

New Drug Update 2021*

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Learning Objectives:

After attending this program, the participant will 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 newsletter: www.pharmacistactivist.com

Disclosures

Daniel A. Hussar declares no conflicts of interest or financial interests in any product mentioned in this presentation.

Hypercholesterolemia

Bempedoic acid (Nexletol – Esperion) – 2020

Description: An adenosine triphosphate-citrate lyase (ACL) inhibitor;

Indication: Administered orally as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin); atorvastatin is the statin used for the comparisons below:

Advantages:

- Has a unique mechanism of action (ACL inhibitor);
- Extends the low-density lipoprotein cholesterol (LDL-C)-lowering effect of the statins;
- Is not likely to cause skeletal muscle adverse events (e.g., myopathy);
- Is less likely to interact with other drugs;

Disadvantages:

- Is not a first-line treatment for lowering LDL-C;
- Effect on cardiovascular morbidity and mortality is not yet known;
- May cause hyperuricemia and gout, and tendon rupture;
- Has not been evaluated in pediatric patients (whereas atorvastatin is indicated for use in patients 10 years of age and older);
- Labeled indications are more limited (whereas atorvastatin reduces other blood lipids [e.g., triglycerides], is indicated for a number of types of dyslipidemias, and has been demonstrated to reduce the risk of myocardial infarction, stroke, and other cardiovascular events);

Recommended dosage: 180 mg once a day with or without food;

Products: Tablets -180 mg; combination tablets (Nexlizet) – 180 mg and 10 mg ezetimibe;

Contraindications/most important risks:

- Hyperuricemia and gout: uric acid concentration should be monitored periodically;
- Tendon rupture: use should be avoided in patients with a history of tendon disorders or tendon rupture; risk is increased in patients over 60, and in patients treated with a fluoroquinolone or corticosteroid;
- Pregnancy: risk of harm based on animal studies and mechanism of action in reducing cholesterol synthesis;
- Lactation: breastfeeding is not recommended;
- Hepatic impairment: has not been studied in patients with severe hepatic impairment;
- Interactions: increases concentrations of pravastatin and simvastatin and may increase risk of myopathy; dosage of pravastatin should not exceed 40 mg daily, and dosage of simvastatin should not exceed 20 mg daily;

Most common adverse events: Upper respiratory tract infection (5%), muscle spasms (4%), hyperuricemia (4%), back pain (3%), abdominal pain/discomfort (3%), bronchitis (3%), pain in extremity (3%), anemia (3%);

Comments: Bempedoic acid inhibits ACL, an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Its effectiveness was evaluated in two placebo-controlled trials as add-on to a maximally tolerated dose of a statin alone or in combination with other lipid-lowering therapies. The primary efficacy outcome measure was the change from baseline to week 12 in LDL-C, and the difference between the drug and placebo in mean percent change was -18% and -17% in the two trials. There were also reductions of at least 10% in total cholesterol, non-HDL cholesterol, and apolipoprotein B. In a study of patients already being treated with a statin, the addition of both bempedoic acid and ezetimibe in the combination formulation provided a 36% reduction in LDL-C, which was significantly greater than that with either of these agents alone.

Insomnia

Lemborexant (Dayvigo – Eisai) – 2020

Description: An orexin receptor antagonist;

Indication: Administered orally for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance;

New Drug Comparison Rating (NDCR) =

Comparable drug: Suvorexant (Belsomra);

Advantages:

---Has been demonstrated to be more effective than zolpidem extended-release 6.25 mg;

Disadvantages:

---Has not been directly compared with suvorexant in clinical studies;

---Concurrent use with strong or moderate CYP3A inhibitors or strong or moderate CYP3A inducers should be avoided (whereas suvorexant may be used concurrently with CYP3A inducers, and in a low dosage with moderate CYP3A inhibitors);

Recommended dosage: 5 mg immediately before going to bed, with at least 7 hours remaining before the planned time of awakening;

---Time to sleep onset may be delayed if taken with or soon after a meal;

---No more than one dose should be taken each night;

---Dosage may be increased to the maximum recommended dose of 10 mg each night;

---Maximum recommended dose is 5 mg at bedtime in patients with moderate hepatic impairment or who are being treated with a weak CYP3A inhibitor;

Products: Film-coated tablets – 5 mg, 10 mg;

Contraindications/most important risks:

---CNS depressant effects and daytime impairment; consumption of alcoholic beverages should be avoided; patients treated with the 10 mg dose should be advised against next-day driving and other activities requiring full alertness;

---Abuse potential: (Schedule IV);

---Sleep paralysis/hallucinations;

---Cataplexy-like symptoms (e.g., periods of leg weakness);

