NCPD 2.5 ANCC CONTACT HOURS

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ZERBOR / SHUTTERSTOCK

PART 1

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Abstract: This article reviews seven drugs recently approved by the FDA, including indications, precautions, adverse reactions, and nursing considerations.

Keywords: bempedoic acid, eptinezumab-jjmr, lasmiditan hemisuccinate, lemborexant, lumateperone tosylate, rimegepant sulfate, ubrogepant

THIS ARTICLE reviews seven recently marketed drugs, including:

- four new treatments for patients with migraine.
- the second orexin receptor antagonist to be approved for insomnia.
- an atypical antipsychotic medication for patients with schizophrenia.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the prescribing information, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions for all these drugs.

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Migraine affects an estimated 39 million people in the US and is about three times more common in women than men.[1] Migraine attacks range from mild to severe in intensity and are typically characterized by a throbbing, unilateral headache and additional signs and symptoms such as nausea and/or vomiting and photophobia and phonophobia. Approximately one-third of individuals with migraine experience aura shortly before the migraine attack.[2] Although migraine attacks may be relatively mild and/or brief, they can be sufficiently severe, persistent, or frequent to become disabling with respect to working and fulfilling other responsibilities.

For patients with moderate to severe migraine, a triptan (serotonin 1B/1D [5-$HT_{1B/1D}$] receptor agonist) is the usual treatment of choice, with up to 40% of patients responding within 2 hours following oral administration.[3] All of the triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) are available in orally administered formulations. Sumatriptan and zolmitriptan are also available in formulations for nasal administration and sumatriptan is also available in a formulation for subcutaneous injection. The triptans increase the risk of complications in patients with certain cardiovascular disorders, and their use is contraindicated in these patients. Other medications that have been used for the treatment of migraine include dihydroergotamine in formulations for parenteral or nasal administration, and ergotamine in combination with caffeine (for example, Cafergot) in formulations for oral or rectal administration. These medications also have potentially serious risks, such as vascular occlusion and rebound headache, and the dosage recommendations must be strictly observed.[4]

The overuse of drugs used to treat acute migraine, such as triptans, ergotamines, opioids, or a combination of these drugs for 10 or more days per month, may result in exacerbation of headache (medication overuse headache); this may present as daily migraine-like headaches or as a marked increase in the frequency of migraine attacks.[5] Detoxification of patients, including withdrawal of the overused drugs and the treatment of withdrawal symptoms, which may include a transient worsening of headache, may be necessary.

Three new drugs were marketed in 2020 for the acute treatment of migraine in adults, and a fourth drug was marketed for preventive treatment. Their properties and use are considered on an individual basis in the following discussions.

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Lasmiditan hemisuccinate

An effective alternative to triptans

Lasmiditan hemisuccinate (*Reyvow*, Lilly) is a serotonin 1F (5-HT_{1F}) receptor agonist that has a more selective action than the triptans and its use has not been associated with vasoconstrictive effects. It is administered orally for the acute treatment of migraine with or without aura in adults.[1]

Lasmiditan 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) such as photophobia or nausea at 2 hours. With a dose of 100 mg of lasmiditan, 28% and 31% of patients were pain-free at 2 hours, compared with 15% and 21%, respectively, of those receiving placebo. At 2 hours, 41% and 44% of patients treated with lasmiditan were MBS-free compared with 30% and 33%, respectively, of those receiving placebo.

The new drug has not been directly compared with triptans in clinical studies, and there are no data to suggest that it is more effective than the triptans. However, for patients with migraine who would be at greater risk with the use of a triptan, lasmiditan may be an effective and safer alternative.

