1.5 ANCC CONTACT HOURS CE 1.5 PHARMACOLOGY CREDITS

New Drugs 2019 PART 2

BY DANIEL A. HUSSAR, PhD
DEAN EMERITUS AND REMINGTON PROFESSOR EMERITUS • PHILADELPHIA COLLEGE OF PHARMACY • UNIVERSITY OF THE SCIENCES
PHILADELPHIA, PA.

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

Keywords: angiotensin II acetate, baricitinib, bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate, Biktarvy, elagolix sodium, ibalizumab-uiyk, lofexidine hydrochloride, sodium zirconium cyclosilicate, tildrakizumab-asmn

THIS ARTICLE reviews eight drugs recently approved by the FDA, including:

- two drugs for treating patients with HIV-1 infection.
- a gonadotropin-releasing hormone receptor antagonist indicated for moderate-to-severe pain associated with endometriosis.
- the first nonopioid indicated to treat symptoms of opioid withdrawal.
- the first therapeutic angiotensin II product indicated to raise BP in adults with septic or other distributive shock.

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.

SELECTED REFERENCES

Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, Inc.; 2019.

Nursing2019 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2019.

Physician's Desk Reference. 71st ed. Montvale, NJ: Medical Economics; 2019.

The author and planners have disclosed no potential conflicts of interest, financial or otherwise.

EPIC CREATIONS / SHUTTERSTOCK

ANTIVIRAL DRUGS

Bictegravir sodium/ emtricitabine/ tenofovir alafenamide fumarate

Three drugs in one tablet

HIV integrase is an enzyme that has an important role in the replication of HIV because it facilitates the integration of viral DNA into the DNA of host cells. Inhibition of this process helps manage HIV infection. Three HIV-1 integrase strand transfer inhibitors (INSTIs) have been marketed in recent years: raltegravir, elvitegravir, and dolutegravir sodium. These are used in combination with other antiretroviral drugs and several combination products are also available.

The fourth INSTI to be approved, bictegravir, is included in a combination formulation: bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate (*Biktarvy*, Gilead).[1] This new combination is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

The active ingredients and indications for Biktarvy are most similar to those of Genvoya, a combination product containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. The differences between these two combinations include the omission from the Biktarvy formulation of cobicistat, a CYP3A inhibitor in Genvoya that inhibits the metabolism and increases the action of elvitegravir but also interacts with many other medications. In addition, Genvoya is indicated for pediatric patients weighing at least 25 kg, whereas Biktarvy is currently indicated only for adults.

Biktarvy has not been evaluated in pregnant women but animal studies suggest that adverse developmental outcomes are unlikely if it is used during pregnancy. However, women who are exposed to the product during pregnancy are advised to register in the Antiretroviral Pregnancy Registry (1-800-258-4263).

Because Biktarvy is a complete regimen, coadministration with other antiretroviral medications for treatment of HIV-1 infection is not recommended.

Precautions: (1) Biktarvy is not recommended in patients with severe hepatic impairment. Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of emtricitabine and tenofovir disoproxil fumarate. If clinical or lab findings suggest lactic acidosis or if pronounced hepatotoxicity occurs, treatment should be suspended. (2) Biktarvy is not recommended in patients with severe renal impairment or an estimated creatinine clearance below 30 mL/min. Some patients have experienced renal impairment, including acute renal failure, with the use of tenofovir prodrugs; serious renal adverse reactions occurred in less than 1% of the patients treated with Biktarvy in clinical studies. Patients with impaired renal function and those taking potentially nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), are at increased risk for developing renal-related adverse reactions. Testing for renal function (serum creatinine, estimated creatinine clearance, and urine protein) should occur before or when initiating treatment, and during treatment with Biktarvy. Serum phosphorus should also be assessed in patients with chronic kidney disease. (3) All patients with HIV-1 infection should be tested for chronic hepatitis B virus (HBV) infection before or when initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B infection such as liver decompensation and liver failure have occurred in some patients who are coinfected with HIV-1 and HBV and who have discontinued products containing emtricitabine and tenofovir disoproxil fumarate. This is the subject of a Boxed Warning in the labeling for Biktarvy. Coinfected patients who discontinue treatment with the new combination should be closely monitored for several months or more following discontinuation of treatment. Initiating anti-HBV therapy may be necessary in some patients. (4) Some patients treated with combination antiretroviral therapy have experienced immune reconstitution syndrome, an inflammatory response to an indolent or residual opportunistic infection such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, or TB. Arising during the initial phase of combination treatment, this response may require further evaluation and treatment. (5) Coadministration of Biktarvy with dofetilide is contraindicated. Concurrent use may increase plasma concentrations of dofetilide, leading to potentially serious adverse reactions. (6) Coadministration of Biktarvy with rifampin is contraindicated. Concurrent use decreases bictegravir and tenofovir concentrations, potentially leading to loss of therapeutic effect and resistance to Biktarvy. (7) For the same reason, coadministration of Biktarvy with St. John's wort is not recommended. (8) In patients taking carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, alternative antiepileptic drugs should

be considered. (9) Consult the prescribing information for details about other potential drug interactions and precautions.

