New Drug Update 2019*

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Objectives:

After attending this activity, the participant should be able to:

1. Identify the new therapeutic agents and explain their appropriate use.
2. Identify the indications and mechanisms of action of the new drugs.
3. Identify the most important adverse events and other risks of the new drugs.
4. State the route of administration for each new drug and the most important considerations regarding dosage and administration.
5. Compare the new therapeutic agents with older medications to which they are most similar in properties and/or use, and identify the most important advantages and disadvantages of the new drugs.

New Drug Comparison Rating (NDCR) system

5 = important advance
4 = significant advantage(s) (e.g., with respect to use/effectiveness, safety, administration)
3 = no or minor advantage(s)/disadvantage(s)
2 = significant disadvantage(s) (e.g., with respect to use/effectiveness, safety, administration)
1 = important disadvantage(s)

Additional information

The Pharmacist Activist monthly newsletter: www.pharmacistactivist.com
Revefenacin (Yupelri – Theravance; Mylan) Bronchodilator

2018 New Drug Comparison Rating (NDCR) =

**Indication:** For oral inhalation via nebulization for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

**Comparable drug:** Glycopyrrolate (Lonhala Magnair inhalation solution for nebulization)

**Advantages:**
--Is administered once a day (whereas glycopyrrolate is administered twice a day)
--May be used with any standard jet nebulizer (whereas glycopyrrolate should only be used with the Magnair system)

**Disadvantages:**
--Has not been directly compared with glycopyrrolate or other long-acting muscarinic antagonists (LAMAs) in clinical studies
--Administration of a dose requires a longer period of time (approximately 8 minutes; compared with 2 to 3 minutes with glycopyrrolate via nebulization)
--Use should be avoided in patients with hepatic impairment
--Concurrent use with certain organic anion-transporting polypeptide (OATP) inhibitors (e.g., cyclosporine, rifampin) is not recommended

**Most important risks/adverse events:** Must not be used for the treatment of acute symptoms or in patients with acutely deteriorating COPD; hypersensitivity reactions; paradoxical bronchospasm (treatment should be discontinued); worsening of urinary retention; worsening of narrow-angle glaucoma; action may be increased by other agents with anticholinergic activity (e.g., tiotropium, tolterodine, diphenhydramine), and concurrent use should be avoided; should not be used in patients with hepatic impairment because exposure of active metabolite may be increased; active metabolite is a substrate of OATP1B1 and OATP1B3 and action may be increased by inhibitors of these transporters (e.g., cyclosporine, rifampin; concurrent use should be avoided)

**Most common adverse events:** Cough (4%), nasopharyngitis (4%), headache (4%), upper respiratory tract infection (3%), back pain (2%)

**Usual dosage:** 175 mcg once a day using a mouthpiece and a standard jet nebulizer connected to an air compressor

**Product:** Inhalation solution for oral inhalation: polyethylene unit-dose vials – 175 mcg in 3 mL of sterile, aqueous solution; vials are wrapped in a foil pouch and should only be removed from the pouch and opened immediately before use

**Comments:** Revefenacin is the fifth long-acting muscarinic antagonist (LAMA) to be approved for use via oral inhalation as bronchodilators in the treatment of patients with COPD, joining tiotropium (Spiriva Respimat), aclidinium (Tudorza Pressair), umeclidinium (Incruze Ellipta), and glycopyrrolate (Seebri Neohaler). The LAMAs are most often administered via oral inhalation using metered-dose delivery devices. However, the effective use of these devices requires manual dexterity and coordination of actuation of the device and inhalation that deviates from regular breathing, which present a challenge for some patients. Approximately 10% of the patients treated for COPD in the United States administer bronchodilators by oral inhalation using a nebulizer. Glycopyrrolate was the first nebulized LAMA to be approved for the treatment of COPD, and it is administered over a period of 2 to 3 minutes twice a day. Revefenacin is the second LAMA to be approved for oral inhalation using nebulization, and the first to be administered once a day. The effectiveness of revefenacin was evaluated in two 12-week, placebo-controlled studies in patients with moderate to very severe COPD. The primary endpoint was the change from baseline in trough (predose) forced expiratory volume in one second (FEV₁). In both studies, revefenacin demonstrated significant improvement in lung function compared to placebo.