Precautions: (1) Because of lasmiditan's central nervous system (CNS) depressant action, patients should be advised not to drive or operate machinery until at least 8 hours after taking a dose. The risk of CNS depression/impairment is increased by the concurrent use of other CNS depressants including alcoholic beverages. (2) Patients treated with lasmiditan have been reported to have higher "drug-liking" scores than those receiving placebo, suggesting the potential for abuse. Consequently, lasmiditan has been included in Schedule V under the provisions of the Controlled Substances Act. (3) As with the triptans, lasmiditan may be infrequently associated with serotonin syndrome, which often includes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.[2] The risk of this potentially life-threatening condition is increased by the concurrent use of other serotonergic drugs such as sertraline, venlafaxine, and amitriptyline. (4) Animal studies suggest a risk of harm if lasmiditan is used during pregnancy or lactation. (5) Lasmiditan has not been studied in patients with severe hepatic impairment and its use in these patients is not recommended. (6) When used concurrently with drugs that lower heart rate such as propranolol, lasmiditan decreases heart rate by an additional 5 beats/minute. Treatment should be closely monitored in patients in whom a reduction in heart rate is a concern. (7) Lasmiditan inhibits P-glycoprotein (P-gp) and breast cancer resistant

protein (BCRP), and its concomitant use with substrates of these drug transporters should be avoided. BCRP and P-gp are membrane-bound efflux transporters that transport multiple chemical classes of compounds and act as barriers to tissue permeability, which regulates tissue exposure of their substrates.[3]

Adverse reactions: dizziness, fatigue, paresthesia, sedation

Supplied as: 50 mg and 100 mg film-coated tablets

Dosage: 50 mg, 100 mg, or 200 mg as needed

Nursing considerations: (1) Lasmiditan may be taken without regard to food. (2) Inform patients that a second dose has not been shown to be effective for the same migraine attack. Warn them to take no more than one dose in a 24-hour period. The safety of treating an average of more than four migraine attacks in a 30-day period has not been established. (3) Warn patients about the drug's CNS depressant effects. (4) Educate patients about the risk of serotonin syndrome and tell them to seek medical attention immediately if they experience signs and symptoms such as mental changes, diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea.

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Ubrogepant

One of two new orally administered CGRP receptor antagonists

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is primarily distributed in the central and peripheral nervous systems and acts as a vasodilator. It is involved in the transmission of pain impulses, and elevated concentrations have been associated with migraine attacks. Three monoclonal antibodies (erenumab, fremanezumab, and galcanezumab) were marketed in 2018 as the first in a new class of CGRP antagonists used in patients who experience migraine. All three of these drugs are administered subcutaneously for the preventive treatment of migraine in adults but are not indicated for the acute treatment of migraine.

Ubrogepant (*Ubrelvy*, Allergan) is one of two new orally administered CGRP receptor antagonists marketed in 2020 for the acute treatment of migraine with or without aura in adults. It is not indicated for preventive treatment.[1] It was evaluated in two placebo-controlled trials in which efficacy was established by an effect on pain freedom and freedom from MBS, such as photophobia or nausea, at 2 hours. After taking a 100 mg dose of ubrogepant, 21% of patients were pain-free at 2 hours, compared with 12% of those receiving placebo. Thirty-eight percent of patients treated with ubrogepant were MBS-free at 2 hours, compared with 28% of those receiving placebo. No data suggest that ubrogepant is more effective than the triptans or other previously marketed drugs, but it may be effective in some patients who do not experience an adequate response with the other agents. In addition, its different mechanism of action and safety profile may benefit patients who cannot tolerate other drugs or who have factors that place them at risk for adverse reactions to alternative treatments.

Ubrogepant is metabolized primarily via the CYP3A4 pathway. It is well tolerated. Unlike the triptans, which are contraindicated in patients with various cardiovascular and other vascular diseases, ubrogepant has not been associated with these risks.

Precautions: (1) Avoid concomitant use with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, and clarithromycin, which increase ubrogepant exposure. (2) Avoid concomitant use with strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort, which reduce ubrogepant exposure. Consult the prescribing information for additional precautions regarding concomitant use with moderate CYP3A4 inhibitors (including grapefruit products) or weak CYP3A4 inhibitors, and inducers or BCRP and/or P-gp only inhibitors. (2) Avoid the use of ubrogepant in patients with end-stage renal disease. A dosage reduction is recommended in patients with severe hepatic or renal impairment.