Adverse reactions: headache, diarrhea, nausea

Supplied as: film-coated tablets containing bictegravir sodium in an amount equivalent to 50 mg of bictegravir, 200 mg of emtricitabine, and tenofovir alafenamide fumarate in an amount equivalent to 25 mg of tenofovir alafenamide

Dosage: one tablet once a day

Nursing considerations: (1) Tell patients they can take the tablet without regard to food. (2) Products containing aluminum, calcium, iron, or magnesium, such as certain antacids and laxatives, oral calcium or iron supplements, sucralfate, and buffered medications, may reduce the activity of bictegravir. To prevent significant interactions, tell patients to take Biktarvy as directed by the healthcare provider. (3) Because of the potential for drug interactions, tell patients not to start any new drug without direction from the healthcare provider. Also advise them to avoid St. John's wort. (4) Instruct women infected with HIV not to breastfeed due to the risk of HIV transmission.

REFERENCE

1. Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. Prescribing information. www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf.

Ibalizumab-uiyk

First biologic drug for treating HIV-1 infection

Most patients with HIV-1 infection can be successfully treated with a combination of two or more antiretroviral drugs. However, as many as 25,000 patients in the US have multidrug-resistant (MDR) HIV-1 infection that is associated with a high risk of complications and death. Ibalizumab-uiyk (*Trogarzo*, TaiMed; Thera), a humanized monoclonal antibody, is the first biologic drug to be approved for patients with HIV-1 infection.[1] Designated as a CD4-directed postattachment HIV-1 inhibitor, it blocks HIV-1 from infecting $CD4^+$ T cells by binding to domain 2 of CD4, interfering with postattachment steps required for the entry of HIV-1 virus particles into host cells, and preventing the viral transmission that occurs via cell-cell fusion. The binding specificity of ibalizumab to domain 2 of CD4 allows it to block viral entry into host cells without causing immunosuppression, so it does not interfere with CD4-mediated immune functions. The new drug is active against HIV-1 resistant to all approved antiretroviral agents, and studies have not revealed cross-resistance with other drugs.

Ibalizumab is administered I.V. and, in combination with other antiretrovirals, is indicated to treat HIV-1 infection in heavily treatment-experienced adults with MDR HIV-1 infection who are failing their current antiretroviral regimen. It was evaluated in a clinical trial of 40 patients with MDR HIV-1 infection who had a viral load greater than 1,000 copies/mL and documented resistance to at least one drug in each of three classes of antiretroviral medications: nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. Enrolled patients had been treated with antiretrovirals for at least 6 months and were failing or had failed therapy in the last 8 weeks. Fifty-three percent of the participants had been treated with 10 or more antiretroviral drugs prior to inclusion in the trial.

The trial was composed of an observational control period to establish baseline HIV viral load, a functional monotherapy period in which all patients received a 2,000 mg loading dose of ibalizumab, and a maintenance period. The primary efficacy endpoint at the end of the functional monotherapy period was a significant decrease in the viral load (HIV-RNA). Most patients (83%) experienced this endpoint 1 week after a loading dose of ibalizumab was added to their failing antiretroviral regimen. At Week 25 of treatment with ibalizumab in combination with other antiretroviral drugs, 43% of patients achieved virologic suppression (HIV-1 RNA less than 50 copies/mL). Treatment was discontinued in 13% of patients because of adverse reactions or death.

Women who are exposed to ibalizumab during pregnancy should be registered in the Antiretroviral Pregnancy Registry (1-800-258-4263). Ibalizumab has not been evaluated in pregnant women but it is known that monoclonal antibodies are transported across the placenta as pregnancy progresses.

Precaution: In the clinical trial, one patient experienced immune reconstitution inflammatory syndrome while being treated with the ibalizumab regimen, as has occurred with other antiretroviral agents. A potential for immunogenicity exists with the use of therapeutic proteins, including the new drug, and patients were tested for the presence of anti-ibalizumab antibodies. However, reduced efficacy or adverse reactions attributable to such a response were not observed.

Adverse reactions: diarrhea, dizziness, nausea, rash, elevated creatinine concentrations

Supplied as: single-dose, 2 mL vials that deliver approximately 1.33 mL containing 200 mg of the drug

Dosage: a single loading dose of 2,000 mg (10 vials) followed by maintenance doses of 800 mg (4 vials) every 2 weeks.