Following oral inhalation, revefenacin is rapidly hydrated to a major active metabolite that can potentially contribute to systemic anticholinergic effects at therapeutic doses.
**Istradefylline** (Nourianz – Kyowa Kirin)  
Antiparkinson Agent

2019  
New Drug Comparison Rating (NDCR) =

**Indication:**  Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson’s disease experiencing “off” episodes

**Comparable drugs:** Dopamine agonists (with ropinirole used for comparison)

**Advantages:**
--Has a unique mechanism of action (adenosine A\textsubscript{2A} receptor antagonism)
--Is not likely to cause hypotension or somnolence
--May be less likely to cause impulse control disorders/compulsive behaviors
--Dosage adjustment is less complex

**Disadvantages:**
--Has not been directly compared with comparable drugs in clinical studies
--Labeled indications are more limited (is not indicated as monotherapy, and ropinirole is also indicated for the treatment of patients with restless legs syndrome)
--May interact with more medications (e.g., CYP3A4 inducers and inhibitors)
--Should be used in a reduced dosage in patients with moderate hepatic impairment, and use should be avoided in patients with severe hepatic impairment

**Most important risks/adverse events:** Dyskinesia (may cause dyskinesia or exacerbate pre-existing dyskinesia); hallucinations/psychotic behavior (use should be avoided in patients with a major psychotic disorder); impulse control disorders/compulsive behaviors (e.g., intense urges to gamble, spend money, or binge eat; increased sexual urges); should not be used during pregnancy and women of reproductive potential should be advised to use effective contraception during treatment); action is decreased by strong CYP3A4 inducers (e.g., carbamazepine, rifampin) and concurrent use should be avoided; action is increased by strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) and dosage should be reduced; action is reduced by tobacco smoking (20 or more cigarettes per day) and should be used in a higher dosage; should be used in a reduced dosage in patients with moderate hepatic impairment, and use should be avoided in patients with severe hepatic impairment

**Most common adverse events:** Dyskinesia (17%), dizziness (6%), insomnia (6%), hallucinations (6%), nausea (6%), constipation (6%)

**Usual dosage:** 20 mg once a day; may be increased to a maximum of 40 mg once a day, based on the need of the patient and tolerability; in patients with moderate hepatic impairment, or who are being treated concurrently with a strong CYP3A4 inhibitor, the maximum recommended dosage is 20 mg once a day; in patients who smoke tobacco in amounts of 20 cigarettes or more per day (or the equivalent of another tobacco product), the recommended dosage is 40 mg once a day

**Products:** Film-coated tablets – 20 mg, 40 mg

**Comments:** The combination of levodopa and carbidopa is the most effective treatment for the motor symptoms of Parkinson’s disease, but its effect diminishes with long-term use (e.g., 3-5 years). As the extent and duration of benefit of levodopa/carbidopa decreases, patients experience more and/or longer “off” episodes, representing periods during treatment in which there is an increase in Parkinson symptoms such as tremor and difficulty walking. Other medications that have been used as adjuncts to levodopa/carbidopa include dopamine agonists (e.g., pramipexole, ropinirole), monoamine oxidase type B inhibitors (selegiline, rasagiline, safinamide [Xadago]), amantadine, and catechol-O-methyltransferases (COMT) inhibitors (e.g., entacapone).

Istradefylline is a xanthine derivative that has a unique mechanism of action as an adenosine A\textsubscript{2A} receptor antagonist. Its effectiveness was evaluated in four placebo-controlled clinical trials. Compared with placebo, patients treated with istradefylline experienced a significant decrease in the percentage of daily awake “off” time, and an increase in “on” time without troublesome dyskinesia.
Solriamfetol hydrochloride (Sunosi – Jazz) Agent for Excessive Daytime Sleepiness

2019 New Drug Comparison Rating (NDCR) =

Indication: To improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA)

Comparable drugs: Modafanil (e.g., Provigil), armodafanil (e.g., Nuvigil)

Advantages:
-- Has a unique mechanism of action (dopamine and norepinephrine reuptake inhibitor)
-- Is less likely to cause hypersensitivity/dermatologic reactions
-- Interacts with fewer medications
-- Dosage adjustment is not necessary in patients with severe hepatic impairment

Disadvantages:
-- Has not been directly compared with comparable drugs in clinical studies
-- Labeled indications are more limited (modafanil and armodafanil are also indicated to reduce excessive sleepiness in patients with shift work disorder)
-- May be more likely to increase blood pressure and heart rate
-- Concurrent use with monoamine oxidase inhibitors is contraindicated
-- Dosage should be reduced in patients with moderate or severe renal impairment

