PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Glucagon Nasal Powder

A new treatment option for severe hypoglycemia—the first that can be administered without injection—has received FDA approval for emergency use in patients aged ≥4 years with diabetes. *Baqsimi* nasal powder increases blood sugar levels in patients with severe hypoglycemia by stimulating the liver to release stored glucose into the bloodstream. In clinical trials, the agent adequately increased blood sugar levels in adults and children. Previously, glucagon injections, which have to be mixed in a multiple-step process, were they only treatment option for patients suffering from severe hypoglycemic episodes. *Baqsimi* will be available in single-use dispensers that can simplify the administration process, which can be critical during a hypoglycemic episode, particularly if the patient has lost consciousness. Patients with pheochromocytoma or insulinoma should not use *Baqsimi*. In addition, use should be avoided after prolonged fasting and in patients with adrenal insufficiency or chronic hypoglycemia as these conditions lead to low levels of releasable glucose. Common adverse effects of *Baqsimi* are similar to injectable glucagon and include nausea, vomiting, and headache. However, because of the administration route nasal congestion and itchy, watery eyes may also develop.

FDA News Release: FDA approves first treatment for severe hypoglycemia that can be administered without an injection. Available at www.fda.gov/news-events/press-announcements.

Cause-Specific Mortality with PPIs

Proton pump inhibitors were associated with increased risk of death from cardiovascular disease, kidney disease, neoplasms, and infectious diseases in a large cohort study. Risk increases were not modified by patient history of cardiovascular or kidney disease or upper GI cancer.

Background: PPIs have previously been associated with serious adverse events and with increased all-cause mortality. This study was undertaken to evaluate specific causes of death that are associated with well-known adverse effects of PPIs.

Methods: The study cohort consisted of patients in the Veterans Administration system who were newly prescribed acid suppressant drugs in 2002–2004 and followed for up to 10 years. To be included in the study cohort, patients were required to receive a 90-day supply of a PPI or an H2 blocker during the 180 days after the first prescription. Users of both types of medication were excluded. The study was designed to emulate a clinical trial as closely as possible, with detailed adjustments to reduce confounding by indication and mimic random treatment assignment. The study outcomes were specific causes of death, based on major system categories in the International Classification of Diseases, 10th Revision (ICD-10). Excess mortality burden associated with new PPI use was estimated based on cumulative incidence rates per 1000 people at 10 years.

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Results: The cohort included nearly 158,000 users of a PPI and nearly 57,000 patients prescribed an H2 blocker. The mean patient age was 65 years and 96% of participants were male. During an average of 10 years of follow-up, more than 80,000 patients (37%) died—37.9% of those taking PPIs and 35.7% of those taking H2 blockers. Mortality was significantly elevated for 4 cause-specific categories. (See table.) For most of these causes, longer duration of PPI exposure was associated with higher mortality. Notably, taking PPIs was not associated with mortality from digestive system diseases. The analysis then examined deaths in subcauses within these categories that have been mapped to well-known PPI adverse effects. PPIs were associated with increased risk of death from cardiovascular disease and chronic kidney disease, but not upper GI cancer or *Clostridium difficile* infections. The risk of cause-specific mortality was increased in both patients with and those without a baseline history of cardiovascular disease, chronic kidney disease, or upper GI cancer.

Excess deaths in users of PPIs compared with users of H2 blockers

Cause	Attributable deaths per 1,000 users	Hazard Ratio*
All-cause mortality	45.2	1.17
Circulatory system diseases	17.47	1.17
Neoplasms	12.94	1.15
Genitourinary system diseases	6.25	1.87
Infectious diseases	4.2	1.61
Subcauses of death		
Cardiovascular	15.48	1.22
Chronic kidney disease	4.19	1.95

Discussion: Previously associations have been reported between PPIs and serious adverse events: cardiovascular disease, acute kidney injury, chronic kidney disease, dementia, pneumonia, gastric cancer, *C. difficile* infections, and osteoporotic fractures. When this study was conducted, PPIs were prescribed less frequently and at lower doses than they are now. In addition, >80% of the patient cohort was exposed to doses that are now available over the counter. These results underscore the need for PPIs to be used only when medically necessary and for the shortest possible durations.