Nursing considerations: (1) Dilute the contents of the appropriate number of vials needed to provide the recommended dose in 250 mL of 0.9% Sodium Chloride Injection. The diluted solution should be administered by an appropriately prepared

healthcare professional as an I.V. infusion in the cephalic vein of the patient's right or left arm. The duration of the loading dose infusion should be no less than 30 minutes. (2) Patients should be observed for 1 hour following administration for at least the first dose. If no infusion-associated adverse reactions occur with the loading dose, the duration of the maintenance dose infusions can be decreased to no less than 15 minutes and the postinfusion observation time can be reduced to 15 minutes. (3) If a maintenance dose is missed by 3 days or longer beyond the scheduled dosing day, a loading dose (2,000 mg) should be administered as soon as possible, and maintenance doses (800 mg) should be resumed every 2 weeks thereafter. (4) Because of the potential for HIV transmission in nursing infants, mothers should not breastfeed if they are receiving ibalizumab. (5) Store vials in a refrigerator.

REFERENCE

1. Trogarzo (ibalizumab-uiyk) injection, for intravenous use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf.

ANTIARTHRITIC DRUG

Baricitinib

Infection, malignancy, and other serious risks

Rheumatoid arthritis is a systemic, chronic, autoimmune disease characterized by inflammation, pain, and eventually joint damage and disability. NSAIDs and/or conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are often used as initial treatment, but many patients do not experience an adequate response or cannot tolerate these regimens. Many patients respond well to biologic DMARDs such as the tumor necrosis factor (TNF) inhibitors (for example, adalimumab) but in some, effectiveness is not maintained with continued use, necessitating the consideration of other options.

Janus kinase (JAK) enzymes are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAK enzymes exert effects that modulate intracellular activity. Inhibiting these enzymes blocks the activation of mediators of inflammation. Four known JAK enzymes have been implicated in the pathogenesis of various inflammatory and autoimmune diseases, including rheumatoid arthritis.

Baricitinib (*Olumiant*, Lilly) is the second JAK inhibitor to be approved for patients with rheumatoid arthritis, joining tofacitinib. It is indicated to treat adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.[1] Either baricitinib or tofacitinib may be used as monotherapy in patients with rheumatoid arthritis or with methotrexate or another nonbiologic DMARD. Like tofacitinib, baricitinib is administered orally, which provides an advantage over the TNF inhibitors and other biologic DMARDs used to treat rheumatoid arthritis.

Precautions: (1) Concurrent use with another JAK inhibitor, biologic DMARD, or a potent immunosuppressant such as azathioprine or cyclosporine is not recommended. (2) Baricitinib should not be used in patients with an active serious infection, including a localized infection. The labeling contains a Boxed Warning about the risks of serious infections. Most patients who developed infections were being treated concurrently with an immunosuppressant, such as methotrexate or a corticosteroid. If a serious infection develops during treatment, therapy should be interrupted until the infection is controlled. (3) Before initiation of treatment with baricitinib, patients should be evaluated for latent or active tuberculosis (TB) infection. The drug should not be used in patients with active TB, and anti-TB therapy should be considered in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB who have risk factors for TB infection. (4) Patients are also at greater risk for invasive fungal infections, as well as bacterial, viral, and other infections caused by opportunistic pathogens. Reactivation of viruses, including herpes viruses, has occurred. If a patient develops herpes zoster, treatment with baricitinib should be interrupted until the episode resolves. (5) Patients should not receive live vaccines while being treated with baricitinib. Discontinuing treatment should be considered in patients who develop a malignancy during therapy with baricitinib. (6) The labeling contains a Boxed Warning about the increased risk of lymphoma and other malignancies. This risk should be considered before initiating treatment with the new drug in patients with a known malignancy other than a successfully treated nonmelanoma skin cancer. (7) The labeling for baricitinib also includes a Boxed Warning regarding thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis. Use the drug with caution in patients who are at increased risk for thrombosis. (8) Gastrointestinal (GI) perforation was reported in the clinical studies of baricitinib. Use the drug with caution in patients at increased risk for this complication, such as those with a history of diverticulitis. (9) Multiple lab abnormalities may develop, including neutropenia, lymphopenia, anemia, elevated liver enzymes, and elevated lipid concentrations. Treatment should not be initiated, or should be interrupted,

in patients with an absolute neutrophil count less than 1,000 cells/mm^3, an absolute lymphocyte count less than 500 cells/mm^3, or hemoglobin less than 8 g/dL. Lab parameters should be evaluated at baseline and periodically thereafter. For example, lipid parameters should be evaluated approximately 12 weeks following initiation of treatment. (10) The new drug is not recommended for use in patients with moderate or severe renal impairment (estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2), or in patients with severe hepatic impairment. (11) Exposure to baricitinib is increased by strong organic anion transporter 3 (OAT3) inhibitors such as probenecid, and concurrent use is not recommended.