Most important risks/adverse events: Contraindicated in patients being treated with a monoamine oxidase (MAO) inhibitor, or within 14 days following the discontinuation of an MAO inhibitor; increased blood pressure and heart rate (use is best avoided in patients with unstable cardiovascular disease, serious arrhythmias, or other serious heart problems; caution should be exercised in patients also taking other drugs that increase blood pressure and heart rate, and/or have a dopaminergic action); caution should be exercised in patients with psychosis or bipolar disorder; if used during pregnancy, women should be enrolled in a pregnancy exposure registry (1-877-283-6220); is included in Schedule IV; dosage should be reduced in patients with moderate or severe renal impairment

Most common adverse events: Headache (16%), decreased appetite (9%), nausea (7%), anxiety (6%), insomnia (5%)

Usual dosage: Administered once a day upon awakening; should not be taken within 9 hours of planned bedtime; recommended initial dosage is 75 mg once a day in patients with narcolepsy and 37.5 mg once a day in patients with OSA; dosage may be doubled at intervals of at least 3 days to the maximum recommended dosage of 150 mg once a day; product labeling should be consulted for dosage recommendations in patients with moderate or severe renal impairment

Products: Tablets – 75 mg, 150 mg; 75 mg tablets are functionally scored so that they can be split in half to provide a dose of 37.5 mg

Comments: Medications with stimulant/wakefulness promoting activity are most often used in the treatment of conditions (e.g., narcolepsy, OSA) associated with excessive sleepiness, and include modafanil, armodafanil, amphetamine salts, and methylphenidate. The central nervous system depressant sodium oxybate (Xyrem) is also approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. Solriamfetol is a phenylalanine derivative that is thought to act by inhibiting dopamine and norepinephrine reuptake. When used in patients with OSA, it does not treat the underlying airway obstruction, and interventions such as continuous positive airway pressure (CPAP) should be employed for at least one month before initiating solriamfetol.

The effectiveness of solriamfetol was evaluated in placebo-controlled studies in which patients were assessed using the Maintenance of Wakefulness Test (MWT), the Epworth Sleepiness Scale (ESS), and the Patient Global Impression of Change (PGIC) scale. Compared with the placebo group, patients with narcolepsy showed significant improvement in these measures with a dosage of solriamfetol of 150 mg daily, and patients with OSA showed significant improvement with doses of 37.5 mg, 75 mg, and 150 mg daily.
**Pitolisant hydrochloride** (Wakix – Harmony)  
Agent for Excessive Daytime Sleepiness

2019  
New Drug Comparison Rating (NDCR) =

**Indication:**  
Treatment of excessive daytime sleepiness in adult patients with narcolepsy

**Comparable drugs:** Modafanil (e.g., Provigil), armodafanil (e.g., Nuvigil)

**Advantages:**
-- Has a unique mechanism of action (histamine-3 [H3] receptor antagonist/inverse agonist)
-- Is not a controlled substance (whereas modafanil and armodafanil are in Schedule IV)
-- Is less likely to increase blood pressure and heart rate
-- Is less likely to cause hypersensitivity and dermatologic adverse events

**Disadvantages:**
-- May be less effective (was not demonstrated to be noninferior to modafanil)
-- Prolongs the QT interval and increases the risk of cardiac arrhythmias
-- Labeled indications are more limited (modafanil and armodafanil are also indicated for the treatment of excessive sleepiness associated with obstructive sleep apnea and shift work disorder)
-- Interacts with more medications
-- Contraindicated in patients with severe hepatic impairment
-- Dosage titration/adjustment is more complex
-- Dosage adjustment is necessary in patients with moderate or severe renal impairment

