyperhidrosis in some, but most complain of sweating nearly all of their waking hours, regardless of mood or weather
- Most standard antiperspirants contain aluminum, which obstructs sweat glands
- Prescription antiperspirants contain higher concentrations of aluminum, but can lead to skin irritation

Hyperhidrosis

- Oral anticholinergic agents have been used off-label but adverse effects may be difficult for some patients to tolerate
- Onabotulinum toxin A injected intradermally into the axillae is a FDA-approved treatment for severe axillary hyperhidrosis and may diminish underarm sweating for 6-9 months
- Can be expensive and painful
- A last resort is ablation or removal of the sweat glands
Glycopyrronium (Qbrexza)

- **Indication:**
  - A pre-moistened cloth containing a long-acting anticholinergic agent for once daily topical treatment of primary axilla hyperhidrosis in patients ≥ 9 years of age

- **Mechanism of Action:**
  - Competitive inhibitor of acetylcholine receptors located on peripheral tissues, including sweat glands, thereby reducing sweating

- **Efficacy:**
  - Two studies showed that once daily treatment was associated with larger reductions from baseline in sweat production than placebo (cloth with no drug)
  - Patients also self-reported an improvement in sweating severity
    - “Thinking about last night and today, how was your underarm sweating? 10 (worst possible sweating) to 0 (no sweating)"

- **Cautions:**
  - Use cautiously in conditions that can exacerbated by anticholinergic effects
  - No data on the use of the medication in pregnancy or lactation
  - The product is considered to be flammable

- **Adverse Effects:**
  - Systemic absorption is minimal but the following anticholinergic effects have been reported:
    - Dry mouth (24%)
    - Local skin reactions (17%)
    - Mydriasis (7%)
    - Ophthalmic pain (6%)
    - Headache (5%)
    - Blurred vision (4%)
    - Uninary hesitation (4%)

- **Drug Interactions:**
  - Coadministration with other anticholinergic drugs could result in additive anticholinergic effects

- **Availability/Cost:**
  - Single-use cloths of a 2.4% glycopyrronium solution in cartons of 30 pouches
  - $550/ carton

- **Dose:**
  - One cloth should be wiped across clean, dry unbroken skin once every 24 hours
  - The same cloth can be used for both underarms
  - Patients should be instructed to wash their hands immediately after application

Opioid Withdrawal

- **Indication:**
  - Opioids reduce norepinephrine concentrations and with continued use, the brain establishes a new equilibrium by increasing norepinephrine production to maintain normal functioning

- **Mechanism of Action:**
  - When an opioid is discontinued or its dosage significantly decreased, the brain’s increased norepinephrine concentrations are no longer offset by the presence of the opioid

- **Adverse Effects:**
  - This results in a norepinephrine surge that produces acute withdrawal symptoms, such as aches/ pain; muscle spasms; twitching; tension; pounding heart, sweating; stomach cramps; nausea; vomiting; insomnia; agitation; and drug craving.

- **Drug Interactions:**
  - The symptoms of acute withdrawal are barriers for patients trying to overcome opioid addiction

- **Availability/Cost:**
  - First non-opioid agent approved to mitigate opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults

- **Mechanism of Action:**
  - A central alpha-2 adrenergic agonist that reduces the release of norepinephrine and decreases sympathetic tone

Lofexidine (Lucemyra)

- **Indication:**
  - First non-opioid agent approved to mitigate opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults

- **Mechanism of Action:**
  - A central alpha-2 adrenergic agonist that reduces the release of norepinephrine and decreases sympathetic tone
Lofexidine (Lucemyra)

- **Efficacy:**
  - Evaluated in two placebo-controlled trials in patients who were dependent on short-acting opioids (heroin, hydrocodone, oxycodone)
  - Primary endpoints were the mean total score on the Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)
  - Higher scores indicate a greater withdrawal symptom severity
  - Both studies showed benefit with lofexidine as compared to placebo

- **Cautions:**
  - Use has not been established in pregnant or breast-feeding patients
  - Avoid in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, marked bradycardia, or congenital long QT syndrome
  - The agent is not a treatment for opioid use disorder and should only be used in conjunction with a comprehensive management program
  - There could be a risk of potential opioid overdose if the patient were to go back to the previous pre-treatment opioid dose

- **Adverse Effects:**
  - Orthostatic hypotension (29-42%)
  - Bradycardia (24-32%)
  - Hypotension (30%)
  - Insomnia (51-55%)
  - Dizziness (23%)
  - Xerostomia (11%)
  - Tinnitus
  - Depression

- **Drug Interactions:**
  - May see increased QT prolongation when given with other medications that cause QT prolongation, such methadone
  - May potentiate the CNS depressant effects of benzodiazepines, barbiturates, alcohol
  - Potentiated by CYP2D6 inhibitors
  - Monitor for orthostatic hypotension and bradycardia

