

# PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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## Erenumab for Migraine Prevention

The fully human monoclonal antibody erenumab (*Aimovig*) has received FDA approval for the prevention of migraine in adults. Erenumab, a once-monthly self-injectable, is the first in class calcitonin-gene-related peptide (CGRP) antagonist to receive approval. Clinical trials have included >3000 patients with chronic or episodic migraines. The most recent results indicate that erenumab can reduce the average number of monthly migraine days by 50% in nearly one-third of patients. Commonly reported adverse effects included injection site reactions and constipation. The agent will be available in 70- and 140-mg single-use prefilled autoinjectors.

In addition to erenumab, there are 3 other agents in the anti-CGRP antibody class; fremanezumab and galcanezumab are currently under FDA review, and the approval process for eptinezumab is expected to begin by year end.

FDA Approves First-in-Class Drug Erenumab (*Aimovig*) for Migraine Prevention. *Medscape Medical News*: available at <https://www.medscape.com/viewarticle/896851>.

## DPP-4 Inhibitors and IBD

In a population-based cohort study, patients taking dipeptidyl peptidase-4 inhibitors for type 2 diabetes had an increased risk of inflammatory bowel disease (IBD). Although the absolute risk increase is low, prescribing DPP-4 inhibitors in patients with a family history of the disease or known autoimmune conditions should be done cautiously.

**Background:** The use of DPP-4 inhibitors as second- or third-line antidiabetic treatment has been increasing, in part because of their neutral effects on body weight and cardiovascular outcomes. The DPP-4 receptor is expressed on a variety of cells including those involved in the immune response, possibly leading to unintended effects. DPP-4 inhibition results in reduced disease activity in animal models of inflammatory bowel disease, but patients with the disease have decreased levels of the DPP-4 enzyme.

**Methods:** The analysis used data from the Clinical Practice Research Datalink, a British database of >700 primary care practices. Cohort members were all adult patients with type 2 diabetes who received a new prescription for a non-insulin diabetes medication between 2007 (the year the first DPP-4 inhibitor was introduced) and 2016. Patients were excluded if they had a diagnosis of IBD or a related condition at baseline or if they received a prescription for insulin before their first non-insulin drug. A comparison group consisted of patients newly prescribed any other antidiabetic drug. Incidence of IBD was compared between the groups.

**Results:** The cohort consisted of >141,000 adults, including 7231 who received a DPP-4 inhibitor. Follow-up averaged nearly 4 years, during which 208 patients received a new diagnosis of IBD. The incidence of inflammatory bowel disease in exposed and unexposed groups were 53.4 and 34.5 per 100,000 per year, respectively (hazard ratio,\* 1.75). The number needed to harm\* was 2291 patients over 2 years to result in

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1 additional case. Incidence reached a peak after 3–4 years of DPP-4 inhibitor use and declined afterward. DPP-4 inhibitors were associated with increased incidence of ulcerative colitis (hazard ratio, 2.23) but not Crohn's disease.

Abrahami D, et al: Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ* 2018; doi 10.1136/bmj.k872. From Jewish General Hospital, Montreal, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research. The authors declared no competing interests.**

\*See Reference Guide.

## Legal Marijuana and Adolescent Health

Survey data suggest that Colorado's legalization of medical marijuana in 2009, followed by recreational use in 2014, was not accompanied by increased use of the drug by adolescents. However, the number of marijuana-related emergency and urgent-care visits to a Colorado pediatric hospital increased nearly 5-fold in subsequent years.

**Methods:** To assess the effect of legalization on one facet of adolescent health, the investigators examined data from admissions to the emergency and urgent-care facilities of a tertiary-care children's hospital system in the Denver metropolitan area. Data were collected from visits between 2005 and 2015 by patients aged 13–20 years with a discharge diagnosis of marijuana/cannabis use or with a positive toxicology screen for tetrahydrocannabinol (THC). Urine drug screens were mandatory for patients admitted for behavioral health disorders.

**Results:** A total of 4202 marijuana-related visits occurred in patients with a mean age of 16 years (54% male) during the study years. The annual total increased steadily over the years, from 161 in 2005 to 777 in 2015. The number of behavioral health evaluations, which were provided for 67% of patients, also showed a steady increase from 84 in 2005 to 500 in 2015. The majority of patients received a diagnosis of cannabis use/abuse/misuse (62%) or substance abuse (33%). Comorbid psychiatric diagnoses were also common and included depression (39%), mood disorder (22%), conduct disorder (13%), anxiety/panic disorder (13%), ADHD (12%), bipolar disorder (6%), schizophrenia (5%), and "other" (31%).

Rates of marijuana-related visits, relative to all emergency/urgent care visits, were compared

for 2009 and 2015, the first full years of medical and recreational marijuana legalization, respectively. The frequency increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015. Marijuana-related behavioral health consultations increased from 1.2 per 1000 visits in 2009 to 3.2 per 1000 visits in 2015.

**Discussion:** Although there has been an increase in the frequency of urine drug screens overall, this does not fully account for the increase in cannabis-related visits. These data should prompt concern now that more than half of states have legalized at least some type of marijuana use, in part because adolescents' risk perception of marijuana may have decreased, even if data do not consistently show an increase in actual use.