**Most important risks/adverse events:** Prolongation of QT interval (use should be avoided in patients with a history of cardiac arrhythmias, or who have risk factors for arrhythmias including congenital prolongation of the QT interval, symptomatic bradycardia, hypokalemia, or hypomagnesemia; use should be avoided in patients taking other medications known to prolong the QT interval such as Class 1 antiarrhythmic agents [quinidine, procainamide, disopyramide], class 3 antiarrhythmic agents [amiodarone, sotalol], antipsychotic agents [ziprasidone, chlorpromazine, thioridazine], and antibacterial agents [moxifloxacin]; risk is increased in patients with hepatic or renal impairment); contraindicated in patients with severe hepatic impairment; dosage should be reduced in patients with moderate hepatic impairment or with moderate or severe renal impairment; is a substrate of the CYP2D6 pathway and dosage should be reduced in patients known to be poor CYP2D6 metabolizers or patients taking a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) concurrently; concurrent use of H1 receptor antagonists that cross the blood-brain barrier (e.g., diphenhydramine, chlorpheniramine) should be avoided; strong CYP3A4 inducers (e.g., carbamazepine, rifampin) may reduce activity and an increase in dosage may be necessary; may induce the CYP3A4 pathway and reduce the activity of sensitive CYP3A4 substrates (hormonal contraceptives, midazolam, cyclosporine); women using hormonal contraception (e.g., ethinyl estradiol) should be advised to use an alternative nonhormonal contraceptive method during treatment with pitolisant and for at least 21 days following the discontinuation of treatment

**Most common adverse events:** Headache (18%), nausea (6%), upper respiratory tract infection (5%), musculoskeletal pain (5%), anxiety (5%), increased heart rate (3%)

**Usual dosage:** Administered once a day in the morning upon awakening; 8.9 mg (two 4.45 mg tablets) daily during Week 1, 17.8 mg daily in Week 2, and may be increased in Week 3 and thereafter to 35.6 mg (two 17.8 mg tablets); product labeling should be consulted for recommendations for patients needing dosage adjustments

**Products:** Film-coated tablets – 4.45 mg, 17.8 mg pitolisant base

**Comments:** The effectiveness of pitolisant is thought to be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H3) receptors. Unlike the comparable drugs, it is not a controlled substance. When compared with placebo, it provided statistically significant reduction/improvement in Epworth Sleepiness Scale scores. However, it was not determined to be noninferior to modafanil.
**Prucalopride succinate** (Motegrity – Shire)  
Agent for Constipation

2019  
New Drug Comparison Rating (NDCR) =  

**Indication:** Treatment of chronic idiopathic constipation (CIC) in adults

**Comparable drugs:** Linaclotide (Linzess), plecanatide (Trulance), lubiprostone (Amitiza)

**Advantages:**
-- Has a different mechanism of action (is a selective serotonin type 4 \(5\text{-HT}_4\) receptor agonist)  
-- Has a lesser risk in pediatric patients (compared with linaclotide and plecanatide; none of the drugs are indicated for use in pediatric patients but linaclotide and plecanatide are contraindicated in children less than 6 years of age)  
-- Is administered once a day (compared with lubiprostone that is administered twice a day)  
-- Dosage adjustment is not necessary in patients with hepatic impairment (compared with lubiprostone with which dosage should be reduced in patients with moderate or severe hepatic impairment)

**Disadvantages:**
-- Is contraindicated in patients with severe inflammatory conditions of the gastrointestinal tract  
-- May be more likely to cause adverse events (based on results of noncomparative studies)  
-- Labeling includes a warning regarding suicidal ideation and behavior (a causal association has not been established)  
-- Dosage adjustment is recommended in patients with severe renal impairment  
-- Labeled indications are more limited (comparable drugs are indicated for the treatment of patients with irritable bowel syndrome with constipation [IBS-C] and lubiprostone is also indicated for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain)

**Most important risks/adverse events:** Contraindicated in patients with intestinal perforation due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn’s disease, ulcerative colitis, and toxic megacolon/megarectum; suicidal ideation and behavior (patients should be monitored for persistent worsening of depression and emergence of suicidal thoughts and behaviors); dosage should be reduced in patients with severe renal impairment

**Most common adverse events:** Headache (19%), abdominal pain (16%), nausea (14%), diarrhea (13%), abdominal distension (5%)

**Usual dosage:** 2 mg once a day; in patients with severe renal impairment, dosage should be reduced to 1 mg once a day

**Products:** Tablets – 1 mg, 2 mg

**Comments:** Chronic idiopathic constipation (CIC) is experienced most often by older adults and more commonly in women than in men. Standard treatments for constipation such as increased fiber and laxatives do not provide adequate relief in many patients. Prucalopride is a selective serotonin type 4 \(5\text{-HT}_4\) receptor agonist that acts as a gastrointestinal prokinetic agent to stimulate colonic peristalsis. Its effectiveness was evaluated in six placebo-controlled clinical trials involving approximately 2,500 patients. For the primary efficacy endpoint, a responder was defined as a patient with an average of 3 or more complete spontaneous bowel movements per week over a 12-week treatment period. In 5 of the 6 studies the responder rate was significantly higher in the patients treated with prucalopride (responder rates ranging from 19% to 38% in the 5 studies) than in those receiving placebo (responder rates ranging from 10% to 18%).

