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Lasmiditan for Migraine

The FDA has approved lasmiditan (*Reyvow*) for acute migraine with or without aura. Lasmiditan is not indicated for preventive treatment.

In controlled trials, >3000 adults, including 22% who were using preventive medications, treated an acute migraine with lasmiditan. The study results indicate that rates of pain relief and resolution of patient's most troubling symptom (e.g., nphonophobia, photophobia, nausea) at 2 hours post dose are significantly higher with lasmiditan than with placebo. Common adverse effects of lasmiditan included dizziness, fatigue, paresthesia, and sedation. Driving impairment is possible, and patients should not drive for ≥8 hours after taking the drug. Lasmiditan causes central nervous system (CNS) depression and should be used cautiously with alcohol or other CNS depressants.

FDA News Release: FDA approves new treatment for patients with migraine. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-patients-migraine.

Rimegepant ODT for Migraine

The investigational calcitonin gene-related peptide (CGRP) receptor antagonist rimegepant, formulated in orally disintegrating tablets, was superior to placebo in the acute treatment of migraine in a double-blind controlled trial.

Background: In previous phase 3 trials, rimegepant in conventional tablets was superior to placebo. The orally disintegrated tablet, designed to provide more rapid absorption and to allow administration without liquids, has been shown to provide peak concentrations at about 1.5 hours, compared with nearly 2 hours for regular tablets.

Methods: Study subjects were adults with a ≥1-year history of migraine, who experienced 2–8 episodes per month of at least moderate severity. Patients with contraindications to triptans were not excluded. All patients were given a single tablet containing 75 mg rimegepant or placebo and instructed to treat a single qualifying migraine occurring within the next 45 days. Before taking the tablet, patients entered data describing their migraine in an electronic diary, which they maintained over the subsequent 48 hours. The primary efficacy endpoints, assessed 2 hours after treatment, were freedom from pain (a score of zero on a 4-point pain intensity scale) and freedom from the symptom they found most bothersome (e.g., phonophobia, photophobia, nausea).

Results: The study randomized 1466 patients, of whom 1375 (mean age, 40 years; 85% women) treated a qualifying migraine within 45 days. At the 2-hour post-dose endpoint, significantly more patients who took rimegepant than placebo were pain free (22% vs 11%; p<0.0001). The symptom rated as most bothersome was absent 2 hours

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post-dose in 35% of the rimegepant group, compared with 27% of the placebo group (p=0.0009). A variety of secondary endpoints (e.g., level of pain relief, relief from each of the main symptoms, ability to function normally, and the use of rescue medications) were assessed 90 minutes, 2 hours, and 2–48 hours post-dose. Rimegepant was superior to placebo for all of the secondary endpoints. Nausea was the most common adverse event with rimegepant, affecting 2% of participants.

Discussion: Although pharmacokinetic parameters may be a misleading proxy for clinical effects in migraine, it is possible that the ODT formulation was a factor in the rapid onset of relief, and the drug's relatively long half-life of 10–12 hours may have a role in the observed sustained benefit up to 48 hours.

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

Croop R, et al: Efficacy, safety, and tolerability of rimegepant orally disintegrating table for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet* 2019;394 (August 31):737–745. doi 10.1016/S0140-6736(19)31606-X. From King's College London, U.K.; and other institutions. **Funded by Biohaven Pharmaceuticals. All 8 study authors disclosed potentially relevant financial relationships with commercial sources including Biohaven.**

***See Reference Guide.**

Breast Cancer Prevention

A revised guideline on the use of medication to reduce breast cancer risk has been published by the U.S. Preventive Services Task Force. The recommendations are largely consistent with the group's previous 2013 guideline but include new information on risks and benefits of using aromatase inhibitors. The guideline recommends offering medication to women aged ≥35 years at increased risk for the disease, including those with previous benign breast lesions, but not those with a diagnosis of breast cancer or ductal carcinoma in situ. Preventive medication is not recommended for women without elevated risk, as the the benefits of the drugs do not outweigh the harms in these patients. The USPSTF also recommends additional approaches to risk reduction, including screening, genetic testing if appropriate, and diet and lifestyle changes.