---Complex sleep behaviors (e.g., sleep-walking, sleep driving);

---Worsening of depression/suicidal ideation;

---Pregnancy: women should be registered in the Dayvigo pregnancy registry (1-888-274-2378);

---Hepatic impairment: use should be avoided in patients with severe hepatic impairment;

---Interactions: use should be avoided in patients treated with strong or moderate CYP3A inhibitors or strong or moderate CYP3A inducers;

---May decrease the activity of CYP2D6 substrates (e.g., bupropion, methadone);

Most common adverse events (with doses of 5 mg and 10 mg, respectively): Somnolence (7%, 10%), headache (6%, 5%), nightmares/abnormal dreams (1%, 2%);

Comments: The orexins are naturally occurring neuropeptides that act in a signaling mechanism as a central promoter of wakefulness. Lemborexant is the second orexin receptor antagonist that blocks the binding of the orexins to their receptors, and is thought to suppress the wake drive. It was evaluated in two clinical trials, one of which was placebo- and active-controlled (zolpidem extended release 6.25 mg). Both 5 mg and 10 mg doses of lemborexant demonstrated statistically significant superiority compared with placebo and zolpidem extended-release 6.25 mg in reducing the time to sleep onset, as well as improvement in sleep efficiency (percentage of time asleep compared with time in bed), and the time awake after sleep onset.

Parkinson's disease

Opicapone (Ongentys – Neurocrine) -2020

Description: A catechol-O-methyltransferase (COMT) inhibitor;

Indication: Administered orally as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes;

New Drug Comparison Rating (NDCR) =

Comparable drug: Entacapone (e.g., Comtan; component of Stalevo [levodopa/carbidopa/entacapone]);

Advantages:

- Has a longer duration of action and is administered once a day (although levodopa/carbidopa with which it is used as adjunctive treatment is administered multiple times a day);
- Is less likely to cause diarrhea;
- Does not cause discoloration of the urine.

Disadvantages:

- Is not available in a combination formulation with levodopa/carbidopa;

Recommended dosage: 50 mg once a day at bedtime; patients should not eat food for 1 hour before and for at least 1 hour after administration;

- Patients with moderate hepatic impairment – 25 mg once a day at bedtime apart from food;

Products: Capsules – 25 mg, 50 mg;

Contraindications/most important risks:

- Contraindication: concomitant use with a non-selective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, tranylcypromine); (selective MAO-B inhibitors [selegiline, rasagiline, safinamide) that are indicated for the treatment of Parkinson's disease may be used concurrently);
- Contraindicated in patients with pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms;
- Dyskinesia;
- Hypotension/syncope;
- Sedation/somnolence (patients should be cautioned about driving and other activities requiring alertness);
- Hallucinations and psychosis;
- Impulse control/compulsive disorders (urges to gamble, spend money, binge eating);
- Withdrawal-emergent hyperpyrexia and confusion when discontinuing treatment;
- Hepatic impairment: dosage should be reduced in patients with moderate impairment and should be avoided in patients with severe impairment;
- Renal impairment: should be avoided in patients with end-stage renal disease;
- Interactions: risk of cardiovascular adverse events (arrhythmias, increased heart rate, blood pressure changes) if used concurrently with other drugs that are metabolized by COMT (e.g., isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine);

Most common adverse events: Dyskinesia (20%), constipation (6%), hypotension/syncope (5%), weight loss (4%);

Comments: Because levodopa is extensively metabolized in peripheral tissues by dopa decarboxylase (DDC), carbidopa is used concurrently as a DDC inhibitor with the results that more levodopa reaches the central nervous system and its effectiveness is increased. When the decarboxylase pathway is inhibited by carbidopa, the primary pathway for the metabolism of levodopa in the peripheral tissues is via COMT. Opicapone was evaluated in two placebo-controlled trials in patients experiencing "off" episodes while being treated with levodopa/carbidopa, with or without other medications used for the treatment of Parkinson's disease. Opicapone reduced "off"-time from a baseline of approximately 6.2 hours by about 2 hours in each study, compared with a reduction of about 1 hour in patients receiving placebo. It also increased "on"-time without troublesome dyskinesia.