Adverse reactions: upper respiratory tract infections, nausea, herpes simplex, herpes zoster

Supplied as: 2 mg film-coated tablets

Dosage: 2 mg once a day

Nursing considerations: (1) Tell patients they can take the medication with or without food. (2) Teach patients to recognize signs and symptoms of DVT and PE. If any occur, tell them to inform the healthcare provider immediately or seek emergency care if indicated. (3) Warn patients to avoid live vaccines while being treated with baricitinib. Advise them to get any recommended immunizations before starting therapy. (4) Educate patients about their increased infection risk and tell them to report any infections, including a herpes virus outbreak, to the healthcare provider. (5) Advise patients at increased risk for skin cancer to undergo periodic skin examinations. (6) Inform patients that lab parameters should be evaluated at baseline and periodically thereafter.

REFERENCE
1. Olumiant (baricitinib) tablets, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf.

DRUG FOR PSORIASIS

Tildrakizumab-asmn

Humanized monoclonal antibody for treating moderate-to-severe plaque psoriasis in adults

Certain naturally occurring interleukins (ILs) have been identified as having a role in the occurrence and worsening of psoriasis, and the development of IL inhibitors has been a focus of recent research programs. Ustekinumab, which inhibits IL-12 and IL-23, was the first IL inhibitor to be marketed for treatment of moderate-to-severe plaque psoriasis. Similarly, guselkumab binds to the p19 subunit of IL-23 and inhibits its interaction with IL-23 receptors.

Tildrakizumab-asmn (*Ilumya*, Sun) joins ustekinumab and guselkumab as the third humanized monoclonal antibody that acts primarily by inhibiting IL-23. Administered subcutaneously, it binds to the p19 subunit of IL-23 and is indicated for adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

The effectiveness of tildrakizumab was evaluated in two placebo-controlled studies. The primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to Week 12 and an improvement in the Physician Global Assessment (PGA) to clear or minimal. Of the patients treated with tildrakizumab, 64% and 61% attained a PASI 75 response, compared with 6% in each study of those receiving placebo, and 14% and 12% of those treated with the new drug attained a PASI 100 response, compared with 1% and 0% of those receiving placebo. Of the patients treated with tildrakizumab, 58% and 55% received a PGA of clear or minimal, compared with 7% and 4% of those receiving placebo.

Tildrakizumab has not been directly compared with other IL inhibitors in clinical studies. However, in the separate studies of tildrakizumab and guselkumab, fewer patients treated with tildrakizumab attained the same study endpoints. Guselkumab has also been evaluated in patients who had not attained an adequate response at Week 16 after initial treatment with ustekinumab, and approximately twice as many patients treated with guselkumab achieved a PGA response of clear or minimal than those who continued treatment with ustekinumab.

The labeling for tildrakizumab and ustekinumab indicates that these drugs should be administered by a healthcare provider. The labeling for guselkumab includes the option for self-injection by patients.

Precautions: (1) Like other medications that suppress immune function, tildrakizumab increases the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. If a clinically important or serious infection occurs during treatment or an infection is not responding to standard therapy, the patient should be closely monitored and consideration given to discontinuation of tildrakizumab. (2) Patients should not receive live vaccines during treatment. (3) Patients should be evaluated for TB infection before initiating treatment with tildrakizumab. The drug should not be used in patients with active TB. In patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, anti-TB therapy should be considered before initiating treatment with tildrakizumab.

Adverse reactions: upper respiratory tract infections, injection site reactions, diarrhea

Supplied as: single-dose prefilled syringes containing 100 mg of the drug in 1 mL of solution

Dosage: 100 mg administered subcutaneously at Weeks 0 and 4, and every 12 weeks thereafter

Nursing considerations: (1) Store syringes in a refrigerator in the original carton. Before administering a dose, allow time for it to reach room temperature (about 30 minutes) after removal from the refrigerator. (2) Advise patients to make sure they are current on recommended vaccinations before starting therapy with tildrakizumab. (3) Tell patients to report any new or worsening infections to the healthcare provider.

REFERENCE

1. Ilumya (tildrakizumab-asmn) injection, for subcutaneous use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/761067s000lbl.pdf.

DRUG FOR ENDOMETRIOSIS

Elagolix sodium

Easing painful symptoms

Endometriosis is estimated to affect up to 10% of women of reproductive age in the US.[1] It occurs when tissue similar to that found in the uterus begins to grow outside of the uterus (for example, on the ovaries, fallopian tubes, or bladder). The lesions can be very painful and debilitating. The disorder is most often associated with menstrual pelvic pain (dysmenorrhea), nonmenstrual pelvic pain, and dyspareunia (painful intercourse). Treatment for endometriosis has included NSAIDs, opioid analgesics, and oral contraceptives. Estrogen stimulates the growth of endometrial lesions and hormonal therapies such as gonadotropin-releasing hormone (GnRH) receptor agonists (for example, leuprolide and nafarelin) and the androgen danazol have been used in some patients. Surgical interventions such as laparotomy or hysterectomy are sometimes necessary, but do not resolve the problem for all patients.