Wang G, et al: Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health* 2018; doi 10.1016/j.jadohealth.2017.12.010. From the University of Colorado Anschutz Medical Campus; and Children's Hospital Colorado, Aurora, CO. **This research was conducted without specific funding. One of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## Mazindol for Adult ADHD

In a phase-II placebo-controlled trial, controlled-release mazindol was effective in adults with ADHD, with an effect size comparable to stimulants. Mazindol is a serotonin, noradrenaline, and dopamine reuptake inhibitor (SNDRI) previously introduced for treatment of obesity but withdrawn from the market because of low sales. This is the first clinical trial of a controlled-release formulation, following promising results of an open-label study of immediate-release mazindol in children with ADHD.

**Methods:** Study participants were 84 adults with a diagnosis of ADHD meeting minimum severity criteria when unmedicated. Patients received mazindol or placebo for 6 weeks, with mazindol dosed flexibly within a range of 1–3 mg/day. The primary efficacy measure was change from baseline in the ADHD Rating Scale for DSM-5 (ADHD-RS-DSM5). Efficacy was also assessed with the Clinical Global Impression–Improvement (CGI-I) scale and with the Target Impairment Scale, which measures changes in 3 functional goals selected by the patient.

**Results:** Mazindol was associated with a significantly larger improvement in ADHD-RS-DSM5 score after 6 weeks of treatment (19 vs 6 points;

p<0.001; effect size,\* 1.09). Effects of mazindol differed statistically from placebo after the first week of treatment, and differences grew larger over the subsequent weeks. Significantly more patients were classified as "excellent responders" (≥50% improvement on the ADHD-RS-DSM5) in the mazindol group beginning at 2 weeks. By 6 weeks, 55% of the mazindol group and 16% of the placebo group were classified as excellent responders (p=0.002). CGI-I ratings of much or very much improved were observed in 62.5% of the mazindol group and 21% of the placebo group (p<0.001). Improvement in target areas was also significantly greater with mazindol.

The most common adverse effects of mazindol, relative to placebo, were dry mouth, nausea, fatigue, increased heart rate, decreased appetite, and constipation. Patients receiving mazindol lost an average of nearly 4 lbs during the 6-week study. However, previous experience indicates the effects of mazindol on weight are short-lived.

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

Wigal T, et al: A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs* 2018;32 (March):289–301. From AVIDA Inc., Newport Beach, CA; and other institutions. **Funded by NLS-1 Pharma AG. All study authors disclosed relevant financial relationships with NLS-1 Pharma AG and other sources.**

**Common Drug Trade Names:** mazindol—*Mazanor, Sanorex*

\*See Reference Guide.

## Lamotrigine Immune System Reaction

The FDA has issued a warning that the anti-convulsant lamotrigine (*Lamictal*) can cause hemophagocytic lymphohistiocytosis (HLH), a rare but serious immune system reaction that can trigger severe inflammation throughout the body. HLH causes an uncontrolled immune response that can lead to serious problems liver, kidney, lung, and blood cell issues. Patients with HLH typically present with persistent fever, rash, or other nonspecific symptoms. The diagnosis of HLH is based upon the patient exhibiting ≥5 of the following 8 symptoms: fever and rash; enlarged spleen; cytopenia; elevated triglyceride levels or low fibrinogen levels; high serum ferritin levels; hemophagocytosis identified through bone marrow, spleen, or lymph node

biopsy; decreased or absent natural killer cell activity; or elevated blood levels of CD25 indicating prolonged immune cell activation. Lamotrigine should be discontinued if HLH is suspected.

Lamictal (lamotrigine): Drug Safety Communication - Serious Immune System Reaction. Available at <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm605628.htm>.

## Lofexidine for Opioid Withdrawal

Physical dependence is an expected physiological response to opioid use. In patients using the medications appropriately, opioid withdrawal is typically accomplished using a slow taper. In patients with opioid use disorder, the abused medication is typically replaced with an alternate opioid medicine, which is then gradually reduced and then followed by transition to maintenance therapy to an agent such as methadone, buprenorphine, or naltrexone.

The FDA recently approved lofexidine hydrochloride, the first nonopioid medication for the alleviation of opioid withdrawal symptoms in adults in order to expedite abrupt discontinuation. Lofexidine is a selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine, the effects of which are thought to have a role in many of the symptoms of opioid withdrawal. The newly approved drug is not a treatment for opioid use disorder; however, it can lessen the severity of withdrawal symptoms including anxiety, agitation, sleep difficulty, muscle ache, runny nose, sweating, nausea, vomiting, diarrhea, and drug craving. In clinical trials, the most common adverse effects associated with lofexidine were hypotension, bradycardia, somnolence, sedation, and dizziness. Because lofexidine can affect cardiac conduction, patients may experience a marked blood pressure increase when the agent is stopped. Safety and efficacy have not been established in children or adolescents, and the approval covers only a 14-day course of treatment in adult patients.

FDA News Release: FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Available at <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm>.

**Common Drug Trade Names:** buprenorphine—*Buprenex*; lofexidine—*Lucemyra*; methadone—*Methadose*; naltrexone—*ReVia*

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**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.

**Number Needed to Harm:** A measure of how many patients need to be exposed to a risk-factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

**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](http://www.alertpubs.com).

**"Change is the law of life and those who look only to the past or present  
are certain to miss the future."—John F. Kennedy**

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