Schizophrenia **Lumateperone tosylate (Caplyta – Intra-Cellular Therapeutics) -2020**

Description: Atypical antipsychotic agent; activity is thought to be mediated through a combination of antagonism at central serotonin 5-HT_{2A} receptors and postsynaptic antagonism at central dopamine D₂ receptors;

Indication: Administered orally for the treatment of schizophrenia in adults;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Other orally-administered atypical antipsychotic agents; risperidone is the drug used for the comparisons below:

Advantages:

---Is less likely to cause extrapyramidal symptoms, weight gain and hyperprolactinemia;

Disadvantages:

---May be less effective;

---Clinical response is less predictable and is supplied in just one potency;

---Has not been evaluated in adolescent and pediatric patients;

---Labeled indications are more limited (whereas risperidone also has labeled indications for bipolar I disorder, and irritability associated with autistic disorder in children and adolescents);

Recommended dosage: 42 mg once a day with food;

Product: Capsules – 42 mg lumateperone (supplied as lumateperone tosylate);

Contraindications/most important risks:

---Increased mortality in elderly patients with dementia-related psychosis (boxed warning);

---Metabolic changes (e.g., hyperglycemia/diabetes, dyslipidemia, weight gain);

---Orthostatic hypotension, syncope, falls;

---Potential for cognitive and motor impairment (patients should be cautioned about driving);

---Tardive dyskinesia; seizures;

---Neuroleptic malignant syndrome;

---Hematologic effects (treatment should be discontinued if absolute neutrophil count falls below 1000/mm³);

---Body temperature dysregulation;

---Pregnancy: third trimester exposure may cause extrapyramidal and/or withdrawal symptoms in neonates; pregnant women should be registered in Pregnancy Registry for Atypical Antipsychotics (1-866-961-2388);

---Lactation: breastfeeding should be avoided;

---Hepatic impairment: use should be avoided in patients with moderate or severe hepatic impairment;

---Interactions: Activity may be increased by moderate or strong CYP3A4 inhibitors, or UGT inhibitors (e.g., valproic acid), or decreased by CYP3A4 inducers; concurrent use should be avoided;

Most common adverse events: Somnolence/sedation (24%), nausea (9%), dry mouth (6%), dizziness (5%), extrapyramidal symptoms (7%; similar to placebo);

Comments: The effectiveness of lumateperone was evaluated in two 4-week placebo-controlled trials in which the primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS) total score. In both studies, lumateperone (42 mg daily) showed a statistically significant reduction from baseline to Day 28 in the PANSS total score compared to placebo. However, a dosage of 84 mg daily was also evaluated in one of the studies and provided less of a reduction in the PANSS total score than the 42 mg daily dosage, and was not statistically different from the response with placebo. Another study was conducted over a period of 6 weeks and raises additional questions regarding the predictability of the effectiveness of lumateperone. The reduction in the PANSS total score was approximately the same for lumateperone (42 mg daily) and placebo, whereas patients receiving risperidone experienced a statistically significant reduction in PANSS total scores compared with placebo.

Multiple sclerosis

Ozanimod hydrochloride (Zeposia – Celgene) – 2020

Description: A sphingosine 1-phosphate (S1P) receptor modulator;

Indication: Administered orally for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Fingolimod (Gilenya), siponimod (Mayzent);

Advantages:

---Does not require first-dose monitoring for bradycardia (compared with fingolimod, and some patients with siponimod);

---Does not require CYP2C9 genotype testing (compared with siponimod);

---Dosage titration has fewer steps (compared with siponimod);

Disadvantages:

---May interact with monoamine oxidase (MAO) inhibitors, adrenergic and serotonergic drugs, and tyramine;

Recommended dosage: 0.23 mg once a day on Days 1-4, 0.46 mg once a day on Days 5-7, and 0.92 mg once a day on Day 8 and thereafter;

---Cardiac evaluation, complete blood count, liver function tests, ophthalmic evaluation, current and prior medications, and vaccinations should be assessed before initiating treatment;

---If a dose is missed during the first week of treatment, the titration regimen should be reinitiated;

Products: Capsules: 0.23 mg, 0.46 mg, 0.92 mg ozanimod (supplied as ozanimod hydrochloride);

Contraindications/most important risks:

---Contraindicated in patients who in the last 6 months have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure;

---Contraindicated in the presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker;

---Contraindicated in patients with severe untreated sleep apnea;

---Contraindicated in patients treated with a MAO inhibitor;

---Bradycardia and AV conduction delays (may cause transient decreased heart rate); increased blood pressure;

---Infections (treatment should not be initiated in patients with active infections);

---Liver injury;

---Macular edema;

---Pregnancy: risk of harm and women of childbearing potential should use effective contraception during treatment and for 3 months after stopping treatment;

---Vaccines: live attenuated vaccines should be avoided during treatment and for 3 months after treatment;

---Interactions: Activity may be increased by strong CYP2C8 inhibitors (e.g., gemfibrozil) and breast cancer resistance protein (BCRP) inhibitors (e.g., cyclosporine), and concurrent use is not recommended; activity may be decreased by strong CYP2C8 inducers (e.g., rifampin), and concurrent use should be avoided; increased risk with concurrent use of antiarrhythmic drugs, QT prolonging drugs, and drugs that decrease heart rate; increased risk of infection in patients treated with antineoplastic, immune-modulating, or immunosuppressive therapies; risk with concurrent use of MAO inhibitors, adrenergic and serotonergic drugs, and tyramine;

Most common adverse events: Upper respiratory infection (26%), hepatic transaminase elevations (10%);

Comments: Ozanimod binds with high affinity to S1P receptors 1 and 5, whereas fingolimod exhibits activity at S1P receptors 1, 3, 4, and 5. The drug was evaluated in two trials and the annualized relapse rate was significantly lower in patients treated with ozanimod than in patients who received interferon beta-1a intramuscularly.

