PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Safety of Long-Acting β2-Agonists

In a combined analysis of FDA-mandated manufacturer-sponsored trials, long-acting β2-agonists (LABAs) were not found to increase risk of serious asthma-related events. This analysis supports the FDA's decision to remove the boxed warning from combination therapies with a LABA plus an inhaled glucocorticoid for asthma treatment.

Background: Safety concerns initially arose from a large postmarketing trial in which LABA use was associated with increased risk of death. Subsequent meta-analyses had mixed findings, and the FDA required the 4 companies that market LABAs to perform prospective, randomized safety studies.

Methods: An independent joint oversight committee analyzed combined data from the 4 trials. Each trial had a target enrollment of nearly 12,000 adolescent and adult patients with persistent asthma. Participants received treatment for 26 weeks with randomly assigned combination therapy (a LABA plus an inhaled glucocorticoid) or the glucocorticoid alone. The primary study outcome was a composite of asthma-related intubation or death. The secondary safety outcome, serious asthma-related events, was a composite consisting of asthma-related hospitalization, intubation, or death

Results: The final sample consisted of about 18,000 patients in each group. During the study period, 4 patients experienced a primary study outcome: 3 asthma-related intubations (1 in the combination group) and 2 asthma-related deaths (both in the combination group). Because there were so few events, between-group comparisons could not be done. Rates of the secondary safety outcome did not differ between the groups: 119 in the combination group and 108 in the comparison group (relative risk,* 1.09). The rate of asthma exacerbation was 9.8% in the combination therapy group and 11.7% in the comparison group, suggesting superior efficacy of combined therapy (relative risk, 0.83; p<0.001).

Discussion: The present results can be widely generalized, not only because of the representative study population, but also because of the use of several different drugs, formulations, and glucocorticoid doses. The observations support current treatment guidelines, which recommend the use of LABAs with glucocorticoids but not as monotherapy.

Busse W, et al: Combined analysis of asthma safety trials of long-acting 2-agonists. *NEJM* 2018;378 (June 28):2497–2505. doi 10.1056/NEJMoa1716868. From the University of Wisconsin School of Medicine and Public Health, Madison; and other institutions. **Funded by ICON Clinical Research; and other sources. Four of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

GLP-1 Analogues for Weight Loss

Semaglutide was an effective weight loss agent across a range of doses in a phase II clinical trial in nondiabetic patients with obesity.[1] The active control medication—liraglutide, another GLP-1

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analogue—also resulted in weight loss. According to an accompanying editorial,[2] prophylactic use of GLP-1 receptor agonists in overweight adults may improve health by reducing weight and preventing diabetes onset.

Methods: The multicenter study (8 countries, 71 sites) enrolled nondiabetic adults with a body mass index (BMI) of ≥30 who had undergone ≥1 unsuccessful nonsurgical weight-loss attempt and were free of depression. To enroll enough men, enrollment of women was capped at 70%. Participants were randomly assigned to receive double-blind treatment with: 1 of 5 dosages of subcutaneous semaglutide (0.05–0.4 mg/day); 3 mg/day subcutaneous liraglutide; or placebo. Semaglutide was started at 0.05 mg/day and increased every 4 weeks to reach the target dose in each of the 5 patient groups. Two additional fast-escalation groups had dosage increases every 2 weeks to 0.3 and 0.4 mg/day. All participants received counseling about nutrition and physical activity. The primary study endpoint was the percent change from baseline in body weight after 52 weeks of treatment.

Results: A total of 957 patients (65% women) participated in the study, with about 100 in each of the drug and dosage groups. Patients had a mean baseline BMI of 39. A total of 180 patients (19%) discontinued treatment before the end of the study year, primarily because of adverse events.

Patients in the dosage groups that received semaglutide on the 4-week titration schedule lost between 6.0% and 14% of their initial weight on average; weight loss was dose dependent. The rapid-escalation groups lost 11% (0.3 mg/day) and 16% (0.4 mg/day) of their initial weight on average. Patients receiving liraglutide lost 8% of their initial weight, and the placebo group lost 2%. All active treatment groups lost significantly more weight than placebo at 1 year. Patients receiving semaglutide had larger categorical weight losses than placebo: 5–35% of the semaglutide groups lost ≥20% of their initial weight, compared with 6% of the liraglutide group and 2% of the placebo group. Semaglutide was also associated with improvement in glucose metabolism and most anthropometric outcomes, as well as some lipid parameters. All active treatments were associated with reductions in systolic and diastolic blood pressure. Adverse effects of semaglutide and liraglutide were generally mild and transient, consisting largely of gastrointestinal effects. Serious adverse events were uncommon and not dose related.