Tegaserod (Zelnorm) is a partial \(5\text{-HT}_4\) receptor agonist that is currently indicated only for the treatment of IBS-C in women, and not for the treatment of patients with CIC. Because of its selective activity at \(5\text{-HT}_4\) receptors, prucalopride has less affinity than tegaserod for \(5\text{-HT}_1\) receptors, an action that may be associated with the risk of adverse cardiovascular events with the latter agent.
Upadacitinib (Rinvoq – AbbVie)  

Antiarthritic Agent

2019  New Drug Comparison Rating (NDCR) =

**Indication:** Treatment of adults with moderately or severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate

**Comparable drugs:** Tofacitinib (Xeljanz, Xeljanz XR), baricitinib (Olumiant)

**Advantages:**
--Labeled indication for rheumatoid arthritis is broader (compared with baricitinib that is indicated for patients who have had an inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies)
--May be used in patients with moderate or severe renal impairment without dosage adjustment (whereas the use of baricitinib is not recommended, and tofacitinib should be used in a reduced dosage)
--May be used in patients with moderate hepatic impairment without dosage adjustment (compared with tofacitinib with which the dosage should be reduced)
--May be used in patients also receiving a CYP3A4 inhibitor without dosage reduction (compared with tofacitinib with which the dosage should be reduced)

**Disadvantages:**
--Labeled indications are more limited (compared with tofacitinib that is also indicated in patients with psoriatic arthritis or ulcerative colitis)
--Interacts with more medications (compared with baricitinib)
--Dosage adjustment flexibility is limited (compared with tofacitinib that is available in immediate-release and extended-release tablet formulations)

**Most important risks/adverse events:** Serious infections (boxed warning; treatment should not be initiated in patients with an active serious infection; patients should be evaluated for active or latent tuberculosis infection; should not be used concurrently with another Janus kinase inhibitor, a biologic disease-modifying antirheumatic drug [DMARD; e.g., TNF inhibitors], or a potent immunosuppressant [e.g., azathioprine, cyclosporine]; live vaccines should not be used concurrently); lymphoma or other malignancies (boxed warning); thrombosis, including deep vein thrombosis, pulmonary embolism, arterial thrombosis (boxed warning); gastrointestinal perforation (caution should be exercised in patients at increased risk [e.g., a history of diverticulitis]); laboratory abnormalities (neutropenia, lymphopenia, anemia; treatment should not be initiated, or should be interrupted, in patients with an absolute neutrophil count less than 1000 cells/mm$^3$, an absolute lymphocyte count less than 500 cells/mm$^3$, or hemoglobin less than 8 grams/dL); elevated liver enzymes and lipid concentrations; risk if used during pregnancy (effective contraception should be used); women with infants should not breastfeed; action may be reduced by strong CYP3A4 inducers (e.g., rifampin) and concurrent use is not recommended; action may be increased by concurrent use of a strong CYP3A4 inhibitor); use in patients with severe hepatic impairment is not recommended

**Most common adverse events:** Upper respiratory tract infection (14%), nausea (4%), cough (2%), pyrexia (1%)

**Usual dosage:** 15 mg once a day

**Product:** Extended-release tablets -15 mg (should not be split, crushed, or chewed)

**Comments:** Upadacitinib is the third Janus kinase (JAK) inhibitor to be approved for the treatment of patients with rheumatoid arthritis, joining tofacitinib and baricitinib. It may be used as monotherapy or with methotrexate or another nonbiologic DMARD. Its effectiveness was primarily evaluated in studies in which the primary endpoint was the proportion of patients who achieved an ACR20 response (i.e., a 20% improvement in criteria established by the American College of Rheumatology) at 12 weeks. Studies included patients who had an inadequate response to methotrexate, and patients who had an inadequate response or intolerance to biologic DMARDs (e.g., TNF inhibitors). A significantly larger number of patients treated with upadacitinib had higher ACR20, ACR50, and ACR70 responses, as well as clinical remission and inhibited radiographic progression.
**Risankizumab-rrzaa (Skyrizi – AbbVie)**  
Agent for Psoriasis  
2019  
New Drug Comparison Rating (NDCR) =  