Elagolix sodium (*Orilissa*, AbbVie) is a nonpeptide small molecule, GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. The administration of elagolix results in dose-dependent suppression of luteinizing hormone and follicle-stimulating hormone, leading to decreased blood concentrations of the ovarian sex hormones estradiol and progesterone. The GnRH *agonists* leuprolide and nafarelin, for which the treatment of endometriosis is a labeled indication, also reduce estrogen concentrations with continued use, but only following an initial increase in estrogen concentrations that may be poorly tolerated.

Taken orally, elagolix is indicated to manage moderate-to-severe pain associated with endometriosis.[2] Its effectiveness was evaluated in two placebo-controlled trials in nearly 1,700 premenopausal women with moderate-to-severe pain associated with endometriosis. Women were defined as responders if they experienced a reduction in dysmenorrhea and nonpelvic pain with no increase in analgesic use (NSAID or opioid) for endometriosis-associated pain.

In the first study, the proportion of responders for dysmenorrhea at Month 3 with the 150 mg once a day and 200 mg twice a day dosage regimens was 46% and 76%, respectively, compared with 20% of those receiving placebo. The proportion of responders for nonmenstrual pelvic pain with the two regimens was 50% and 55%, respectively, compared with 36% of those receiving placebo. Similar results were achieved in the second study.

Dyspareunia associated with endometriosis was evaluated as a secondary endpoint. In both studies, women treated with elagolix in a dosage of 200 mg twice a day showed statistically significantly greater reduction in dyspareunia from baseline to Month 3 than women given placebo. However, statistical significance was not achieved with the dosage of 150 mg once a day.

Precautions: (1) Elagolix is contraindicated in patients with osteoporosis. The reduction in estrogen concentrations from elagolix treatment is associated with a dose-dependent and duration-dependent decrease in bone mineral density (BMD) that may not be completely reversible when treatment is discontinued. The assessment of BMD should be considered in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss. To reduce the extent of bone loss, the dosage recommendations for elagolix identify specific durations of treatment. (2) Elagolix is contraindicated in pregnant women because exposure early in pregnancy may increase the risk of pregnancy loss. Pregnancy should be excluded before treatment is initiated. If pregnancy is suspected, pregnancy testing should be performed and the drug should be discontinued if pregnancy is confirmed. (3) Elagolix is contraindicated in patients with severe hepatic impairment. The dosage should be adjusted in patients with moderate hepatic impairment. (4) Do not use elagolix concurrently with estrogen-containing contraceptives, which may reduce the efficacy of elagolix. The effect of progestin-only contraceptives on the effectiveness of the new drug is not known. (5) Concurrent use with strong organic anion transporting polypeptide 1B1 inhibitors such as cyclosporine and gemfibrozil is contraindicated. Many other drugs have the potential to interact with elagolix and/or affect its efficacy. See the Prescribing Information for guidelines and recommendations regarding the concurrent use of elagolix with other drugs. (6) In clinical trials, one patient committed suicide and suicidal ideation and behavior and exacerbation of mood disorders were reported in other patients. Patients with depressive symptoms should be promptly evaluated and treated appropriately; for example, by discontinuing elagolix and referring the patient to a behavioral health professional. (7) Some patients have experienced dose-dependent asymptomatic elevations in alanine aminotransferase and dose-dependent increases in serum cholesterol and triglyceride concentrations with the use of elagolix.

Adverse reactions: hot flushes or night sweats, headache, nausea, insomnia, mood alteration/swings, amenorrhea, depression-related adverse events. The frequency of most of these adverse reactions was significantly greater in women who were treated with elagolix at the higher dosage (200 mg twice a day).

Supplied as: 150 mg and 200 mg tablets

Dosage: 150 mg once a day for a maximum duration of 24 months. In patients with dyspareunia, initiating treatment with a dosage of 200 mg twice a day should be considered, and treatment should be continued for a maximum duration of 6 months. In patients with moderate hepatic impairment and in those taking or who are being treated concurrently with a strong CYP3A inhibitor or rifampin, the recommended dosage is 150 mg once a day for up to 6 months. The dosage regimen of 200 mg twice a day is not recommended in patients with moderate hepatic impairment or in those who are being treated concomitantly with rifampin. The concurrent use of elagolix in a dosage of 200 mg twice a day with a strong CYP3A inhibitor for more than 1 month is not recommended.

Nursing considerations: (1) Elagolix should not be taken by women who are pregnant or trying to become pregnant. Advise women who are sexually active to use effective nonhormonal contraception during treatment with elagolix and for 1 week following discontinuation of treatment. Women treated with elagolix may experience a reduction in the amount, intensity, or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of pregnancy in a timely manner. (2) Tell patients to report signs and symptoms such as jaundice that may indicate liver injury. (3) Inform women about the potential for mood alterations or suicidal ideation. Instruct them to report depression or mood changes to the healthcare provider right away. (4) Elagolix may be administered with or without food.