Migraine

Lasmiditan hemisuccinate (Reyvow – Lilly) – 2020

Description: A serotonin 1F (5-HT_{1F}) receptor agonist;

Indication: Administered orally for the acute treatment of migraine with or without aura in adults;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Serotonin 1B/1D (5-HT_{1B/1D}) receptor agonists (triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan); sumatriptan (oral) is the triptan used for the comparisons below:

Advantages:

- Has a more selective action and has not been associated with vasoconstrictive effects;
- Is safer for use in a broader range of patients (whereas sumatriptan is contraindicated in patients with peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, Wolff-Parkinson-White syndrome, or a history of coronary artery disease/vasospasm, stroke, transient ischemic attack, or hemiplegic or basilar migraine, patients with severe hepatic impairment, or patients with recent [within 24 hours] use of another triptan or ergotamine-containing medication, or concurrent or recent [past 2 weeks] use of a monoamine oxidase-A inhibitor);
- Is less likely to cause chest/throat/neck/jaw pain or pressure, or lower seizure threshold (whereas sumatriptan must be used with caution in patients with epilepsy);
- Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment;

Disadvantages:

- Has not been directly compared with triptans in clinical studies;
- Is more likely to cause a CNS depressant action and interact with other CNS depressants;
- Is a controlled substance (Schedule V; risk of problems is low);
- Is more likely to interact with heart rate-lowering drugs, and P-glycoprotein (P-gp) substrates;
- A second dose has not been shown to be effective for the same migraine attack;
- Formulations and routes of administration are more limited (whereas sumatriptan is also available in formulations for use as a nasal spray and subcutaneous injection);

Recommended dosage: 50 mg, 100 mg, or 200 mg, with or without food;

- Should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery;
- No more than one dose should be taken in 24 hours; a second dose has not been shown to be effective for the same migraine attack;

Products: Film-coated tablets – 50 mg, 100 mg;

Contraindications/most important risks:

- CNS depression/impairment: patients should not drive or operate machinery until at least 8 hours after taking a dose;
- Serotonin syndrome: risk is increased in patients also taking other serotonergic drugs;
- Abuse: Schedule V; “drug-liking” scores higher than placebo but lower than alprazolam;
- Pregnancy: risk of harm based on animal studies;
- Hepatic impairment: not recommended in patients with severe hepatic impairment;
- Interactions: May further lower heart rate when used concurrently with heart rate-lowering drugs;
- Inhibits P-gp *in vitro* and concomitant use with P-gp substrates should be avoided;

Most common adverse events (dose of 100 mg); Dizziness (15%), paresthesia (7%), sedation (6%), fatigue (5%);

Comments: Lasmiditan was evaluated in two placebo-controlled clinical trials in which efficacy was established by an effect on pain freedom at 2 hours, and Most Bothersome Symptom (MBS; e.g., photophobia, nausea) freedom at 2 hours. Approximately 30% of patients were pain free at 2 hours, and approximately 43% were MBS free at 2 hours.

Migraine

Ubrogepant (Ubrelvy – Allergan) – 2020

Description: A calcitonin gene-related peptide (CGRP) antagonist;

Indication: Administered orally for the acute treatment of migraine with or without aura in adults;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Serotonin 1B/1D (5-HT_{1B/1D}) receptor agonists (triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan); sumatriptan (oral) is the triptan used for the comparisons below:

Advantages:

---Is safer for use in a broader range of patients (whereas sumatriptan is contraindicated in patients with peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, Wolff-Parkinson-White syndrome, or a history of coronary artery disease/vasospasm, stroke, transient ischemic attack, or hemiplegic or basilar migraine, patients with severe hepatic impairment, or patients with recent [within 24 hours] use of another triptan or ergotamine-containing medication, or concurrent or recent [past 2 weeks] use of a monoamine oxidase-A inhibitor);
---Is less likely to cause chest/throat/neck/jaw pain or pressure, or lower seizure threshold (whereas sumatriptan must be used with caution in patients with epilepsy);

Disadvantages:

---Has not been directly compared with triptans in clinical studies;
---May be less effective (based on data for individual agents in the absence of comparative studies);
---Concurrent use with strong CYP3A4 inhibitors is contraindicated, and concurrent use with strong CYP3A4 inducers should be avoided);
---Dosage adjustment is recommended in patients also taking moderate or weak CYP3A4 inhibitors and inducers, or P-glycoprotein (P-gp) inhibitors;
---Formulations and routes of administration are more limited (whereas sumatriptan is also available in formulations for use as a nasal spray and subcutaneous injection);

Recommended dosage: 50 mg or 100 mg, with or without food;

---If needed, a second dose may be administered at least 2 hours after the initial dose;
---Maximum dose in a 24-hour period is 200 mg;
---Dosage should be reduced in patients being treated with a moderate or weak CYP3A4 inhibitor, a P-gp inhibitor, or patients with severe hepatic or severe renal impairment;
---Dosage should be increased in patients being treated with a moderate or weak CYP3A4 inducer;

Products: Tablets – 50 mg, 100 mg;

Contraindications/most important risks:

---Contraindicated in patients also being treated with a strong CYP3A4 inhibitor;
---Pregnancy: risk of harm based on animal studies;
---Hepatic impairment: dosage should be reduced in patients with severe hepatic impairment;
---Renal impairment: severe renal impairment (reduce dosage); avoid in patients with end-stage renal disease;
---Interactions: Activity is increased in patients also being treated with a strong CYP3A4 inhibitor (contraindicated), as well as moderate or weak CYP3A4 inhibitors and P-gp inhibitors (dosage should be reduced);
---Activity is decreased by strong CYP3A4 inducers (concurrent use should be avoided), as well as moderate and weak CYP3A4 inducers (dosage of ubrogepant should be increased)

Most common adverse events (dose of 100 mg): Nausea (4%), somnolence (3%), dry mouth (2%);

Comments: Ubrogepant is the first CRGP antagonist for oral administration for the treatment of migraine. It was evaluated in two placebo-controlled trials in which efficacy was established by an effect on pain freedom at 2 hours, and Most Bothersome Symptom (MBS; e.g., photophobia, nausea) freedom at 2 hours. With a dose of 100 mg of ubrogepant, 21% of patients were pain free at 2 hours, and 38% of patients were MBS free at 2 hours.

Migraine

Rimegepant sulfate (Nurtec ODT – Biohaven) – 2020

Description: A calcitonin gene-related peptide (CGRP) antagonist;

Indication: Administered orally for the acute treatment of migraine with or without aura in adults;

New Drug Comparison Rating (NDCR) =

Comparable drug: Ubrogapant (Ubrelvy);

Advantages:

---Has a longer duration of action and a second dose is not needed during each 24-hour period of treatment;
---Is supplied in an orally disintegrating tablet (ODT) formulation that disintegrates in saliva and additional liquid is not needed;

Disadvantages:

---Has not been evaluated in studies designed to directly compare it with triptans;
---May be more likely to cause hypersensitivity reactions;
---Use should be avoided in patients being treated with a moderate CYP3A inducer or inhibitors of P-glycoprotein (P-gp), (whereas ubrogapant in an adjusted dosage may be used concurrently);
---Use should be avoided in patients with severe hepatic impairment (whereas ubrogapant may be used in a reduced dosage);

Recommended dosage: 75 mg; tablet is placed on or under the tongue, allowed to disintegrate in the saliva and swallowed;

---Maximum dose in a 24-hour period is 75 mg;

---In patients being treated with a moderate CYP3A4 inhibitor, another dose should be avoided within 48 hours;

Product: Orally-disintegrating tablets – 75 mg; the foil covering of a blister pack should be pulled back and the tablet gently removed (the tablet should not be pushed through the foil covering);

Contraindications/most important risks:

---Hypersensitivity reactions;

---Use should be avoided in patients being treated with strong CYP3A4 inhibitors, strong and moderate CYP3A4 inducers, and P-gp inhibitors;

---Pregnancy: risk of harm based on animal studies;

---Hepatic impairment: use should be avoided in patients with severe hepatic impairment;

---Renal impairment: use should be avoided in patients with end-stage renal disease;

---Interactions: Activity is increased in patients being treated with strong CYP3A4 inhibitors and P-gp inhibitors (avoid concurrent use), as well as moderate CYP3A4 inhibitors (another dose should be avoided in 48 hours);

---Activity is decreased by strong and moderate CYP3A4 inducers (avoid concurrent use);

Most common adverse events: Nausea (2%);

Comments: Rimegepant is the second CGRP antagonist for oral administration for the treatment of migraine. It was evaluated in a placebo-controlled trial in which efficacy was established by an effect on pain freedom and Most Bothersome Symptom (MBS; e.g., photophobia, nausea) freedom at 2 hours. Twenty-one percent of patients treated with rimegepant were pain free at 2 hours, and 35% were MBS free at 2 hours.