**Indication:** Administered subcutaneously for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or for phototherapy  

**Comparable drugs:** Guselkumab (Tremfya), tildrakizumab (Ilumya)  

**Advantages:**  
--May be more effective (based on noncomparative studies)  
--Is administered less frequently (every 12 weeks for maintenance treatment compared with guselkumab that is administered every 8 weeks)  
--May be self-administered (compared with tildrakizumab that is administered by a healthcare provider)  

**Disadvantages:**  
--Each dose requires two injections (compared with a single injection of the comparable drugs)  

**Most important risks/adverse events:** Infections (treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated; if a serious infection occurs during treatment or an infection is not responding to standard therapy, discontinuation of risankizumab should be considered); tuberculosis (patients should be evaluated for tuberculosis prior to initiating treatment); live vaccines should not be administered during the period of treatment  

**Most common adverse events:** Upper respiratory tract infection (13%), headache (4%), fatigue (3%), injection site reactions (2%), tinea infections (1%)  

**Usual dosage:** Administered subcutaneously – 150 mg (two injections) at Weeks 0 and 4, and every 12 weeks thereafter  

**Product:** Single-dose prefilled syringes – 75 mg (should be stored in a refrigerator)  

**Comments:** Certain interleukins (primarily IL-23 and IL-17A) have been identified as having a role in the occurrence and worsening of psoriasis, and risankizumab is the seventh monoclonal antibody that inhibits specific ILs that have been approved for the treatment of patients with psoriasis. The p19 and p40 subunits of IL-23 are present in higher concentrations in psoriatic lesions. Ustekinumab (Stelara) inhibits the p40 subunit that is shared by IL-23 and IL-12, and was the first IL inhibitor to be marketed (2009) for the treatment of patients with moderate-to-severe plaque psoriasis. Guselkumab, tildrakizumab, and risankizumab, marketed in 2017, 2018, and 2019, respectively, bind to the p19 subunit of IL-23, thereby inhibiting its binding to the IL-23 receptor and also preventing subsequent release of pro-inflammatory cytokines such as IL-17A. Secukinumab (Cosentyx), ixekizumab (Taltz), and brodalumab (Siliq) are inhibitors of IL-17A, and were marketed in 2015, 2016, and 2017, respectively.  

The effectiveness of risankizumab was evaluated in four clinical trials in which the co-primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 90% (PASI 90) from baseline to Week 16 and an improvement in the Physician Global Assessment (PGA) score to 0 (clear) or 1 (almost clear). In two of the studies, risankizumab, ustekinumab, and placebo were evaluated; PASI 90 responses for the three agents were 75%, 42%, and 5%, respectively, in the first study, and 75%, 48%, and 2% in the second study. PASI 100 responses were reported in 36%, 12%, and 0%, and 51%, 24%, and 2% of patients in the two studies, respectively. PGA scores of clear and almost clear were also significantly improved in patients treated with risankizumab. At Week 52, PASI 90 responses (82%; 81%) and PASI 100 responses (56%; 60%) with risankizumab in both studies were significantly higher than with ustekinumab. Results of another study in which risankizumab and adalimumab (Humira) were evaluated show significantly better response rates with risankizumab.
**Romosozumab-aqqg** (Evenity – Amgen)  
Agent for Osteoporosis

2019  
New Drug Comparison Rating (NDCR) =

**Indication:** Administered subcutaneously for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy

**Comparable drugs:** Abaloparatide (Tymlos), teriparatide (Forteo)

**Advantages:**
- May be more effective in reducing the risk of vertebral fractures in some patients
- Has a unique mechanism of action (sclerostin inhibitor)
- Has not been associated with the occurrence of osteosarcoma (risk is identified in boxed warnings in labeling of comparable drugs)
- Has not been associated with the occurrence of hypercalcemia
- Is administered less frequently (once a month compared with once a day with comparable drugs)

**Disadvantages:**
- May be less effective in reducing the risk of nonvertebral fractures
- Labeled indications are more limited (compared with teriparatide that is also indicated for increasing bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture, and for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture)
- Has been associated with a risk of myocardial infarction, stroke, and cardiovascular death (boxed warning)
- May cause hypocalcemia
- Treatment should not be continued for more than 12 months (because of a decline in effectiveness; comparable drugs are used for up to 24 months)
- Should be administered by a healthcare provider (whereas comparable drugs are self-administered)