Discussion: Liraglutide has been approved for weight reduction in the U.S. at the 3.0-mg dosage used in this study, higher than the dosage used to treat type 2 diabetes. Semaglutide induces at least comparable weight loss, which the investigators attribute to its appetite-suppressant effects. At the higher doses, weight loss continued throughout the year of treatment, in contrast with other FDA-approved weight loss medications whose effects plateau. No firm conclusion could be drawn about the efficacy and tolerability of rapid dose titration.

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

[1]O'Neil P, et al: Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;392 (August 25):637–649. From the Medical University of South Carolina, Charleston; and other institutions. **Funded by Novo Nordisk A/S. All study authors disclosed relevant financial relationships with commercial sources, including Novo Nordisk.**

[2]Kluger A, McCullough P: Liraglutide and GLP-1 analogues as weight-loss agents [editorial]. *Lancet* 2018;392 (August 25):615–616. From Baylor Heart and Vascular Institute, Dallas, TX; and other institutions. **The authors declared no competing interests.**

Common Drug Trade Names*: liraglutide—*Saxenda*; semaglutide—*Ozempic

***See Reference Guide.**

New Indication for Dupilumab

The monoclonal antibody dupilumab (*Dupixent*), previously indicated for the treatment of moderate-to-severe atopic dermatitis, has now received FDA approval as an add-on to maintenance therapy for patients aged ≥12 years with moderate-to severe eosinophilic or oral corticosteroid-dependent asthma. Dupilumab, an interleukin (IL)-4 and 13 inhibitor, reduces inflammatory biomarkers that underlie asthma. The agent will be available in prefilled syringes for subcutaneous injection every other week. Injections can be administered in clinic or by patients at home. In clinical trials, the most common adverse effects of dupilumab included injection site reactions, sore throat, and increased eosinophil levels.

FDA Approves Dupilumab for Moderate-to-Severe Asthma. Medscape Oct 22, 2018. Available at www.medscape.com/viewarticle/903761.

Antihypertensive Recalls

The FDA has announced voluntary recalls of several agents containing the angiotensin receptor blockers (ARBs) irbesartan, losartan, and valsartan due to contamination with trace amounts of *N*-Nitrosodiethylamine (NDEA) and possibly *N*-Nitrosodimethylamine (NDMA). The contaminating substances naturally occur in some foods, drinking water, air pollution, and industrial processes and have been classified as a probable human carcinogen. Included in the recall are losartan–hydrochlorothiazide, irbesartan, and agents containing valsartan alone and in combination with amlodipine and hydrochlorothiazide. Information on specifically affected lots is available on the FDA website, and the agency is continuing to test all ARBs for the presence of the contaminants. Patients affected by the recall should not stop their antihypertensive, as abruptly stopping treatment without a replacement agent poses a health risk.

FDA Drug Safety Communication: FDA updates on angiotensin II receptor blocker (ARB) recalls. Available at www.fda.gov/Drugs/DrugSafety/ucm613916.htm.

Common Drug Trade Names*: irbesartan—*Avapro*; losartan–hydrochlorothiazide—*Hyzaar*; valsartan—*Diovan*; valsartan–amlodipine—*Exforge*; valsartan–hydrochlorothiazide—*Diovan HCT

Beta-Blocker Safety in Pregnancy

In a large cohort study, use of beta-blockers during pregnancy was not associated with increased risk of congenital malformations.

Background: Beta-blockers are a first-line therapy for hypertension in pregnancy and are also widely used by nonpregnant hypertensive women of reproductive age. These drugs cross the placenta, and results of some studies in animal models suggest a potential teratogenic effect. A meta-analysis identified increased risk of some malformations, but it included many studies that had numerous flaws, including failure to account for the mother's underlying hypertension.

Methods: Study data were collected from nationwide health registries for women living in the 5 Scandinavian countries who gave birth between 1996 and 2010, and from a U.S. Medicaid database of women who gave birth between 2000 and 2010. The study comparison was restricted to women who had hypertension and who gave birth to a live singleton infant. The analysis also excluded pregnancies with a chromosomal abnormality and those exposed to known teratogens and to other categories of antihypertensive drug, some of which are suspected of teratogenicity. Birth outcomes in >18,000 patients were compared between those who filled a prescription for a beta-blocker during the first trimester and those who received no antihypertensive medication.