Migraine

Eptinezumab-jjmr (Vyepti – Lundbeck) – 2020

Description: A monoclonal antibody that acts as a calcitonin gene-related peptide (CGRP) antagonist;

Indication: Administered intravenously for the preventive treatment of migraine in adults;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Erenumab (Aimovig), fremanezumab (Ajovy), galcanezumab (Emgality);

Advantages:

---Is administered once every 3 months (whereas erenumab and galcanezumab are administered once a month, and fremanezumab is administered once a month or once every 3 months);

---Is not likely to cause injection site reactions;

---Has not been associated with the occurrence of constipation with serious complications and hypertension (compared with erenumab with which these events have been reported);

Disadvantages:

---Is administered by intravenous infusion (whereas the comparable drugs may be self-administered subcutaneously);

---May be more likely to cause hypersensitivity reactions;

---Labeled indications are more limited (compared with galcanezumab that also has a labeled indication for the treatment of episodic cluster headache);

Recommended dosage: 100 mg as an intravenous infusion over approximately 30 minutes every 3 months;

---Some patients may benefit from a dosage of 300 mg every 3 months;

Product: Injection in single-use vials – 100 mg/mL (should be stored in a refrigerator);

---Must be diluted before use in 100 mL of 0.9% Sodium Chloride Injection;

---Diluted solution must be infused within 8 hours;

---Infusion bags must be made of polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO);

---Infusion set with a 0.2 micron or 0.22 micron in-line or add-on sterile filter should be used;

Contraindications/most important risks:

---Hypersensitivity reactions (including angioedema);

---Potential for immunogenicity, but data are limited;

Most common adverse events: Nasopharyngitis (6%; similar to placebo), hypersensitivity reactions (1%);

Comments: Like fremanezumab and galcanezumab, eptinezumab binds to CGRP ligand and inhibits its binding to the receptor, whereas erenumab binds to the CGRP receptor and inhibits its activation. Eptinezumab was evaluated in two placebo-controlled trials, one in patients with episodic migraine (4 to 14 migraine days per month (i.e., monthly migraine days [MMD]), and the second in patients with chronic migraine (15 or more headache days per month with at least 8 MMD). Study endpoints were measured at 12 weeks. Patients with episodic migraine experienced, on average, reductions of MMD of 3.9 and 4.3 with dosages of 100 mg and 300 mg, respectively, compared with a reduction of 3.2 with placebo. In the second study, patients with chronic migraine experienced, on average, reductions in MMD of 7.7 and 8.2 with dosages of 100 mg and 300 mg, respectively, compared with a reduction of 5.6 with placebo.

Seizures/epilepsy

Cenobamate (Xcopri – SK Life) – 2020

Description: Antiseizure agent that inhibits voltage-gated sodium currents and modulates the gamma-aminobutyric acid (GABA_A) ion channel;

Indication: Administered orally for the treatment of partial-onset seizures in adult patients;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Numerous antiepileptic drugs (AEDs) are approved for the treatment of patients with partial-onset seizures; levetiracetam (e.g., Keppra XR) is used for the comparisons below:

Advantages:

---May be more effective in some patients;

Disadvantages:

---May shorten the QT interval and increase the risk of arrhythmias;

---Dosage titration is more complex;

---May interact with more medications;

---Has not been evaluated in pediatric patients (whereas Keppra XR is indicated for patients 12 years and older);

Recommended dosage: 12.5 mg once a day during Weeks 1 and 2; titrated during Weeks 3-10 to the recommended maintenance dosage of 200 mg once a day; maximum dosage is 400 mg once a day;

---In patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200 mg once daily;

---When treatment is discontinued, dosage should be gradually reduced;

Products: Tablets – 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg;

Contraindications/most important risks:

---Contraindicated in patients with familial short QT syndrome;

---Suicidal behavior and ideation;

---CNS effects (e.g., somnolence, dizziness; patients should be cautioned about driving and other risky activities);

---Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity;

---Pregnancy: Risk of harm based on animal studies;

---Hepatic impairment: reduced dosage should be used in mild or moderate impairment; not recommended in severe impairment;

---Renal impairment: dosage reduction may be needed; avoid use in end-stage renal disease undergoing dialysis;

---Abuse: Schedule V; “drug-liking” scores higher than placebo;

---Interactions: May increase the activity of phenytoin, phenobarbital, and clobazam;

---May decrease the activity of carbamazepine and lamotrigine;