**Most important risks/adverse events:** Risk of myocardial infarction, stroke, and cardiovascular death (boxed warning; treatment should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year); contraindicated in patients with hypocalcemia (hypocalcemia should be corrected before initiating treatment; patients with severe renal impairment or receiving dialysis are at greater risk and serum calcium concentrations should be monitored; adequate supplementation with calcium and vitamin D should be provided); hypersensitivity reactions; osteonecrosis of the jaw; atypical femoral fracture (new or unusual thigh, hip, or groin pain should be evaluated)

**Most common adverse events:** Arthralgia (13%), headache (7%), muscle spasms (5%)

**Usual dosage:** 210 mg once a month subcutaneously; should be administered by a healthcare provider; two separate syringes are needed to provide the dose of 210 mg and should be administered one after the other; duration of treatment should be limited to 12 months because of subsequent decline in effectiveness

**Product:** Injection in single-use prefilled syringes – 105 mg (should be stored in a refrigerator)

**Comments:** Sclerostin is a glycoprotein that is a regulatory factor in bone metabolism which inhibits activation of osteoblast function and bone formation. Romosozumab is a monoclonal antibody that is the first sclerostin inhibitor. By inhibiting sclerostin, it stimulates osteoblastic activity and increases bone formation. In one clinical trial, either romosozumab or placebo was used for the first 12 months, and both groups were then treated with denosumab (Prolia) for the next 12 months. Romosozumab significantly reduced the occurrence of new vertebral fracture (0.5%), in the first 12 months, compared with 1.8% of those receiving placebo. At month 24, 0.6% of patients treated with romosozumab experienced a new vertebral fracture, compared with 2.5% of those receiving placebo followed by denosumab. In a second trial, romosozumab was compared with oral alendronate; 4.1% of patients treated with romosozumab followed by alendronate experienced a new vertebral fracture through month 24, compared with 8% of those who were treated with alendronate alone for 24 months.
Omadacycline tosylate (Nuzyra – Paratek)  Antibacterial Agent

2019  New Drug Comparison Rating (NDCR) =

**Indications:** Administered intravenously or orally for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: *Streptococcus pneumoniae, Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*; is also indicated for the treatment of adults with acute bacterial skin and skin-structure infections (ABSSSI) caused by the following susceptible microorganisms: *Staphylococcus aureus* (methicillin-susceptible and –resistant isolates), *Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Enterococcus faecalis, Enterobacter cloacae,* and *Klebsiella pneumoniae.*

**Comparable drug:** Tigecycline

**Advantages:**
--Labeled indications include a larger number of susceptible bacteria
--May be effective in some patients whose infections are resistant to other agents
--Is available for both intravenous and oral use (whereas tigecycline is only administered intravenously)
--Labeling does not include a boxed warning regarding all-cause mortality

**Disadvantages:**
--Labeled indications are more limited (tigecycline is also indicated for the treatment of complicated intra-abdominal infections)

**Most important risks/adverse events:** Contraindicated in patients with a known hypersensitivity to any of the tetracyclines; may cause adverse developmental effects if used during pregnancy; may cause permanent discoloration of the teeth, and inhibit bone growth, if it is used during the second and third trimesters of pregnancy, infancy, childhood up to the age of 8 years, and in nursing mothers; photosensitivity; *Clostridium difficile*-associated diarrhea; mortality imbalance in patients with CABP; may depress plasma prothrombin activity and, in patients being treated with an anticoagulant, it may be necessary to reduce the dosage of the anticoagulant; activity may be reduced by multivalent cation-containing products (e.g., aluminum, magnesium, calcium, iron; should not be administered intravenously with any solution containing cations such as calcium and magnesium through the same intravenous line; when omadacycline is administered orally, cation-containing products should not be taken for 4 hours)

**Most common adverse events:** In patients with CABP: hypertension (3%), insomnia (3%), increased ALT (4%), increased gamma-glutamyl transferase (3%); in patients with ABSSSI: nausea (22%), vomiting (11%), infusion site reactions (5%), headache (3%), diarrhea (3%), increased ALT (4%), increased AST (4%)

**Usual dosage:** Exposure is similar between a 300-mg oral dose and a 100-mg intravenous dose; patients should fast for at least 4 hours prior to oral administration, and the dose should be taken with water; following oral administration, no food or beverage (except water) should be consumed for at least 2 hours; in patients with either CABP or ABSSSI, the dosage on Day 1 is 200 mg by intravenous infusion over 60 minutes or 100 mg by intravenous infusion over 30 minutes twice during Day 1; maintenance dosage is 100 mg by intravenous infusion over 30 minutes once a day, or 300 mg orally once a day; an alternative oral regimen for patients with ABSSSI is a loading dose of 450 mg once a day on Days 1 and 2, followed by a maintenance dosage of 300 mg once a day; treatment is continued for 7-14 days

