PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXIX / October 2018 / Number 10 www.alertpubs.com

Important Reminder . . . Delivery of *Primary Care Drug Alerts* is now 100% electronic.

Baloxavir Approved for Influenza Treatment

A new antiviral treatment, baloxavir marboxil (*Xofluza*), has received expedited FDA approval through the Priority Approval Process for the treatment of acute uncomplicated influenza in patients aged ≥12 years who have been symptomatic for ≤48 hours. Safety and efficacy of the agent were demonstrated in 2 controlled trials, comprising >1800 patients, in which patients who received baloxavir experienced a shorter time to alleviation of symptoms than those who received placebo. In 1 trial, time to symptom alleviation did not differ between baloxavir and an alternate antiviral. Although there are now several antivirals approved to treat emergent influenza, none are considered a substitute for prophylactic vaccination.

FDA News Release: FDA approves new drug to treat influenza. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624226.htm.

Psychiatric Effects of Oseltamivir

Prophylactic use of oseltamivir (*Tamiflu*) is associated with a small but statistically significant increase in psychiatric adverse events, according to an analysis of adverse-event data from clinical study reports.[1]

Background: Following the reports of 2 suicides in adolescents who received treatment with oseltamivir, as well as >100 reports of neuropsychiatric adverse effects with the drug, the FDA issued an alert in 2006 warning that patients should be carefully monitored for abnormal behavior during treatment.[2] Analyses of neuropsychiatric adverse effects conducted since then, including several Cochrane Reviews based on published trials, have been inconclusive. Clinical study reports—produced by manufacturers seeking regulatory approval of drugs and containing individual patient-level data on adverse events with a high level of detail, including duration and severity—have recently been made available to researchers by the European Medicines Agency and by some manufacturers. To further clarify the risk of neuropsychiatric effects with prophylactic oseltamivir use, the present study evaluated adverse events in clinical study reports.

Methods: The present analysis was based on clinical study reports from 4 placebo-controlled trials of oseltamivir. The analysis was limited to prophylactic trials to avoid counting any psychiatric symptoms related to existing influenza. Data on clinical adverse events classified under the psychiatric system organ class, representing a change from baseline that occurred after study treatment began, were collected from the reports irrespective of whether study investigators believed it was related to oseltamivir treatment. The primary outcome of the analysis was the proportion of days patients suffered from psychiatric adverse events. This method allowed grouping of multiple adverse events, regardless of their

Primary Care Drug Alerts® (ISSN 1559-5668) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: donna@alertpubs.com. Subscription $105.00 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Individual issues are available for $10.00 each. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

nature—e.g., days suffering from depression and from anxiety by a single patient could be combined. In a secondary analysis, adverse events were weighted based on severity.

Results: The main analysis was based on combined data from 1 trial conducted in adults (n=1559) and 2 trials in elderly nursing-home residents (n=920), all of whom received oseltamivir or placebo for 6 weeks. An additional short-term trial was conducted in adults and adolescents (n=955) who received treatment for 7 days. Psychiatric adverse events were not reported in the journal publications from any of the trials.

A total of 35 psychiatric adverse events (10 of depression) occurred with oseltamivir and 15 with placebo. Excluding the 7-day trial, which reported very few events, the proportion of days patients suffered from a psychiatric adverse event was significantly greater with oseltamivir than placebo (odds ratio,* 4.12). There was little difference between oseltamivir and placebo for less severe adverse events, but severe events occurred on more days with oseltamivir (odds ratio, 34.5). However, the absolute difference between oseltamivir and placebo was small: For every 290 days of treatment, there was 1 additional day of suffering from a psychiatric adverse event of any level of severity.

Discussion: The increasing chance of more severe adverse events with oseltamivir suggests a causal relationship. Although the relative effect of oseltamivir is very high for severe events, the absolute increase is small in the context of all patients included in the trials.

[1]Jones M, Tett S, Del Mar C: Psychiatric adverse events in oseltamivir prophylaxis trials: novel comparative analysis using data obtained from clinical study reports. *Pharmacoepidemiology and Drug Safety* 2018; doi 10.1002/pds.4651. From the University of Queensland, Brisbane; and Bond University, Gold Coast, Australia. **This research was conducted without specific funding. All 3 authors disclosed potentially relevant financial relationships.**

[2]Maxwell S: Tamiflu and neuropsychiatric disturbance in adolescents: the case is not proved but caution is advisable. *British Medical Journal* 2007;334 (June 16): 1232–1233.

