PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XL / January 2019/ Number 1 www.alertpubs.com

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Romosozumab for Fracture Prevention

Estimates suggest that 1 in 3 women aged >50 years will experience a fragility fracture associated with osteoporosis, which will remain undiagnosed in 4 out of 5 women even after the fracture occurs. The FDA Bone, Reproductive and Urological Drugs Advisory Committee has recommended the approval of romosozumab (*Evenity*) for prevention of fractures in postmenopausal women at high risk. Romosozumab is a monoclonal antibody that has the potential to build new bone in women with osteoporosis and to slow existing bone loss. The FDA is not required to follow the committee recommendations, and romosozumab marketing approval is not guaranteed.

Amgen and UCD receive positive vote from FDA advisory committee in favor of approval for Evenity (romosozumab): potential new treatment option for the treatment of postmenopausal women with osteoporosis at high risk for fracture [press release]. Thousand Oaks, Ca; Amgen:January 16, 2019. Available at www.amgen.com/media/news-releases/2019/01/amgen-and-ucb-receive-positive-vote-from-fda-advisory-committee-in-favor-of-approval-for-evenity-romosozumab.

Phentermine: Long-Term Safety, Efficacy

Data presented at the Obesity Week 2018 conference suggest that long-term use of phentermine (*Adipex-P*) for weight loss is both safe and effective. The agent is currently approved only as a short-term adjunct to lifestyle interventions for weight loss, primarily because of concerns about cardiovascular events and addiction with long-term use.

Methods: Electronic records for nearly 14,000 patients with a body mass index (BMI) of ≥27 kg/m^2 who received a first prescription for phentermine between 2010 and 2015 were evaluated. Treated patients were stratified by length of phentermine use into 5 categories: short-term users (1 treatment episode of ≤3 months; n=6764); short-term intermittent users (multiple episodes all of ≤3 months in duration; n=2938); medium-term continuous users (1 episode lasting 3–12 months; n=1703); medium-term intermittent users (multiple episodes including ≥1 lasting 3–12 months; n=2423); and long-term continuous users (1 episode of >12 months in duration; n=144). Safety was evaluated as a composite outcome of myocardial infarction, stroke, cardiovascular intervention, and death.

Results: After adjustment for multiple confounders, percentage of weight lost was associated with duration of phentermine exposure. At 6 months, the average weight loss was 2.7% in the short-term use group, compared with 7–8% in medium and long-term continuous users. At 12- and 24-month assessments, short-term users had regained much of the weight they had lost, while the continuous users maintained or increased their weight loss. The composite safety outcome occurred in 41 patients (0.3%). Compared with short-term use, the hazard ratio* was 0.72 in both the short- and medium-term intermittent groups and 1.54 for the combined continuous-use groups. None of the between-group differences were significant.

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.

Discussion: Although the population was large, the study was underpowered to detect a safety signal, and the results should be replicated in an adequately powered study. However, because phentermine is available in generic form, this type of study would likely require government funding.

Tucker M: Long-term phentermine for weight loss appears to be safe, effective. *Medscape* November 15, 2018.

***See Reference Guide.**

Lorcaserin: Long-Term Metabolic Effects

In a 3-year placebo-controlled trial, the appetite suppressant lorcaserin (*Belviq*), added to lifestyle interventions, led to improvements in glycemic control in overweight and obese patients with or without diabetes. These improvements, which were probably mostly weight-loss-dependent and occurred against a background of as-needed diabetes medication, are evidence that modest durable weight loss can improve cardiometabolic health.

Methods: The trial, CAMELLIA-TIMI 61, was conducted in 8 countries and enrolled 12,000 patients. Participants were overweight or obese (body mass index [BMI] ≥27 kg/m^2) and had either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors. Double-blind randomized treatment consisted of 10 mg lorcaserin b.i.d. or placebo. Cardiovascular outcomes of this trial have been reported previously. For the present analysis, the primary outcome was the time to incident diabetes in patients with prediabetes at baseline.