REFERENCES

1. Endometriosis.org. FAQs. http://endometriosis.org/frequently-asked-questions-faq.

2. Orlissa (elagolix) tablets, for oral use. Prescribing information. www.rxabbvie.com/pdf/orilissa_pi.pdf.

DRUG FOR OPIOID WITHDRAWAL

Lofexidine

First nonopioid approved to treat symptoms of opioid withdrawal

Morphine and other opioids reduce norepinephrine concentrations. With continued opioid use, the brain establishes a new equilibrium by increasing norepinephrine production in order to maintain normal functioning. When an opioid is discontinued or its dosage is significantly reduced, the brain's increased norepinephrine concentrations are no longer offset by the presence of the opioid, resulting in a norepinephrine surge that produces acute withdrawal signs and symptoms such as myalgia, arthralgia, tachycardia, mydriasis, hypertension, diaphoresis, abdominal cramps, nausea, vomiting, diarrhea, insomnia, anxiety, agitation, and drug craving.[1] The discomfort, pain, and intensity of these responses are significant barriers to patients seeking help to overcome opioid addiction.

In patients for whom opioids have been prescribed as analgesics and who no longer need long-term opioid use, withdrawal symptoms can be avoided or lessened by gradually reducing the dosage of the medication as its use is discontinued. For patients with opioid use disorder (OUD), the addiction and withdrawal are often managed with the substitution of the partial opioid agonist buprenorphine or the opioid agonist methadone, as well as other adjunctive medications for specific signs and symptoms.

Lofexidine hydrochloride (*Lucemyra*, US WorldMeds; Salix) is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone. Indicated for mitigation of opioid withdrawal symptoms in adults, lofexidine is the first nonopioid treatment approved for this purpose. Although it may reduce the severity of withdrawal symptoms, it may not completely prevent them, and the recommended duration of treatment is only up to 14 days. Therefore, it is not viewed as a treatment for OUD, but rather as part of a broader, long-range treatment plan.[2,3]

The effectiveness of lofexidine was evaluated in two placebo-controlled studies in patients who were physically dependent on short-acting opioids (heroin, hydrocodone, or oxycodone). The primary endpoints were the mean total score on the Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop), a patient-reported outcome instrument to evaluate opioid withdrawal symptoms, and the proportion of patients who completed the period of treatment. In both studies, the mean SOWS-Gossop scores were lower for patients treated with lofexidine compared with placebo, reflecting lesser severity of withdrawal symptoms.

The initial part of the first study was conducted in approximately 600 patients over 7 days; 41% and 28% of the patients treated with lofexidine or placebo, respectively, completed the treatment. Of the 264 patients in the second study who were treated for 5 days, 49% and 33% of those receiving lofexidine (0.72 mg four times a day) or placebo, respectively, completed the treatment. Insomnia was the most frequently reported adverse reaction associated with lofexidine, occurring in slightly more than 50% of patients; however, the incidence was similar in patients receiving placebo (48%) and was most likely related to opioid withdrawal.

Adverse reactions: orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, dry mouth

Precautions: (1) Patients should be educated about the risk of hypotension, bradycardia, and related complications. Outpatients should be willing and able to self-monitor and report adverse reactions. (2) Lofexidine should be avoided in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, and chronic renal failure, and in those with marked bradycardia. (3) Lofexidine should not be used concurrently with other medications that decrease heart rate or BP. (4) Lofexidine prolongs the QT interval and should not be used in patients with congenital long QT syndrome. Its use should be closely monitored in patients with heart failure, bradydysrhythmias hepatic impairment, renal impairment, and in those taking other medications that may cause QT prolongation, such as methadone or moxifloxacin. If both lofexidine and methadone are included in a treatment plan for patients with OUD, ECG monitoring is recommended. (5) If present, hypokalemia or hypomagnesemia should be corrected before treatment with lofexidine starts. (6) Lofexidine may potentiate the central nervous system depressive effect of benzodiazepines, barbiturates, alcohol, and other sedating agents. (7) The dosage of lofexidine should be reduced in patients with hepatic or renal impairment. (8) Medications such as paroxetine that inhibit the CYP2D6 pathway may increase the activity of lofexidine and concurrent use should be closely monitored. (9) The efficacy of orally administered naltrexone may be reduced if it is administered within 2 hours of lofexidine. However, this interaction is not expected if naltrexone is administered by other routes.

Supplied as: film-coated tablets containing 0.18 mg of lofexidine

Dosage: Initially, 0.54 mg (3 tablets) taken 4 times daily during the period of peak withdrawal symptoms (generally the first 5 to 7 days following the last use of an opioid). A period of 5 to 6 hours should separate doses. No single dose should exceed 0.72 mg (4 tablets) and the total daily dosage should not exceed 2.88 mg (16 tablets). Dosage adjustments should be guided by the assessment of symptoms. Treatment may continue for up to 14 days.