***See Reference Guide.**

Expanded Gardasil Use

The human papillomavirus (HPV) 9-valent vaccine, recombinant (*Gardasil 9*) indication has been expanded to include women and men aged 27–45 years. Effectiveness of *Gardasil 9* was evaluated in >3000 women in that age range who were followed for an average of 3.5 years. The vaccine was 88% effective at preventing the combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine. Effectiveness of the vaccine in men is inferred from this data in women, along with efficacy data in younger males.

FDA News Release: FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm.

Galcanezumab for Migraine Prevention

In a phase III trial, the calcitonin gene-related peptide (CGRP) antagonist galcanezumab reduced the frequency of episodic migraines.[1] The agent also reduced migraine-related disability and improved patient functioning.

Methods: The multicenter trial enrolled patients with a ≥1-year history of migraine with onset before age 50 years, who had experienced ≥2 migraine attacks with 4–14 migraine days during the month before the baseline observation period. Patents who had failed to respond to ≥3 classes of migraine preventive treatments were excluded from the study. Patients who had received botulinum toxin were required to have discontinued treatment ≥4 months before screening, and all other migraine preventive treatments were subject to a washout before the baseline observational month. Patients were randomly assigned to receive galcanezumab by subcutaneous injection (either 120 mg per month with a 240-mg loading dose or 240 mg per month) or placebo injections. The primary efficacy outcome was overall mean change from baseline in monthly headache days during 6 months of double-blind treatment.

Results: A total of 858 patients were randomized and received ≥1 injection. At baseline, patients had a mean of 9.1 monthly headache days, 5.7 monthly migraine attacks, and 60.6 monthly headache hours. The study dropout rate was 18%, but <5% of the patients withdrew because of adverse events, with similar proportions in the medication and placebo groups.

During treatment, both doses of galcanezumab were associated with about 2 fewer migraine days per month than placebo (p=0.02). About 60% of patients who received galcanezumab achieved a

≥50% response, compared with 39% of the placebo group (p=0.02). Rates of 75% and 100% response were nearly 40% and about 15%, respectively, with galcanezumab, compared with 6–19% with placebo (p=0.02). The migraine reductions with galcanezumab translated to approximately 8 weeks of additional migraine-free days per year, on average. The onset of action was within the first month of treatment.

Galcanezumab was also associated with superior outcomes measured using the Migraine-Specific Quality of Life Questionnaire, the Patient Global Impression of Severity, and the Migraine Disability Assessment. The active agent was associated with about 30 fewer migraine hours per month on average. There was no significant difference between the 2 galcanezumab dosage groups for any outcome.

Injection site pain was the most frequently reported adverse effect in all groups, including placebo. Rates of injection site erythema, pruritus, and reaction were higher in patients receiving the active agent, but these reactions were usually mild or moderate in severity.

Discussion: The recent FDA approval of galcanezumab was based in part on the results of this study.[2] Galcanezumab joins 2 other recently approved anti-CGRP agents, erenumab and fremanezumab, as options for migraine prevention.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Stauffer V, et al: Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2018.1212. From Eli Lilly and Company, Indianapolis, IN; and other institutions. **Funded by Eli Lilly and Company. All study authors disclosed financial relationships with commercial sources including Eli Lilly and Company.**

[2]Brauser D: FDA Greenlights Galcanezumab (*Emgality*) for Migraine Prevention. Available at https://www.medscape.com.

Common Drug Trade Names*: erenumab—*Aimovig*; fremanezumab—*Ajovy*; galcanezumab—*Emgality

***See Reference Guide.**

Lisdexamfetamine: Raynaud's Phenomenon

A 16-year-old boy presented with a 3-year history of ADHD that had been temporarily controlled with immediate-release methylphenidate and then an extended-release preparation. Neither agent produced significant adverse effects. When symptom control waned with the extended-release preparation, the patient was switched to 30 mg/day lisdexamfetamine. Symptom control improved, but after 1 week, the patient began to experience symptoms of secondary Raynaud's phenomenon (i.e., pallor and cyanosis of his fingers followed by redness and tingling). Episodes occurred 1–2 times per day, lasted 5–10 minutes each, and were distressing to the patient. He underwent screening for collagen vascular diseases, but no physical cause was uncovered. Because secondary Raynaud's phenomenon has been described with other stimulants, the lisdexamfetamine was stopped and replaced with atomoxetine. The Raynaud's episodes resolved gradually over the subsequent 2 weeks.