Adverse reactions: nausea, somnolence

Supplied as: 50 mg and 100 mg tablets

Dosage: 50 mg or 100 mg. If needed, a second dose may be administered at least 2 hours after the first dose. The maximum dose in a 24-hour period is 200 mg. Consult the prescribing information for dosage adjustments in patients taking medications that may interact with ubrogepant.

Nursing considerations: (1) Ubrogepant may be taken without regard to food. (2) Teach patients to take the medication as directed and not to take more than two doses in 24 hours. (3) Instruct patients not to take a second dose within 24 hours if they consume grapefruit or grapefruit juice or are taking certain medications including verapamil, cyclosporine, ciprofloxacin, fluconazole, and fluvoxamine.

REFERENCE

1. Ubrelvy (ubrogepant) tablets, for oral use. Prescribing information. https://media.allergan.com/products/Ubrelvy_pi.pdf.

Rimegepant sulfate

Oral disintegrating tablets for acute migraine treatment

Rimegepant sulfate (*Nurtec ODT*, Biohaven) was the second orally administered CGRP receptor antagonist to be marketed in 2020. Like ubrogepant, it is indicated for the acute treatment of migraine with or without aura in adults.[1] It was evaluated in a placebo-controlled trial in which efficacy was established by an effect on pain freedom and MBS freedom at 2 hours. Twenty-one percent of patients treated with rimegepant were pain-free at 2 hours, compared with 11% of those receiving placebo. Thirty-five percent of patients treated with rimegepant were MBS-free at 2 hours, compared with 27% of those receiving placebo. It has not been directly compared with triptans or other drugs used for the acute treatment of migraine, but it may be effective in some patients who do not respond adequately to the other medications. It is not indicated for the preventive treatment of migraine.

Like ubrogepant, rimegepant is primarily metabolized via the CYP3A4 pathway. Its activity is increased by CYP3A4 inhibitors and inhibitors of BCRP and P-gp efflux transporters. It is formulated to be placed on the tongue, where it dissolves in saliva and can be swallowed; alternatively, it can be administered sublingually.

Precautions: (1) Avoid use in patients with severe hepatic impairment because of significantly higher plasma concentrations. Dosage adjustment is not necessary in patients with mild or moderate hepatic impairment. (2) Rimegepant has not been studied in patients with end-stage renal disease or in those on dialysis and its use should be avoided in these patients. No dosage adjustment is needed for patients with mild, moderate, or severe renal impairment. (3) Avoid concurrent use with CYP3A4 inhibitors and inhibitors of BCRP and P-gp efflux transporters, which increase the activity of rimegepant. The dosage of rimepegant should be adjusted in patients being treated with a moderate CYP3A4 inhibitor. (4) Avoid concurrent use with strong or moderate CY3A4 inducers, which may reduce the activity of the new drug. (5) Although rare, severe hypersensitivity reactions including dyspnea and rash have occurred, and this can develop days after administration.

Adverse reaction: nausea

Supplied as: 75 mg orally disintegrating tablets provided in blister packs of 8 tablets

Dosage: 75 mg; this is also the maximum dose that may be taken in a 24-hour period. Patients being treated with a moderate CYP3A4 inhibitor should not take a second dose within 48 hours.

Nursing considerations: (1) To administer the drug, patients should place a tablet on or under the tongue, let it disintegrate in saliva, and swallow. (2) Warn patients about the risk of allergic reactions, which may be delayed. Tell them to seek medical attention immediately if they experience serious signs and symptoms such as edema of the face, mouth, tongue, or throat, or trouble breathing. (3) Teach patients to take the drug as directed and warn them not to take more than one dose in a 24-hour period.

REFERENCE

1. Nurtec ODT (rimegepant) orally disintegrating tablets, for sublingual or oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2020/212728s000lbl.pdf.