Nursing considerations: (1) Inform patients that lofexidine may mitigate but not completely prevent withdrawal symptoms. (2) Tell patients to be mindful of the risk of hypotension and bradycardia during treatment. Advise them to sit or lie down if they feel lightheaded or dizzy. (3) Warn patients to avoid concurrent use with alcohol and drugs that depress CNS function, such as benzodiazepines and barbiturates, because they will increase lofexidine's sedative effects. Tell them not to drive or engage in other activities requiring alertness until they know how lofexidine affects them. (4) Warn them not to discontinue lofexidine without first consulting the healthcare provider. (5) Inform patients that after a period of not using opioid drugs, they may be more sensitive to the effects of opioids and at greater risk for overdosing. (6) Lofexidine may be taken without regard to food.

REFERENCES

1. Severino KA. Opioid withdrawal in adults: clinical manifestations, course, assessment, and diagnosis. UpToDate. 2017. www.uptodate.com.
2. US Food and Drug Administration. FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. News release. May 16, 2018.
3. Lucemyra (lofexidine) tablets, for oral use. Prescribing information. https://hcp.lucemyra.com/LUCEMYRA-PI.pdf.

DRUG FOR HYPERKALEMIA

Sodium zirconium cyclosilicate

Not indicated for emergency treatment due to delayed onset of action

Hyperkalemia is characterized by elevated serum potassium concentrations (generally above 5 mEq/L), and may be associated with complications such as cardiac dysrhythmias. It is most often experienced by patients with kidney disease or heart failure, particularly those who are taking medications that inhibit the renin-angiotensin-aldosterone system (RAAS). These include angiotensin-converting enzyme inhibitors such as lisinopril, angiotensin receptor blockers such as losartan, the direct renin inhibitor aliskiren, and aldosterone antagonists such as spironolactone and eplerenone.

Managing hyperkalemia involves reducing the dosage or using therapeutic alternatives to medications that increase serum potassium concentrations, restriction of foods and beverages with a high potassium content, and the use of diuretics that promote the excretion of potassium as well as sodium. The cation-exchange resin sodium polystyrene sulfonate has been used orally or as an enema in the treatment of hyperkalemia. However, it may cause serious GI adverse reactions and sodium and fluid retention.

Patiromer sorbitex calcium was marketed for the treatment of hyperkalemia in 2016. It consists of the active moiety, patiromer, a nonabsorbed potassium-binding polymer, and a calcium-sorbitol counterion. When administered orally, the calcium-sorbitol counterion is exchanged for potassium that binds with patiromer in the lumen of the GI tract. This exchange increases fecal potassium excretion and reduces serum potassium concentrations.

Sodium zirconium cyclosilicate (*Lokelma,* AstraZeneca) is a nonabsorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium. It has a high affinity for potassium ions, even in the presence of other cations such as calcium and magnesium. By binding with potassium in the lumen of the GI tract, sodium zirconium cyclosilicate increases fecal potassium excretion and reduces serum potassium

concentrations. It is indicated for the treatment of hyperkalemia in adults.[1]

The effectiveness of sodium zirconium cyclosilicate was evaluated in placebo-controlled studies with multiple phases. Reductions in serum potassium concentrations were observed 1 hour after initiation of therapy, and concentrations continued to decline over the 48-hour treatment period.

The availability of sodium zirconium cyclosilicate and patiromer provides the opportunity to reduce the risk of hyperkalemia in patients with chronic diseases such as kidney disease, heart failure, and diabetes for whom the continued use of RAAS inhibitors in recommended dosages is beneficial notwithstanding their tendency to increase serum potassium concentrations.

Each 10 g dose of sodium zirconium cyclosilicate contains approximately 800 mg of sodium, and edema (generalized and/or peripheral) was the most commonly reported adverse reaction in the clinical studies. Hypokalemia (serum potassium less than 3.5 mEq/L) occurred in 4% of patients treated with the new drug in clinical studies, but this resolved after dosage reduction or discontinuation of treatment. Because the new drug is not absorbed, systemic exposure is not expected if it is used during pregnancy or by nursing mothers.

Precautions: (1) Because of its delayed onset of action, the new drug should not be used as an emergency treatment for life-threatening hyperkalemia. (2) Monitor patients for signs of edema, particularly in those who should restrict their sodium intake or who are vulnerable to fluid overload, such as patients with heart failure or kidney disease. As appropriate, patients should be advised to adjust dietary sodium, and the dosage of diuretics should be increased if needed. (3) Avoid using sodium zirconium cyclosilicate in patients with severe constipation or impaction, including abnormal postoperative bowel motility disorders. It may be ineffective and/or exacerbate the GI disorder. (4) In general, other oral medications should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate.

Adverse reactions: mild-to-moderate edema

Supplied as: a powder in foil-lined packets containing 5 g and 10 g of the drug

Dosage: Initially, 10 g three times daily for up to 48 hours. For continued treatment, the recommended dosage is 10 g once a day.