Xie Y, et al: Estimates of all-cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. *BMJ* 2019; doi 10.1136/bmj.l1580. From the Department of Veterans Affairs St. Louis Health Care System, MO; and other institutions. **Funded by the Department of Veterans Affairs; and Washington University, St. Louis. The authors declared no competing interests.**

***See Reference Guide.**

Tofacitinib Boxed Warning

Following a review of safety data from an ongoing trial, the FDA is requiring the addition of a Boxed Warning regarding increased risk of blood clots and death to the package labeling for tofacitinib (*Xeljanz, Xeljanz XR*). Additionally, use of the drug will now be restricted to patients who experience serious adverse effects or have not been treated effectively with other medications.

As a treatment for rheumatoid arthritis (RA) and ulcerative colitis, tofacitinib decreases immune system activity. Following the initial approval in 2012 for treatment of RA the FDA required a postmarketing trial to evaluate cardiac, infectious, and cancer-related risks of the drug. An interim analysis found the occurrence of blood clots and death are increased in patients treated with 10 mg tofacitinib b.i.d, compared with those receiving the 5 mg b.i.d dosage or a tumor necrosis factor blocker. The FDA warns that patients should stop taking tofacitinib and receive emergency treatment if they experience symptoms of a blood clot including sudden shortness of breath, chest pain that worsens with breathing, arm or leg swelling, and/or pain, tenderness, or skin discoloration in the swollen limb. Tofacitinib prescription should be avoided in patients at increased risk of thrombosis and should be used at the lowest possible dose.

FDA Drug Safety Communication: FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (*Xeljanz, Xeljanz XR*). Available at www.fda.gov/drugs/drug-safety-and-availability.

Nabilone for Alzheimer's-Related Agitation

In a controlled trial, the synthetic oral THC analogue nabilone (*Casamet*) was moderately effective at reducing agitation in patients with moderate-to-severe Alzheimer's disease.

Methods: Study participants (n=38) met DSM-5 criteria for major neurocognitive disorder due to Alzheimer's Disease, had Mini-Mental State Examination (MMSE) scores of ≤24, and exhibited clinically significant agitation. Those taking cholinesterase inhibitors or psychotropics were required to have been receiving stable doses for ≥1–3 months. Patients received nabilone flexibly dosed to a target of 2 mg/day or placebo for 6 weeks each in randomized order, with a 2-week placebo washout between treatments. The primary study outcome measure was the Cohen Mansfield Agitation Inventory (CMAI), a 29-item scale that measures agitation, including physically aggressive and nonaggressive behaviors as well as verbally aggressive behaviors.

Results: Of the 38 patients who began randomized treatment (mean age, 87 years; 77% men), 2 died during the study and 9 were withdrawn early because of a serious adverse event. Five of these events occurred during nabilone treatment and 4 during placebo. After titration, participants received a mean nabilone dose of 1.6 mg/day.

Mean CMAI total scores decreased from 68 at study entry to 56 following 6 weeks of nabilone treatment, compared with 66 after 6 weeks of placebo (effect size,* 0.52; p=0.003). Nabilone was also associated with greater improvement in many of the study's secondary measures, including the Neuropsychiatric Inventory (NPI) Nursing Home version total score (p=0.004) and caregiver distress subscale (p=0.041) and the sMMSE, an adapted version of the MMSE (p=0.026). Clinical Global Impressions rating indicated 47% of patients demonstrated at least "minimal" improvement with nabilone and 23% with placebo. Sedation was the most common adverse event during nabilone treatment (17 patients, vs 6 with placebo). Sedation usually improved when the nabilone dose was reduced. Nabilone and placebo did not differ in the frequency of treatment-limiting sedation or in falls.