According to the Naranjo probability scale,* the association between lisdexamfetamine and Raynaud's phenomenon was probable. This appears to be the first reported case of Raynaud's associated with lisdexamfetamine. Although the reaction is uncommon, clinicians should be aware of the potential as it could adversely affect medication compliance.

Gnanavel S: Lisdexamfetamine and secondary Raynaud's phenomenon [letter]. *Primary Care Companion for CNS Disorders* 2018;20(5):17l02240. From Child and Adolescent Mental Health Services, Northumberland; and Tyne and Wear NHS Foundation Trust, Morpeth, U.K. **The author declared no competing interests.**

Common Drug Trade Names*: atomoxetine—*Strattera*; lisdexamfetamine—*Vyvanse*; methylphenidate, extended-release—*Concerta*; methylphenidate, immediate-release—*Ritalin

***See Reference Guide.**

Perimenopausal Depression Guidelines

Although perimenopause has been recognized as a window of vulnerability for the development of both depressive symptoms and major depressive episodes, clinical recommendations are lacking. The North American Menopause Society and the National Network of Depression Centers Women and Mood Disorders Task Group convened an expert panel to review the literature on depressive symptoms and disorders in midlife women and to develop guidelines addressing epidemiology, clinical presentation, antidepressant treatment, hormone therapy, and other therapies for affected women.

According to the panel, midlife depression in women commonly presents with the classic depressive symptoms, combined with menopausal complaints such as vasomotor symptoms,

sleep and sexual disturbances, weight and energy changes, and concentration problems. Often the situation is further complicated by bereavement and other losses and stressors such as career shifts or caring for an aging parent. Contrary to previous beliefs, grown children leaving the home (the "empty nest") is believed to have positive rather than negative effects on mood.

Antidepressants, cognitive behavioral therapy, and other proven psychotherapies should remain first-line treatment options for depression during menopause. Women with a history of successfully treated depression should receive the previously effective agent. Desvenlafaxine, the only agent that has been investigated specifically in perimenopausal women, has shown efficacy in short-term trials. Small open-label studies have shown SSRIs (e.g., citalopram, escitalopram, fluoxetine, sertraline, vortioxetine), SNRIs (e.g., desvenlafaxine, duloxetine, venlafaxine), and mirtazapine improved mood in perimenopausal women and also had positive effects on vasomotor symptoms, sleep, and other menopausal symptoms. Bupropion is often prescribed because it produces less weight gain, sexual dysfunction, and sleepiness than other agents.

Some evidence suggests concomitant estrogen can improve response to antidepressant drugs, but it is not FDA approved to treat depression. Hormonal contraceptives may improve mood in women approaching menopause. This and other evidence suggests there may a window of opportunity with estrogen that does not extend into the postmenopausal period. The available evidence is insufficient to recommend herbal or other alternative remedies for perimenopausal depression.

Maki P, et al: Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause: The Journal of the North American Menopause Society* 2018; doi 10.1097/GME.0000000000001174. From the University of Illinois at Chicago; and other institutions. **These guidelines were created without funding. Five of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mirtazapine—*Remeron*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vortioxetine—*Trintellix

Lower-Dose EpiPen Alternative

A new lower-dose version of the prefilled epinephrine syringe (*Symjepi*) has received FDA approval for use in children weighing between 33 and 65 lbs. The new dosage strength, 0.15 mg, joins the 0.3-mg dose approved in 2017 for children weighing <66 lbs. Both strengths are indicated for the emergency treatment of allergic reactions including anaphylaxis.

FDA OKs pediatric version of alternative to EpiPen (*Symjepi*). Medscape: September 28, 2018. Available at www.medscape.com.

Reference Guide

Naranjo Probability Scale: A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ).

Statement of Editorial Policy: All of the information and opinions presented in each *Primary Care Drug Alerts* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone (973-898-1200) 9:00–3:00 Eastern time Monday–Friday, or by e-mail (Donna@alertpubs.com).