---May decrease the activity of CYP2B6 substrates (e.g., bupropion), CYP3A substrates (e.g., midazolam), and oral hormonal contraceptives (additional or alternative non-hormonal birth control should be used);

---May increase the activity of CYP2C19 substrates (e.g., omeprazole);

Most common adverse events: Somnolence (22%), dizziness (22%), fatigue (14%), headache (12%);

Comments: Cenobamate reduces repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a modulator of the GABA_A ion channel. It was evaluated in two placebo-controlled studies in patients whose seizures were not adequately controlled with 1 to 3 concomitant AEDs who had a mean duration of epilepsy of 24 years and median baseline seizure frequency of 8.5 seizures per 28 days. Patients treated with cenobamate had a median percent reduction of 55% from baseline seizure frequency per 28 days in both studies, compared with a median percent reduction of 22% and 24%, respectively, in those receiving placebo.

Bacterial infection **Cefiderocol sulfate tosylate (Fetroja – Shionogi) – 2020**

Description: A cephalosporin antibacterial agent that functions as a siderophore and binds to iron;

Indication: Administered intravenously for the treatment of adult patients (who have limited or no alternative options [subsequently deleted]) for the treatment of complicated urinary tract infections (cUTI) caused by susceptible gram-negative bacteria (e.g., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*); has been subsequently approved for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP);

New Drug Comparison Rating (NDCR) =

Comparable drugs: Ceftolozane/tazobactam (Zerbaxa), ceftazidime/avibactam (Avycaz);
---(was compared with imipenem/cilastatin in primary clinical study);

Advantages:

---May be effective in some patients with infections that are resistant to other antibacterial agents;
---Has a unique mechanism of action (functions as a siderophore);

Disadvantages:

---Has been observed to increase all-cause mortality in patients with carbapenem-resistant gram-negative infections;
---Labeled indications are more limited (ceftolozane/tazobactam and ceftazidime/avibactam are also indicated for the treatment of patients with complicated intra-abdominal infections (in combination with metronidazole);

Recommended dosage: 2 grams every 8 hours by intravenous infusion over 3 hours for 7 to 14 days;

---dosage should be adjusted in patients with a creatinine clearance less than 60mL/min or 120 mL/min or greater;

Product: Powder for injection in single-use vials – 1 gram (should be stored in a refrigerator);

---Contents of a vial should be constituted and further diluted with an appropriate diluent;

Contraindications/most important risks:

---Contraindicated in patients with a known history of severe hypersensitivity to the drug and other beta-lactam antibacterial agents;
---Increase in all-cause mortality in patients with carbapenem-resistant gram-negative bacterial infections;
---*Clostridioides difficile*-associated diarrhea;
---Seizures and other CNS adverse events;

Most common adverse events: Diarrhea (4%), infusion site reactions (4%), constipation (3%), rash (3%);

Comments: Cefiderocol is most similar structurally to cefepime and ceftazidime. However, it contains a substituent group that results in it functioning as a siderophore that binds to extracellular free ferric iron. Via a siderophore iron uptake mechanism, cefiderocol is actively transported across the outer cell membrane of bacteria. It binds to penicillin-binding proteins and exhibits bactericidal activity by inhibiting cell wall biosynthesis.

Resistance to cephalosporins and carbapenems has increased because certain bacteria are able to produce extended-spectrum beta-lactamases and carbapenemases that break the beta-lactam ring and inactivate beta-lactam antibacterial agents. New beta-lactam antibacterial agents, alone or combined with a beta-lactamase inhibitor, have been developed that are effective against some resistant gram-negative bacteria, but some patients experience serious infections that are multi-drug resistant for which treatment options are very limited. In addition to its action resulting from binding with penicillin-binding proteins, cefiderocol is unique among the beta-lactam antibacterial agents by functioning as a siderophore that is thought to increase activity within bacterial cells. Cefiderocol was evaluated in a trial in which it was compared with imipenem/cilastatin, and for which efficacy was assessed as a composite of microbiological eradication and clinical cure. Efficacy was demonstrated in 73% of patients treated with the new drug, compared with 55% of those treated with imipenem/cilastatin. Cefiderocol appears to be active against certain carbapenem-resistant bacteria and, in another study, was of similar effectiveness (~50%) to the best available treatment (most often colistin-based combination regimens).