Results: Study participants were followed for a median of 3.3 years. At baseline, 57% of the study population had diabetes, 33% had prediabetes, and 10% had normoglycemia. Patients had a median age of 64 years, and a median BMI of 35. Average weight loss over the first study years was significantly greater with lorcaserin than with placebo in all groups, averaging nearly 6 lbs more than placebo with diabetes or prediabetes, and 7 lbs in those with normoglycemia. These differences from placebo persisted over the remaining study years and occurred regardless of the weight effects of glucose-lowering medications.

In study participants with prediabetes, lorcaserin reduced the risk of incident diabetes by 19%, corresponding to a number needed to treat* of 56 to prevent diabetes onset in 1 patient over 3 years. The effect was similar in an analysis that included both patients who were prediabetic and those who were normoglycemic at baseline. In patients who were diabetic at study entry, lorcaserin was associated with a mean reduction of 0.33% in HbA1c, relative to placebo, with more modest effects in patients with prediabetes or normoglycemia. Lorcaserin was associated with less use of glucose-lowering medication and a higher rate of discontinuation of glucose-lowering medication in patients who initially had diabetes. More patients taking lorcaserin than placebo experienced remission of initial diabetes in the absence of glucose-lowering medication (16% versus 14%). Microvascular complications—a composite of microalbuminuria, diabetic retinopathy, and diabetic neuropathy—were reduced by 21% in patients with diabetes receiving lorcaserin. Severe hypoglycemia with serious complications was rare, but affected more initially diabetic patients taking lorcaserin than placebo (12 versus 4 patients).

Discussion: The mechanism by which lorcaserin improves glycemic and microvascular outcomes in unknown, and larger studies are needed to confirm these findings. However, taken together the current findings suggest that even modest, durable weight loss with lorcaserin can improve cardiometabolic health.

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

Bohula E, et al: Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI61): a randomised, placebo-controlled trial. *Lancet* 2018; doi 10.1016/S0140-6736 (18)32328-6. From Brigham and Women's Hospital, Boston, MA; and other institutions including Eisai, Woodcliff Lake, NJ. **Funded by Eisai. Nineteen of 27 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Cholesterol Management Guideline

A new clinical practice guideline for managing high blood cholesterol has been published by the American College of Cardiology/American Heart Association and related organizations. The updated guideline is similar to the previous 2013 document but contains recommendations on the use of newer, non-statin medications.

Because lifestyle is the foundation of atherosclerotic cardiovascular disease (ASCVD) risk reduction in young adults, most of the recom-

mendations regarding statins for primary prevention of ASCVD pertain to patients aged 40–75 years. A discussion including a review of major risk factors, costs and risks of statins, and patient preferences should take place before statins are started for primary prevention. Recommendations for primary prevention in this age group are summarized below.

Patients without diabetes:

- LDL-C 70–189 mg/dL and 10-year ASCVD risk 7.5–19.9%—Consider measuring coronary artery calcium (CAC). If score=0, statins can be withheld based on other risk factors. Intermediate scores favor statin therapy, and statins are indicated for scores ≥100.

- 10-year ASCVD risk 7.5– 19.9% with risk-enhancing factors (e.g., family history, metabolic syndrome)—Statins are favored.

- LDL-C ≥70 mg/dL and 10-year ASCVD risk 7.5%—Moderate-intensity statin regimen is indicated. CAC measurement may resolve uncertainty about risk status.

Patients with diabetes:

- LDL-C ≥70 mg/dL—Start moderate-intensity statin regimen without calculating 10-year ASCVD risk. Consider high-intensity statins if patient is aged 50–75 years or has multiple risk factors.

Patients with severe primary hypercholesterolemia:

- LDL-C ≥190 mg/dL—Begin high-intensity statin therapy without calculating 10-year ASCVD risk. If necessary, consider adding ezetimibe and, subsequently, a PCSK9 inhibitor (e.g., alirocumab).