**Products:** Capsules – 150 mg; single-dose vials – 100 mg - lyophilized powder to be reconstituted and then diluted

**Comments:** Omadacycline is an aminomethyltetracycline with activity against certain bacteria that have mechanisms to resist the action of most other tetracyclines. In patients with CABP, it was noninferior to moxifloxacin, with clinical response rates of 88% and 85%, respectively. In two studies in patients with ABSSSI, it was noninferior to linezolid, with clinical response rates for both agents in each study between 81% and 86%.
Lefamulin acetate (Xenleta – Nabriva)  

**Antibacterial Agent**

2019  

**New Drug Comparison Rating (NDCR) =**

**Indication:** Administered intravenously or orally for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*  

**Comparable drug:** Moxifloxacin  

**Advantages:**  
-- Is the first pleuromutilin antibacterial agent to be approved for the treatment of a systemic infection  
-- May be effective in some patients who have had an inadequate response to, or have experienced hypersensitivity or other risks with other antibacterial agents  
-- Has not been associated with the occurrence of tendon problems, peripheral neuropathy, central nervous system effects, or exacerbation of myasthenia gravis (are the subjects of boxed warnings in the labeling for moxifloxacin)  

**Disadvantages:**  
-- Is administered every 12 hours (whereas moxifloxacin is administered every 24 hours)  
-- Labeled indications are more limited (moxifloxacin is also indicated for the treatment of uncomplicated skin and skin structure infections, complicated intra-abdominal infections, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and plague)  
-- Is more likely to cause gastrointestinal adverse events (e.g., diarrhea)  
-- Oral use is not recommended in patients with moderate or severe hepatic impairment, and dosage for intravenous use should be reduced in patients with severe hepatic impairment (whereas moxifloxacin use is not limited)  

**Most important risks/adverse events:** QT prolongation and increased risk of cardiac arrhythmias (use should be avoided in patients with known prolongation of the QT interval, ventricular arrhythmias, and in patients treated with other medications that may prolong the QT interval [e.g., quinidine, procainamide, disopyramide, amiodarone, sotalol, ziprasidone, thioridazine, moxifloxacin]; concurrent use of tablets with sensitive CYP3A substrates known to prolong the QT interval [e.g., pimozone] is contraindicated; risk is increased in patients with hepatic impairment or patients in renal failure who require dialysis); *Clostridium difficile*-associated diarrhea; may cause adverse developmental effects if used during pregnancy (women of reproductive potential should be advised to use effective contraception during treatment and for 2 days after the final dose); lactating women should pump and discard milk for the duration of treatment and for 2 days after the final dose; effectiveness may be reduced by strong and moderate CYP3A and/or P-gp inducers (e.g., rifampin) and concurrent use should be avoided; action of lefamulin tablets may be increased by strong CYP3A and/or P-gp inhibitors (e.g., ketoconazole) and concomitant use should be avoided; oral use is not recommended in patients with moderate or severe hepatic impairment  

**Most common adverse events:** Oral administration: Diarrhea (12%), nausea (5%), vomiting (3%); Intravenous administration: Administration site reactions (7%), hepatic enzyme elevations (3%), nausea (3%), hypokalemia (3%), insomnia (3%)  

**Usual dosage:** Oral: 600 mg every 12 hours for 5 days, administered at least 1 hour before a meal or 2 hours after a meal; Intravenous: 150 mg infused over 60 minutes every 12 hours for 5 to 7 days (may be switched to tablets during treatment); should be reduced to 150 mg every 24 hours in patients with severe hepatic impairment  

**Products:** Tablets – 600 mg; single-dose vials – 150 mg in 15 mL (should be stored in a refrigerator); contents should be diluted in 250 mL of a citrate buffered solution that is supplied in infusion bags with product  

**Comments:** Lefamulin is the first pleuromutilin antibacterial agent to be approved for treating a systemic infection. Retapamulin (Altabax) was the first pleuromutilin marketed for the topical treatment of impetigo. Lefamulin was evaluated in two clinical trials in which it was compared with moxifloxacin. In both studies, each agent was effective, as determined by early clinical response rates in approximately 90% of patients.