Viral infection

Fostemsavir tromethamine (Rukobia – Viiv) – 2020

Description: A human immunodeficiency virus 1 (HIV-1) gp120-directed attachment inhibitor;

Indication: Administered orally in combination with other antiretrovirals for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations;

Comparable drug: Ibalizumab (Trogarzo);

New Drug Comparison Rating (NDCR) =

Advantages:

- Has a unique mechanism of action (is a HIV-1 gp120-directed attachment inhibitor)
- May be more effective in some patients;
- Is administered orally (whereas ibalizumab is administered intravenously)

Disadvantages:

- May prolong the QT interval;
- May increase hepatic transaminases in patients with hepatitis B or C co-infection;
- Interacts with numerous medications;

Recommended dosage: 600 mg twice a day; tablets should not be chewed, crushed, or split;

Product: Extended-release tablets – 600 mg fostemsavir (supplied as fostemsavir tromethamine);

Contraindications/most important risks:

- Contraindicated in patients being treated with a strong CYP3A4 inducer (may result in loss of virologic response);
- QT interval prolongation;
- Immune reconstitution syndrome;
- Hepatic transaminase elevations in patients with hepatitis B or C co-infection;
- Pregnancy: Patients should be registered in the Antiretroviral Pregnancy Registry (1-800-258-4263);
- Lactation: Breastfeeding is not recommended because of the potential for HIV-1 transmission;
- Interactions: Activity is decreased by strong CYP3A4 inducers, and concurrent use is contraindicated;
- May increase the activity of ethinyl estradiol (daily dose of ethinyl estradiol should not exceed 30 mcg);
- May increase the activity of the statins (the lowest possible starting dose of a statins should be used);
- May increase the activity of grazoprevir and voxilaprevir (alternative HCV regimens should be considered);
- May exhibit additive activity when used concurrently with other drugs that prolong the QT interval;

Most common adverse events: Nausea (10%), diarrhea (4%), headache (4%);

Comments: Most patients with HIV-1 infection can be successfully treated with a combination of two or more antiretroviral agents. However, some patients have multidrug resistant infection that is associated with a high risk of complications and death. Fostemsavir is a prodrug that is hydrolyzed to the active moiety, temsavir, which is an HIV-1 attachment inhibitor. Temsavir binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing attachment. Temsavir also can inhibit gp120-dependent post-attachment steps required for viral entry into host cells.

Fostemsavir was evaluated in a placebo-controlled trial in patients with multiclass HIV-1 resistance. A primary efficacy endpoint was a significant decrease in the viral load (HIV-RNA), and 65% of the patients experienced this endpoint at Day 8 of treatment, compared with 19% in the placebo group.

Viral infection

Remdesivir (Veklury – Gilead) – 2020

Description: A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor;

Indication: Administered intravenously in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization;

Comparable drugs: None

New Drug Comparison Rating (NDCR) =

Advantages:

---Is the first drug to be demonstrated to be active against SARS-CoV-2;
---Has reduced the time to recovery from COVID-19 in hospitalized patients;

Disadvantages:

---Has not been demonstrated to reduce the mortality rate in patients with COVID-19;

Recommended dosage: A single loading dose of 200 mg on Day 1 followed by once daily maintenance doses of 100 mg from Day 2 through Day 5 infused intravenously over 30 to 120 minutes; for patients who do not demonstrate clinical improvement, treatment may be extended for up to 5 additional days; for patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), the recommended duration of treatment is 10 days;

Products: Single-dose vials (for injection) – 100 mg lyophilized powder;
---should be reconstituted with Sterile Water for Injection and then diluted in a 100 mL or 250 mL 0.9% sodium chloride infusion bag;

Single-dose vials (injection) – 100 mg/20 mL (should be stored in a refrigerator);
---should be diluted in a 250 mL 0.9% sodium chloride infusion bag;

Contraindications/most important risks:

---Hypersensitivity reactions (e.g., infusion-related and anaphylactic reactions);
---Hepatic transaminase elevations (should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation);
---Activity may be reduced by hydroxychloroquine or chloroquine (concurrent use is not recommended);
---Renal impairment (not recommended in patients with eGFR less than 30 mL/minute);

Most common adverse events (incidence with 5-day course of treatment): Nausea (5%), increased ALT (2%), increased AST (3%);

Comments: Remdesivir is the first drug to be approved for the treatment of COVID-19. It is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to a nucleoside monophosphate intermediate by carboxyesterase 1 and/or cathepsin A. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with high selectivity over the natural ATP substrate for incorporation into nascent RNA chains.

The effectiveness of remdesivir was demonstrated in three clinical trials in patients hospitalized with mild-to-severe COVID-19. The primary goal of the largest trial was time to recovery, with recovery defined as either being discharged from the hospital or being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days for the remdesivir group compared to 15 days for the placebo group. The likelihood of clinical improvement at Day 15 were also statistically significantly higher in the remdesivir group. The overall 29-day mortality was 11% for the remdesivir group compared with 15% for the placebo group, but this difference was not statistically significant.