Tamoxifen, raloxifene, and aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) effectively reduce risk of breast cancer according to a systematic review of clinical trials. Risk-reducing effects are likely to be even larger in women with a predicted breast cancer risk of ≥3% over 5 years. Of these agents, only tamoxifen is indicated for risk reduction in premenopausal women. No medication was found to reduce risk of ER-negative or noninvasive breast cancer or to reduce all-cause or breast cancer mortality. Additional benefits of these medications may include pre-vention of fractures. Harms of tamoxifen and raloxifene include increased risk of venous thromboembolism and vasomotor symptoms. Aromatase inhibitors may cause vasomotor symptoms, gastrointestinal symptoms, and musculoskeletal pain. No medication was reported to increase risk of deep vein thrombosis, pulmonary embolism, or coronary heart disease events.

In clinical trials, women typically used risk-reducing medications for 3–5 years. Benefits of tamoxifen were shown to persist for up to 8 years beyond discontinuation, while risks rapidly reverted to background levels. Data on long-term benefits and harms are not available for the other agents.

Owens D, et al: Medication use to reduce risk of breast cancer. US Preventive Services Task Force Recommendation Statement. *JAMA* 2019;322 (September 3):857–867. doi 10.1001/jama.2019.11885. From the Veterans Affairs Palo Alto Health Care System, Palo Alto, CA; and other institutions. **Funded by the Agency for Healthcare Research and Quality.**

Common Drug Trade Names: **anastrozole—*Arimidex*; exemestane—*Aromasin*; letrozole—*Femara*; raloxifene—*Evista*; tamoxifen—*Nolvadex***

Antivirals and Parkinson's Disease

In a cohort of patients with hepatitis C infection (HCV), the incidence of Parkinson's disease was reduced by the use of interferon-based antiviral therapy. These results contrast a previous suggestion that these drugs may induce parkinsonism.

Background: Neuroinflammation, such as may be caused by chronic HCV, is a characteristic pathologic finding in Parkinson's disease. Virus-related systemic inflammation, exposure to neurotoxin, and a disrupted blood-brain barrier could damage the neuron. Interferon is capable of crossing the blood-brain barrier and could prevent central nervous system (CNS) damage by the virus.

Methods: Data was collected from Taiwan's national health insurance database, and cohort members were >188,000 individuals with a new diagnosis of HCV after 2003, when the program

began paying for interferon-based antiviral therapy. Treated patients received a combination of interferon α-2b and ribavirin for ≥16 weeks. Nearly 40,000 case patients treated with antiviral therapy were propensity-score matched* for age, sex, relevant comorbidities, and some concomitant medications, with patients with HCV who did not receive antiviral therapy.

Results: The incidence of Parkinson's disease was significantly lower in the treated group, beginning in the 5th year of observation (hazard ratio,* 0.75) and extending to the end of follow-up (hazard ratio, 0.71). Subgroup analyses found the benefits of antiviral treatment were particularly pronounced in patients taking concomitant dihydropyridine calcium channel blockers (e.g. amlodipine, nifedipine), which have previously been associated with reduced Parkinson's disease risk. Patients receiving these agents had half the relative incidence of Parkinson's disease as nonusers (p=0.02).

Discussion: The advantage of antiviral therapy for prevention of Parkinson's disease may be limited to early treatment before the premotor stage of the disease, as suggested by the significant between group difference only after 5 years. Nevertheless, the results do suggest that the increased risk of Parkinson's disease in patients with HCV is likely related to the infection rather than its treatment.

Lin W, et al: Association of antiviral therapy with risk of Parkinson disease in patients with chronic hepatitis C infection. *JAMA Neurology* 2019;76 (September):1019–1027. doi 10.1001/jamaneurol.2019.1368. From Landseed International Hospital, Taiwan; and other institutions. F**unded by Chang Gung Memorial Hospital, Taiwan. The authors declared no competing interests.**

Common Drug Trade Names*: amlodipine—*Norvasc*; interferon α-2b—*Ontron A*; nifedipine—*Adalat*, *Procardia*; ribavirin—*Rebetol

***See Reference Guide.**

Ranitidine Recalls

The FDA recently issued a warning regarding the presence of N-Nitrosodimethylamine (NDMA), a probable carcinogen, in samples of some ranitidine formulations. As a result of the potential contamination, multiple manufacturers have issued voluntary recalls for their ranitidine products. (See below.) The FDA continues to test ranitidine products from multiple manufacturers for the contaminant. Patients using a ranitidine product can consider alternatives such as famotidine, cimetidine, esomeprazole, lansoprazole, and omeprazole. Preliminary tests of these alternatives have not found traces of NDMA at this time.