Results: Beta-blockers were prescribed for 19% of the Nordic cohort and for 11% of the U.S. cohort. After adjustment for multiple risk factors, beta-blocker use was not associated with an overall increased risk of congenital malformation in either cohort or when the 2 cohorts were pooled (incidence, 5.4% and 4.3% in exposed and unexposed groups, respectively; adjusted relative risk,* 1.07). Analysis of specific malformations with a suspected association (i.e., cardiac malformations, cleft lip/palate, central nervous system malformations) found beta-blocker use was also not associated with higher risk. A separate analysis estimating the potential effects of excluding pregnancies that did not result in a live birth indicated that under the most extreme hypothetical conditions, the relative risk estimate would shift from 1.07 to 1.26 for all malformations.

Discussion: Cardiac malformations are the most commonly occurring of the studied outcomes. The present results were able to rule out large increases in overall malformations as well as cardiac malformations specifically. However, the incidence of the other malformation types (0.1–0.7%) was too low to allow for definitive conclusions, but any increase is likely to be modest.

Bateman B, et al: β-blocker use in pregnancy and the risk for congenital malformations: an international cohort study. *Annals of Internal Medicine* 2018; doi 10.7326/M18-0338. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and other sources. Four of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Personal Pharmacogenetic Testing Approved

The 23andMe Personal Genome Service Pharmacogenetic Reports test has gained FDA approval for direct-to-consumer sale.[1] The test provides information about genetic variants that may be related to patients' ability to metabolize certain medications. The FDA cautions that these test results do not determine which medications are appropriate for a patient, provide medical

advice, or diagnose any health conditions. Rather, the results should be used to help inform discussions with the patient's healthcare provider.

In a separate news release, the FDA cautions that some genetic tests claim to predict how a person will respond to specific medications.[2] However, these claims have not been reviewed by the FDA and may not be backed by sufficient scientific or clinical evidence. They warn that changing treatment based on the results of these tests could lead to inappropriate decisions and potentially serious health consequences. The agency acknowledges that there are a limited number of cases for which at least some evidence supports a correlation between a genetic variant and drug levels. However, in these cases, the evidence is described in the labeling for approved genetic tests and medications.

[1]FDA News Release: FDA allows marketing of first direct-to-consumer tests that provide genetic risk infor-mation for certain conditions. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnoun cements/ucm551185.htm.

[2]FDA Drug Safety Communication: The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications. Available at: www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm.

Amitriptyline for Chronic Back Pain

In a randomized controlled trial in patients with chronic low back pain, a low dose of the tricyclic antidepressant amitriptyline was associated with reduced disability at 3 months, but not with other significant positive outcomes. Based on these results, the authors conclude that low-dose amitriptyline merits large-scale trials and consideration as an alternative in patients whose only other option is an opioid.

Methods: The trial recruited 146 adults, aged ≤75 years, with chronic nonspecific low back pain lacking a specific cause and present for >3 months. Patients were randomly assigned to receive 25 mg/day amitriptyline or 1 mg/day benztropine, a comparator with similar adverse effect profile but no known effect on low back pain. Outcomes were assessed at 3 and 6 months. The primary efficacy measure was pain intensity at 6 months, measured with a visual analog scale. Disability, the secondary outcome, was measured with the Roland Morris Disability Questionnaire.

Results: At study entry, the mean pain score was 41.6 out of 100. Average pain intensity decreased from baseline to 6 months by 13 points in the amitriptyline group and by 5 points in the control group (p=0.05). After accounting for missing data, the difference was no longer significant. Amitriptyline was associated with significantly reduced disability at 3 months, but not at 6 months. The treatment groups did not differ significantly at 3 or 6 months for any other outcomes—i.e., absence from work, interference with work, global improvement, depression, general health, or fear of movement.

Discussion: Antidepressants are commonly used to treat low back pain, but treatment guidelines are inconsistent. There have been few high-quality studies of low-dose antidepressants. Despite a lack of evidence, low-dose amitriptyline is often used to treat chronic pain, in the absence of depression. The present observations suggest a statistically significant pain reduction might be observed in a trial with a larger sample size.

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

Urquhart D, et al: Efficacy of low-dose amitriptyline for chronic low back pain: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.4222. From Monash University, Melbourne, Australia; and other institutions. **Funded by the National Health and Medical Research Council, Australia. The authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline—*Elavil*; benztropine—*Cogentin

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Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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).