Discussion: The mean improvement in CMAI scores with nabilone versus placebo was larger than that reported in previous trials of atypical antipsychotics or antidepressants. Improvements in neuropsychiatric symptoms and caregiver burden were also larger than those reported with atypicals and most antidepressants. In contrast to other trials, nabilone was not associated with cognitive worsening. These observations suggest that cannabinoids, with their distinct pharmacological profile, may offer an alternative to atypical antipsychotics as a second-line treatment for agitation. Additional trials of nabilone appear to be warranted.

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

Herrmann N, et al: Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. *American Journal of Geriatric Psychiatry* 2019; doi: 10.1016/j.ajgp.2019.05.002. From Sunnybrook Health Sciences Centre, Toronto, Canada; and other institutions. **Funded by the Alzheimer's Drug Discovery Foundation; and other sources. Five of 7 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

***See Reference Guide.**

Anticholinergics and Dementia

A large case-control study found strong anticholinergic drugs are associated with increased risk of dementia. Types of anticholinergic drugs associated with the greatest risk include antidepressants, antiparkinsonian drugs, antipsychotics, antiepileptics, and bladder antimuscarinics. Anticholinergic antihistamines and GI antispasmodics were not associated with increased risk.

Methods: The study population comprised all patients aged ≥55 years registered in a British primary case database between 2004 and 2016 and with ≥10 years of available medication data. Case patients were those who had onset of dementia during the study period. Each case was matched with up to 5 controls by age, sex, and other characteristics. To reduce bias due to anticholinergic prescription in early dementia, exposure was defined as the cumulative dose of anticholinergics during 1–11 years before the diagnosis in cases or the same index date in controls. In addition, patients with diagnostic codes for subtypes of dementia associated with Huntington disease, Parkinson disease, Creutzfeldt-Jakob disease, or HIV were also excluded to reduce indication bias. The analysis included 56 drugs grouped by their main indication into 11 categories. Cumulative drug exposure was summed into 5 categories of total standardized daily doses.

Results: Out of a base cohort of more than 3.6 million patients, dementia developed during follow-up in >128,000. After applying the study's strict exclusion criteria, the analysis included nearly 59,000 case patients and 226,000 matched controls. About 60% received a diagnosis of

Alzheimer's or mixed dementia, 36% of vascular dementia, and 4% of other types.

For anticholinergics as a whole, dementia risk increased incrementally from the lowest level of cumulative exposure, 1–90 standard daily doses, (odds ratio,* 1.06) to the highest, equivalent to 3 years of daily use of a single strong anticholinergic medication at the minimum effective dose recommended for older people, (odds ratio, 1.49). Of the 11 categories of anticholinergic medication 5 were significantly associated with increased risk of dementia at the highest level of cumulative exposure. (See table.) Anticholinergic drug types that were not associated with increased dementia risk were antihistamines, antivertigo and antiemetic drugs, muscle relaxants, GI antispasmodics, antiarrhythmics, and antimuscarinic bronchodilators.

Odds ratios for dementia in patients with the highest cumulative anticholinergic drug exposure

Anticholinergic category	Adjusted odds ratio
Antipsychotics (n=1812)	1.70
Bladder antimuscarinics (n=6864)	1.65
Antiparkinson agents (n=292)	1.52
Antiepileptics (n=1411)	1.39
Antidepressants (n=15,938)	1.29

The association of anticholinergics with dementia was stronger in patients who received the dementia diagnosis before age 80 years, compared with those diagnosed at older ages. Associations were also stronger for vascular dementia than for Alzheimer's.

Discussion: Causality cannot be attributed with this type of study. However, if the association is causal, about 10% of dementia diagnoses could be attributed to anticholinergic drugs. This proportion is comparable to other known modifiable risk factors for dementia, such as smoking, diabetes, or physical inactivity. Although the analysis accounted for a wide range of potential confounding factors including the possibility of treatment for prodromal symptoms, some possibility for residual confounding and indication bias may remain. The stronger association with vascular dementia is a novel finding that raises questions about how anticholinergic drugs might influence the development of dementia.

Coupland C, et al: Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Internal Medicine* 2019; doi 10.1001/jamainternmed.2019.0677. From the University of Nottingham, U.K.
Funded by the National Institute for Health Research; and other sources. Two of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

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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.

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