- Apotex (labeled by Walgreens, Walmart, and Rite-Aid)—All over-the-counter (OTC) ranitidine tablets (75 and 150 mg)
- Dr Reddy's Laboratories—All prescription and OTC ranitidine tablets and capsules
- Sanofi—All OTC ranitidine
- Perrigo—All OTC ranitidine tablets in all pack sizes
- Novitium Pharma—All unexpired lots and quantities of ranitidine capsules
- Lannett Company—All unexpired lots of prescription ranitidine syrup (15 mg/mL)

FDA News Release: FDA announces voluntary recall of Sandoz ranitidine capsules following detection of impurity. Available at www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine.

Common Drug Trade Names*: cimetidine—*Tagamet*; esomeprazole—*Nexium*; famotidine—*Pepcid*; lansoprazole—*Prevacid*; omeprazole—*Prilosec*; ranitidine—*Zantac

Antidepressants and Adverse Outcomes

A synthesis of evidence from previously published meta-analyses found no conclusive evidence supporting an association between antidepressant use and commonly reported adverse health outcomes. The few associations that were initially supported were likely due to confounding by indication.

Background: While randomized clinical trials provide strong evidence for the efficacy and acceptability of antidepressants, safety assessment is inherently biased by methodological weaknesses including small and unrepresentative samples, and short exposure durations in the studies. In contrast, observational studies provide real-world data and may provide a more accurate safety picture. The present umbrella review* was undertaken to synthesize the evidence from observational studies regarding potential adverse outcomes with antidepressant treatment.

Methods: Peer-reviewed meta-analyses of observational cohort, case–control, or nested case-control studies examining antidepressant use and any adverse health outcome were identified by systematic literature search. Significant associations found in the individual meta-analyses were categorized according to the strength of the findings (i.e., sample size, strength of the association, and assessment of the presence of biases) and

stratified into mutually exclusive credibility categories: convincing; highly suggestive; suggestive; or weak. (See table.)

Criteria for Credibility of Evidence Categories	
Convincing Evidence	>1000 Cases Significant summary associations No evidence of small-study effects No evidence of excess of significance bias Prediction intervals not including the null value Largest study at least nominally significant ($p < 0.05$) No large heterogeneity
Highly Suggestive Evidence	>1000 Cases Significant summary associations Largest study at least nominally significant ($p < 0.05$)
Suggestive Evidence	>1000 Cases Significant summary associations
Weak Evidence	All other associations with at least nominal significance ($p<0.05$)

Results: A total of 45 meta-analyses were included in the umbrella review: 695 studies assessing 13 presumed antidepressant risks found >100 significant associations. The most commonly examined associations, in 62% of the studies, concerned pregnancy-related or maternal complications, and most associations (67%) related to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Convincing evidence supported only 3 of the 102 significant associations: SSRI use and increased risk of suicide attempt or completion in children and adolescents; antidepressant exposure before pregnancy and autism in the offspring; and SSRI use during pregnancy and autism in the offspring. Several other adverse health outcomes including bleeding, fracture, cataracts, maternal complications of pregnancy, poor neonatal outcomes, and ADHD in exposed offspring, all of which had been found to be significantly associated with antidepressant use, were supported by highly suggestive evidence. None of the associations were proven to be causal and none remained convincing after accounting for confounding by indication.

Discussion: Overall, these results suggest that the previously reported associations between antidepressant use and adverse health outcomes are not supported by convincing evidence. Antidepressant use appears to be safe, and no absolute contraindications were found. However, additional study is warranted to clarify the degree of confounding by indication.

Dragioti E, et al: Association of antidepressant use with adverse health outcomes: a systematic umbrella review. *JAMA Psychiatry* 2019; doi :10.1001/jamapsychiatry.2019. 2859. From Linkoping University, Sweden; and other institutions. **Funded by South London and Maudsley NHS Foundation Trust; and King's College London. Four of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Reference Guide

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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). The rating checklists are posted at www.alertpubs.com.

Umbrella Review: A study design that allows the findings of reviews to be compared and contrasted. The most characteristic feature is that this type of evidence synthesis only considers the highest level of evidence, namely other systematic reviews and meta-analyses, for inclusion.