Eptinezumab-jjmr

Administered I.V. for preventive migraine treatment

Patients who experience 4 to 14 migraine days per month, or monthly migraine days (MMD), are classified as having episodic migraines; those with 15 or more headache days per month with at least 8 MMD are classified as having chronic migraine.[1] When migraine triggers cannot be identified or avoided, patients who experience frequent migraine attacks may be candidates for preventive management to reduce the frequency and severity of attacks. Certain beta-blockers, such as propranolol and timolol, and antiepileptic drugs, such as divalproex sodium and topiramate, have labeled indications for migraine prevention. However, many patients do not respond adequately to these drugs or experience unacceptable adverse reactions and other risks.

Eptinezumab-jjmr (*Vyepti*, Lundbeck) joins the three CGRP antagonists previously approved for the preventive treatment of migraine (erenumab, fremanezumab, and galcanezumab).[1] Unlike the previously approved drugs, which are administered subcutaneously, eptinezumab is administered I.V. Eptinezumab was evaluated in two placebo-controlled trials, one in patients with episodic migraine and the other in patients with chronic migraine. Study endpoints were measured at 12 weeks. Patients with episodic migraine experienced, on average, reductions in 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. Fifty percent and 56% of patients treated with dosages of 100 and 300 mg, respectively, experienced at least a 50% reduction from baseline in MMD, compared with 37% of those receiving placebo.

In the second study, patients with chronic migraine experienced, on average, reductions of MMD of 7.7 and 8.2 with dosages of 100 and 300 mg, respectively, compared with a reduction of 5.6 with placebo. Fifty-eight percent and 61% of patients treated with dosages of 100 mg and 300 mg, respectively, experienced at least a 50% reduction from baseline in

MMD, compared with 39% of those receiving placebo.

Erenumab has been associated with constipation with serious complications and hypertension, but these were not reported in clinical studies of eptinezumab.

Precautions: (1) Contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients. (2) Hypersensitivity reactions may include angioedema, urticaria, facial flushing, and rash. If a hypersensitivity reaction occurs, clinicians should consider discontinuing the infusion and initiate appropriate therapy.

Adverse reactions: nasopharyngitis, hypersensitivity

Supplied as: single-dose vials containing 100 mg of the drug in 1 mL

Dosage: 100 mg every 3 months administered as an I.V. infusion over approximately 30 minutes. Some patients may benefit from 300 mg every 3 months.

Nursing considerations: (1) Store vials in a refrigerator. (2) The contents of a vial must be diluted before use in 100 mL of 0.9% Sodium Chloride Injection. Infusion bags must be made of polyvinyl chloride, polyethylene, or polyolefin. An infusion set with a 0.2 micron or 0.22 micron in-line or add-on sterile filter should be used. (3) Administer the diluted solution within 8 hours. (4) Inform patients that hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, can occur. If they experience signs or symptoms of a hypersensitivity reaction, advise them to call 911 or contact their healthcare provider immediately, depending on severity.

REFERENCE

1. Vyepti (eptinezumab-jjmr) injection, for intravenous use. Prescribing information. www.lundbeck.com/upload/us/files/pdf/Products/Vyepti_PI_US_EN.pdf.

HYPNOTIC

Lemborexant

Second orexin receptor antagonist to be approved for insomnia

Insomnia is most often characterized by difficulties in falling asleep (sleep-onset insomnia) and/or sleep maintenance. The most frequently prescribed medications for treatment of insomnia are zolpidem and eszopiclone, which act as benzodiazepine receptor agonists although they differ structurally from the benzodiazepines. Other options include benzodiazepines such as temazepam, the orexin receptor antagonist suvorexant, the tricyclic antidepressant doxepin in a low dosage, and hypnotics with a short duration of action including zaleplon and the melatonin receptor agonist ramelteon. Certain nonprescription antihistamines and the dietary supplement melatonin are also used as sleep aids.

The orexins are naturally occurring neuropeptides that act in a signaling mechanism as a central promoter of wakefulness. This wake-promoting action results from the binding of orexin A and orexin B to orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R) receptors.