Nursing considerations: (1) Instruct the patient to empty the entire contents of a packet into a drinking glass containing 3 tablespoonfuls or more of water, stir well, and drink it immediately. If powder remains in the drinking glass, the patient should add more water, stir, and drink the mixture in order to consume the entire dose. (2) Monitor serum potassium levels. The dosage will be adjusted based on the serum potassium concentration and the desired target range. During maintenance treatment, the dosage may be increased based on the serum potassium concentration at intervals of 1 week or longer and in increments of 5 g. The dosage may be decreased or discontinued if the serum potassium is below the desired target range. Recommended maintenance dosages range widely from 5 g every other day to 15 g daily. (3) Advise the patient to monitor and reduce sodium intake as directed by the healthcare provider. (4) Instruct the patient to take other oral medications either 2 hours before or 2 hours after a dose of sodium zirconium cyclosilicate.

REFERENCE

1. Lokelma (sodium zirconium cyclosilicate) for oral suspension. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/207078s000lbl.pdf.

VASOPRESSOR

Angiotensin II acetate

Using nature's vasopressor to boost BP in patients with septic shock

A reduced ability to maintain adequate blood flow to vital tissues may result in shock, organ failure, and death. Treatment for shock usually includes administration of I.V. fluids and vasopressors such as norepinephrine, vasopressin, phenylephrine, epinephrine, and dopamine. However, in some patients, these measures are insufficient to prevent irreversible organ damage and/or death.

Angiotensin II is a naturally occurring peptide hormone of the RAAS that causes vasoconstriction, increasing BP. However, it has not previously been available as a medication for therapeutic use. Angiotensin II acetate (*Giapreza,* La Jolla) is now approved for use via continuous I.V. infusion to increase BP in adults with septic or other distributive shock such as neurogenic shock.[1]

The effectiveness of angiotensin II was evaluated in a study of 321 adults with shock who remained hypotensive despite fluid and vasopressor therapy. More than 90% of the patients had septic shock, and 83% had received two or more vasopressors and 47% three or more vasopressors before administration of angiotensin II. Doses of angiotensin II or placebo were titrated to a target mean arterial pressure (MAP) of at least 75 mm Hg during the first 3 hours of treatment while doses of other vasopressors were maintained (although patients were not necessarily on maximum doses of other vasopressors). From Hour 3 to Hour 48, angiotensin II or placebo was titrated to maintain MAP between 65 and 70 mm Hg while reducing doses of other vasopressors. The primary endpoint was the percentage of subjects who achieved either a MAP of at least 75 mm Hg or at least a 10 mm Hg increase in MAP without an increase in baseline vasopressor therapy at 3 hours.

The primary endpoint was achieved by 70% of patients treated with angiotensin II, compared with 23% of those receiving placebo. Mortality through Day 28 was 46% for patients on angiotensin II and 54% for those on placebo.

The plasma half-life of angiotensin II is less than 1 minute, which is why it must be given via continuous I.V. infusion. The clearance of angiotensin II is not dependent on renal or hepatic function, so activity is not expected to be altered in patients with renal or hepatic impairment. The concurrent use of an angiotensin-converting enzyme inhibitor such as lisinopril may increase the response to angiotensin II, whereas the concurrent use of an angiotensin II receptor blocker such as losartan may decrease the response.

Precaution: Because of the risk of thrombosis, patients should receive concurrent venous thromboembolism prophylaxis.

Adverse reactions: thromboembolic events, thrombocytopenia, tachycardia, fungal infection, delirium, acidosis

Supplied as: an injection in an amount equivalent to 2.5 mg of angiotensin II per mL in vials containing 2.5 mg and 5 mg

Dosage: The recommended starting dosage of angiotensin II is 20 nanograms (ng)/kg/min via continuous I.V. infusion, preferably through a central venous access device. Based on BP response, the dosage is titrated every 5 minutes by increments of up to 15 ng/kg/min as needed to achieve or maintain target BP. A dosage of 80 ng/kg/min should not be exceeded in the first 3 hours of treatment. Maintenance dosages should not exceed 40 ng/kg/min. Once the underlying shock has sufficiently improved, the dosage should be titrated down every 5 to 15 minutes by increments of up to 15 ng/kg/min based on BP.

Nursing considerations: (1) Dilute the contents of a vial in 0.9% Sodium Chloride Injection to achieve a final concentration of 5,000 ng/mL or 10,000 ng/mL. (2) Store vials in a refrigerator. The diluted solution may be stored at room temperature or under refrigeration, but should be discarded after 24 hours. ■

REFERENCE

1. Giapreza (angiotensin II) injection for intravenous infusion. Prescribing information. www.giapreza.com/giapreza-prescribing-information.pdf.

DOI-10.1097/01.NURSE.0000554609.18148.78