- **Availability/ Cost:**
  - 0.18 mg tablets
  - $24.83 each

Lofexidine

- **Dose:**
  - Three 0.18 mg tablets taken orally four times daily at 5 to 6 hour intervals
  - Should be used during peak withdrawal (usually first 5 to 7 days following the use of last opioid)
  - Treatment may be continued for up to 14 days with dosing guided by symptoms
  - The dose should be tapered through gradual dose reduction over 2 to 4 days for discontinuation
  - For renal impairment:
    - Creatinine clearance: 30-89.9 ml/min: two tablets four times a day
    - Creatinine clearance: <30 ml/min: one tablet four times a day
  - For hepatic impairment:
    - Mild: No dosage adjustment
    - Moderate: two tablets four times a day
    - Severe: one tablet four times a day
  - Patients should clearly be informed of the risks, such as the CNS depression, hypotension, and bradycardia that can occur with the medication

Hyperkalemia

- Characterized by elevated serum potassium concentrations (generally >5 mEq/L) and may be associated with complications, such as cardiac arrhythmias
- Most often experienced by patients with kidney disease or heart failure
- Management includes:
  - Reduction in dose of potassium supplements or medications that can increase potassium levels
  - Restriction of foods or beverages with a high potassium content
  - Use of diuretics to promote the excretion of potassium, along with other electrolytes
  - Use of medications to specifically treat the hyperkalemia
Sodium zirconium cyclosilicate (Lokelma)

- **Indication:**
  - An oral potassium binder indicated for the treatment of hyperkalemia in adults

- **Mechanism of Action:**
  - Non-absorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium
  - Very high affinity for potassium ions
  - By binding with potassium in the lumen of the gastrointestinal tract increases fecal potassium excretion and reduces potassium concentrations

- **Efficacy:**
  - There were multiple placebo-controlled studies including patients with chronic kidney disease, heart failure, or diabetes
  - Some patients were also taking medications that could increase potassium levels, such as drugs that impact the renin-angiotensin-aldosterone system
  - In each of the various phases, there was a greater reduction in serum potassium levels than placebo for the acute stage
  - Patients with a higher starting concentration of potassium (>5.5 mEq/L) had a greater response of mean potassium reduction
  - Efficacy was also established in longer studies for the maintenance stage

- **Cautions:**
  - Should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action
  - Avoid use in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative motility disorders
  - Use cautiously in patients that are prone to fluid overload

- **Adverse Effects:**
  - Edema (6%)
  - Hypokalemia
  - Each 10 gram dose contains 800 mg sodium

- **Drug Interactions:**
  - In general, other oral medications should be administered at least 2 hours before or 2 hours after

- **Availability/ Cost:**
  - 5 gram packet
    - $26.20
  - 10 gram packet
    - $26.20

- **Dose:**
  - Initial
    - 10 grams three times a day for up to 48 hours
    - Adjust dose by 5 grams daily at one week intervals as needed based on serum potassium
  - Maintenance
    - 10 grams once daily with a maximum dose of 15 grams
    - Serum potassium levels should be monitored and the dosage adjusted based on the concentration and desired target range

- **Notes:**
  - The entire contents of the packet should be emptied into a drinking glass containing at least 3 tablespoons of water
  - The mixture should be stirred well and the entire contents should be drunk immediately
  - If there is powder in the glass, more water should be added and stirred and the patient should drink that in order to get the complete dose

Aripiprazole with Digital Ingestion Tracking (Abilify MyCite)

- **Monitoring adherence of psychiatric patients to oral medication may be especially difficult**
  - First drug with a digital ingestion tracking system to be approved in the United States
  - It is indicated for treatment of adults with schizophrenia, bipolar disorder, or major depressive disorder
  - Whether the ingestion tracking system actually improves patient adherence compared to other aripiprazole formulations is unknown
Aripiprazole with Digital Ingestion Tracking

- **Mechanism of Action:**
  - Cuprous chloride and magnesium in the tablets react with gastric fluid to activate the embedded 1 mm sensor
  - The sensor will then communicate with a patch worn on the left side of the torso just above the lower edge of the rib cage
  - The patch transmits ingestion data via Bluetooth to a smartphone app
  - The data can then be viewed on a web-based portal

- **Cautions:**
  - Ingestion is usually detectable within 30 minutes after taking the drug, but sometimes not for two hours, and occasionally not at all
  - The patch is not MRI-safe

- **Availability/ Cost:**
  - 2, 5, 10, 15, 20, 30 mg tablets
  - $1650.00/ 30 tablets
  - Includes 30 tablets, 7 patches, smartphone app, and web-based portal

- **Dose:**
  - Tablets taken daily must be swallowed whole
  - Patches should be replaced weekly
  - Should not be placed on compromised skin
  - Should not be placed on a site that overlaps the previous patch site

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**Conclusions**
- We have covered a load of material today!!
- Medications, guidelines, and the world of pharmacy is continually changing
- The number of new medications approved in 2018 is significant
- Necessary to stay as updated as possible
- Medication regimens are more complicated than ever
- Always consider potential drug-drug interactions and think drugs first when dealing with new symptoms

**Questions?**

Thank You!

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