Lemborexant (*Dayvigo*, Eisai) is the second orexin receptor antagonist to be approved for the treatment of patients with insomnia, joining suvorexant. By blocking the binding of the orexins to their receptors, these drugs are thought to suppress the wake drive. Like suvorexant, lemborexant is indicated to treat adults with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[1]

The effectiveness of lemborexant was evaluated in two clinical trials, one of which was conducted in adults age 55 and older (median age, 63) over a period of 1 month with 5 mg and 10 mg doses of the new drug, and was placebo- and active-controlled with zolpidem extended-release 6.25 mg. Both doses of lemborexant demonstrated statistically significant superiority compared with placebo and zolpidem extended-release in reducing the time to sleep onset, the primary efficacy endpoint, as well as improvement in sleep efficiency (percentage of time asleep compared with time in bed) and the time awake after sleep onset. The other study was a 6-month placebo-controlled trial in adults age 18 and older, in which both doses of lemborexant demonstrated statistically significant superiority in the efficacy measures.

Like suvorexant, lemborexant is classified as a Schedule IV controlled substance. However, in the controlled studies, no evidence of physical dependence was found with the prolonged use of the drugs and withdrawal symptoms were not reported after discontinuation of treatment.

The risk of adverse reactions if used during pregnancy appears to be low but women who are exposed to the drug during pregnancy should be registered in the Dayvigo pregnancy registry by calling 1-888-274-2378. Because lemborexant and its metabolites are likely to be present in human milk, infants exposed to the drug through breast milk should be monitored for excessive sedation.

Precautions: (1) Contraindicated in patients with narcolepsy. The loss of orexin receptors has been reported in patients with narcolepsy and the antagonism of orexin receptors by lemborexant may be associated with signs and symptoms of narcolepsy/cataplexy. Symptoms similar to those of mild cataplexy, such as periods of leg weakness, can occur. (2) Sleep paralysis (an inability to speak or move for up to several minutes) and hallucinations have been infrequently reported. (3) Because lemborexant is a central nervous system (CNS) depressant, daytime wakefulness and driving skills may be impaired. CNS depressant effects and related risks increase with dosage and the concurrent use with other CNS depressants,

including alcohol. Patients should avoid alcohol consumption during treatment with lemborexant, and patients treated with the higher (10 mg) dose should be advised against next-day driving and other activities requiring complete mental alertness. (4) The use of hypnotics has been associated with complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake (such as preparing and eating food, making phone calls, and having sex), and patients usually do not remember these events. Treatment should be immediately discontinued in patients who experience these effects. (5) Worsening of depression and suicidal ideation has been associated with hypnotics. Clinicians must take appropriate precautions when evaluating, treating, and monitoring patients with respect to these risks. Because intentional overdose is more common in this group of patients, only the lowest number of tablets that is feasible should be prescribed at any one time. (6) Use with caution in patients with compromised respiratory function. Lemborexant has not been studied in patients with moderate to severe obstructive sleep apnea or in patients with chronic obstructive pulmonary disease. (7) Lemborexant has not been studied in patients with severe hepatic impairment, and its use in these patients is not recommended. Patients with mild hepatic impairment may experience an increased risk of somnolence, and a lower dosage should be used in patients with moderate hepatic impairment. (8) Dosage adjustment is not necessary in patients with renal impairment, although patients with severe renal impairment may have an increased risk of somnolence. (9) The activity of lemborexant may be increased by drugs that are CYP3A inhibitors and decreased by CYP3A inducers. Avoid concurrent use of lemborexant with a strong or moderate CYP3A inhibitor, such as clarithromycin, itraconazole, fluconazole, or verapamil, or with a strong or moderate CYP3A inducer, such as carbamazepine, rifampin, St. John's wort, efavirenz, or modafinil. A lower dosage of lemborexant should be used in patients treated concurrently with a weak CYP3A inhibitor. (10) Lemborexant may reduce the activity of bupropion and methadone. It may be necessary to increase the dosage of these drugs when lemborexant is used concurrently.

Adverse reactions: somnolence following the period of sleep, headache, nightmare, or abnormal dreams

Supplied as: 5 mg and 10 mg film-coated tablets

Dosage: 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dosage may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Consult the prescribing information for recommended dosage adjustments for special patient groups, such as those with moderate hepatic impairment.

Nursing considerations: (1) Tell patients to take lemborexant as directed right before bedtime when they can stay in bed for a full night (at least 7 hours). Inform them that the drug has a prompt onset of action but its maximum concentration and time to sleep onset may be delayed if it is taken with or soon after a meal. (2) Teach patients about the potential for CNS depression and tell them to avoid alcohol, which may worsen this effect. (3) Warn patients that they may feel drowsy the day after taking lemborexant and to avoid driving and other activities requiring alertness until they feel fully awake, especially if they have had less than 7 hours of sleep or they took more medication than prescribed. (4) Teach patients about other potentially serious adverse reactions, including worsening depression and/or suicidal ideation and complex sleep behaviors. Tell them to immediately report these to the healthcare provider. (5) Because many drugs interact with lemborexant, tell patients to inform the healthcare provider about all medications, herbal products, and supplements they take, and to check with the provider before taking any new medications or over-the-counter products.

REFERENCE

1. Dayvigo (lemborexant) tablets, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf.

LIPID-REGULATING DRUG

Bempedoic acid

Beware of risk for hyperuricemia and gout

Heart disease, recently surpassed by COVID-19 as the leading cause of adult mortality in the US, is responsible for approximately 650,000 deaths each year.[1,2] Hypertension, hypercholesterolemia, and smoking are key risk factors for heart disease, and almost one-half of Americans have at least one of these risk factors.[3] Diabetes, overweight/obesity, physical inactivity, unhealthy diet, and excessive alcohol use can also put people at a higher risk for heart disease.

Familial hypercholesterolemia is an inherited condition that is associated with high concentrations of low-density lipoprotein cholesterol (LDL-C). The statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) have been widely prescribed as the standard of therapy for reducing elevated LDL-C concentrations and the related risks of cardiovascular disease. Although the statins are highly effective, some patients do not tolerate them well and others who are treated with a maximally tolerated dose of a statin still require additional lowering of LDL-C.

Other medications that have been used to regulate LDL-C and other

blood lipid concentrations, sometimes in conjunction with a statin, include fibric acid derivatives, the cholesterol absorption inhibitor ezetimibe, bile acid sequestrants, and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors. The PCSK9 inhibitors are administered subcutaneously, whereas the other medications are administered orally.

Bempedoic acid (*Nexletol*, Esperion) has a unique mechanism of action in reducing cholesterol synthesis in the liver and lowering LDL-C in blood via upregulation of LDL receptors. It acts by inhibiting adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. The new drug is administered orally and indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.[4]

The effectiveness of bempedoic acid was evaluated in two placebo-controlled trials that enrolled more than 3,000 patients as add-on to a maximally tolerated dose of a statin alone or in combination with other lipid-lowering therapies. In the two trials, the primary efficacy outcome measure was the percent change in LDL-C from baseline to Week 12. The difference between the drug and placebo in mean percent change was -18% and -17%, with the maximum LDL-C lowering effects occurring at Week 4 in both studies. There were also reductions of at least 10% in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B. HDL-C and triglycerides (TG) were examined as exploratory endpoints, and the changes in these parameters were -6% for HDL-C in both studies, and +3% and -2% for TG.

The labeled indication for bempedoic acid is much more limited than for the statins. Based on long-term studies and clinical use, the statins have demonstrated effectiveness in multiple dyslipidemias and in reducing the risk of myocardial infarction, stroke, and other complications in patients with multiple risk factors. Although the effect of bempedoic acid on cardiovascular morbidity and mortality has not been demonstrated, the LDL-C-lowering effect of the new drug is additive to that of the statins and it can be anticipated that the benefits identified for the statins will be extended.

Soon after bempedoic acid was approved, the FDA approved a fixed-dose combination product (Nexlizet) that also includes ezetimibe. In a study of patients already being treated with a statin, the addition of both bempedoic acid and ezetimibe provided a 36% reduction in LDL-C that was significantly greater than that with either of these drugs alone.

Precautions: (1) Bempedoic acid may increase blood uric acid concentrations; hyperuricemia was reported in 4% of the patients in the clinical trials. Gout was reported in 1.5% of patients taking the new drug compared with 0.4% of patients receiving placebo. Monitor patients for signs and symptoms of gout such as severe pain, redness, warmth, and swelling, especially at the base of the great toe (first metatarsophalangeal joint), and assess uric acid concentrations as clinically indicated.[5] (2) Avoid use of bempedoic acid in patients with a history of tendon problems; bempedoic acid is associated with an increased risk of tendon rupture or injury. Tendon rupture involving the rotator cuff, biceps tendon, or Achilles tendon occurred in 0.5% of patients in the clinical studies compared with 0% of the patients receiving placebo. The risk of tendon rupture is increased in patients over age 60, in those taking a fluoroquinolone or corticosteroid, and in those with renal failure. The drug should be immediately discontinued if a patient experiences a tendon rupture and discontinuation of treatment should be considered if a patient experiences joint pain, swelling, or inflammation. (3) Bempedoic acid has been associated with an increased risk of benign prostatic hyperplasia; increases in liver enzymes, creatinine, blood urea nitrogen, and platelet counts; and decreases in hemoglobin and leukocytes. However, these changes are generally asymptomatic and do not require intervention. (4) The concurrent use of bempedoic acid increases the concentrations of pravastatin and simvastatin and may increase the risk of myopathy with the latter two drugs. When the new drug is used concomitantly, the dosage of pravastatin should not exceed 40 mg daily, and the dosage of simvastatin should not exceed 20 mg daily.

Adverse reactions: upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes

Supplied as: 180 mg tablets

Dosage: in combination with maximally tolerated statin therapy, 180 mg once a day

Nursing considerations: (1) Bempedoic acid may be taken without regard to food. (2) Lipid concentrations should be assessed within 8 to 12 weeks following initiation of therapy. (3) Teach patients to recognize and immediately report signs and symptoms of tendon rupture, such as pain, swelling, and bruising, in tendons of the arm, shoulder, and back of the ankle. If they experience any such signs and symptoms, they should stop taking the drug immediately and contact their healthcare provider. (4) Teach patients to recognize and report signs and symptoms of gout, such as severe pain in toe joints. (5) Tell patients to inform the healthcare provider about all medications they take, including prescription and

over-the-counter drugs, vitamins, and herbal supplements, and to check with the provider before taking any additional medications or products.

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ANTIPSYCHOTIC DRUG

Lumateperone tosylate

Not indicated for dementia-related psychosis

Schizophrenia, which affects more than 2 million individuals in the US, is often initially diagnosed during adolescence or young adulthood and is typically a lifelong challenge.[1,2] It is usually characterized by a combination of "positive" symptoms such as agitation, delusions, and hallucinations, and "negative" symptoms such as apathy and social withdrawal.[2] Although first-generation antipsychotic agents such as the phenothiazines and haloperidol are used to a limited extent, atypical (second-generation) antipsychotic agents such as risperidone are preferred for most patients, primarily because they may be better tolerated.

Among the atypical antipsychotic drugs, clozapine is the most effective. However, because of the risk of serious adverse reactions such as severe neutropenia, its use is reserved for patients with treatment-resistant schizophrenia. The other atypical antipsychotic agents act primarily at certain dopamine receptors and certain serotonin receptors. They are generally similar in effectiveness, although many patients who do not experience an adequate response with one drug may respond to another. The risks of these drugs are also generally similar, as are the types of adverse reactions; however, the incidence of the most common adverse reactions, such as extrapyramidal symptoms (akathisia, parkinsonism, and dystonias), diabetes, weight gain, and sedation, vary widely. Accordingly, the selection of the particular agent with which to initiate treatment is based on a consideration of factors, including patient risk factors for certain adverse reactions, potential interactions with other drugs the patient is taking, and cost.

Lumateperone tosylate (*Caplyta*, Intra-Cellular Therapeutics) is an atypical antipsychotic drug indicated to treat schizophrenia in adults.[3] This labeled indication is more limited than the indications for risperidone and most other atypical antipsychotics. Although the specific mechanism of action for lumateperone is not known, its effectiveness may be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors.

The effectiveness of lumateperone was evaluated in two 4-week placebo-controlled clinical trials, in which the primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS total score may range from 30 to 210, with higher scores reflecting greater overall symptom severity. In both studies, the recommended dosage of lumateperone (42 mg daily) showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. A dosage of 84 mg daily of lumateperone was also evaluated in one of the studies and, surprisingly, provided less of a reduction in the PANSS total score than the 42 mg daily dosage and was not statistically different from the total score of those receiving placebo.

Risperidone (4 mg daily) was used as an active comparator in a group of patients in this study, although the study was not designed to compare lumateperone and risperidone. Risperidone provided a reduction in the PANSS total score that was very similar to that attained with the 42 mg daily dosage of lumateperone.

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 the new drug (42 mg daily) and placebo, whereas patients receiving risperidone experienced a statistically significant reduction in PANSS total scores compared with placebo.

Like other antipsychotic agents, lumateperone is labeled with a boxed warning that older adults with dementia-related psychosis are at increased risk for death if treated with an antipsychotic drug. None of these drugs has been approved for treatment of patients with dementia-related psychosis, who are also at risk for cerebrovascular events, including stroke.

Data are insufficient to assess the risk of using lumateperone during pregnancy but exposure to the drug during the third trimester may result in extrapyramidal and/or withdrawal symptoms in neonates. When the drug's anticipated benefit outweighs the risk, pregnant women should be registered in the National Pregnancy Registry for Atypical Antipsychotics by calling 1-866-961-2388.

Precautions: (1) Risks associated with the use of atypical antipsychotic drugs, including lumateperone, include neuroleptic malignant syndrome, tardive dyskinesia, seizures, orthostatic hypotension, syncope, falls, metabolic changes (such as hyperglycemia/diabetes, dyslipidemia, and weight gain), leukopenia, neutropenia, agranulocytosis, body temperature dysregulation, dysphagia, and the potential for cognitive and motor impairment. Patients who

are at greater risk or who have experienced signs and symptoms characteristic of these events should be closely monitored. In some patients, the type and/or severity of adverse reactions may warrant discontinuation of treatment. (2) Because of the potential for impairment of judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they determine how lumateperone affects them. (3) Lumateperone is not recommended for use in patients with moderate or severe hepatic impairment. (4) Avoid concurrent use with strong or moderate CYP3A4 inhibitors (such as clarithromycin, fluconazole, itraconazole, verapamil, and grapefruit juice), CYP3A4 inducers (such as carbamazepine, rifampin, and St. John's wort), and uridine 5'-diphosphoglucuronosyltransferase inhibitors such as valproic acid and probenecid.

Adverse reactions: somnolence/sedation, dry mouth

Supplied as: 42 mg capsules

Dosage: 42 mg once a day

Nursing considerations: (1) Tell patients to take each capsule with food. (2) Teach patients to recognize and report signs and symptoms of serious adverse reactions. Warn them that the medication may cause somnolence, syncope, and orthostatic hypotension, and advise them to use caution with driving and other activities requiring alertness until they learn how the medication affects them. ■

REFERENCES

1. Intra-Cellular Therapies. About schizophrenia. www.caplyta.com/about-schizophrenia.
2. National Institutes of Health/National Institute of Mental Health. Schizophrenia. www.nimh.nih.gov/health/topics/schizophrenia/index.shtml.
3. Caplyta (lumateperone) capsules, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2019/209500s000lbl.pdf.

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