In patients with clinical ASCVD, high-intensity or maximally tolerated statin therapy should be prescribed, with a target of reducing LDL-C levels by ≥50%. Nonstatins should be considered in patients with very high-risk ASCVD and LDL-C 70 mg/dL, beginning with added ezetimibe (*Zetia*). Very high risk is indicated by a history of multiple major ASCVD events or 1 event plus multiple risk factors. A PCSK9 inhibitor can be added if LDL-C remains elevated, although the long-term safety of these agents is uncertain and their economic value is questionable.

Medication adherence, cholesterol-lowering response, and lifestyle changes should be assessed with repeat lipid measurement 4–12 weeks after statin initiation. Measurements should be repeated every 3–12 months as needed.

Grundy S, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018; doi 10.1161/CIR.0000000000000624.From the University of Texas Southwestern Medical Center at Dallas; and other institutions.

Common Drug Trade Names*: alirocumab—*Praluent*; ezetimibe—*Zetia

Pediatric Antidepressant Use

A systematic review of pediatric depression trials conducted in the last decade suggests that the evidence continues to support escitalopram and fluoxetine as first-line treatment and that the risk of emerging suicidality may be lower than previously suggested.[1]

Methods: This updated review was based on 7 clinical trials of antidepressant treatment for major depressive disorder in pediatric patients that were conducted after a previous meta-analysis indicated antidepressants have a small positive effect on depression in young patients.[2] Studies of treatment-resistant and bipolar depression were excluded, as were those in patients whose depression was comorbid with any other major psychiatric disorder (i.e., ADHD, substance use). The 7 trials include 4 of acute-phase treatment, 3 of extension-phase treatment, and 2 of relapse prevention.

Results: The 4 acute-phase trials evaluated fixed- and flexible-dose duloxetine, transdermal selegiline, and escitalopram. Response rates with duloxetine and selegiline were similar to those with placebo, and the trials were regarded as inconclusive as a result of high placebo response rates. The escitalopram trial showed superior efficacy of active treatment versus placebo, with a response rate of 64% for escitalopram and 53% for placebo (effect size,* 0.27).

The duloxetine studies included 26-week extension periods, during which fluoxetine, the active control in both studies, was also continued. Rates of remission did not differ between duloxetine and fluoxetine in these studies. The escitalopram study, also extended for 16–26 weeks, found significantly higher rates of remission with active treatment than with placebo (51% vs 36%; p=0.002).

Maintenance treatment with fluoxetine and sertraline was evaluated in 1 study each.

Fluoxetine was found to be significantly superior to placebo for relapse prevention, with an odds ratio* for relapse of 3.2 in the placebo group. Adolescents receiving sertraline relapsed at a lower rate than their respective placebo group, but the results did not reach statistical significance, possibly because of small sample size and a high dropout rate.

Regardless of the measure, there were no differences in rates of suicidal events between active medication and placebo in any of the acute-treatment studies. However, rates were higher in the studies that used a validated rating scale (about 5–10%) than in the study that considered only adverse event reports (about 3%). While rates of suicidality were higher in the extension studies, there continued to be no significant between-group differences. The relapse prevention trials evaluated suicidality as a self-reported adverse effect leading to medication discontinuation. These found higher rates of suicidality with placebo than with fluoxetine (4% vs 2%) and no reported suicidality with either placebo or active treatment in the sertraline trial.

Study Rating*—16 (89%): This study met most criteria for a systematic review, but the source of funding was not disclosed.

[1]Ignaszewski M, Waslick B: Update on randomized placebo-controlled trials in the past decade for treatment of major depressive disorder in child and adolescent patients: a systematic review. *Journal of Child and Adolescent Psychopharmacology* 2018;28:668–675. doi 10.1089/cap.2017.0174. From Boston Children's Hospital, MA; and other institutions. **Source of funding not stated. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

[2]Bridge J, et al: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683–1696.

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; selegiline transdermal—*Emsam*; sertraline—*Zoloft

***See Reference Guide.**

Reference Guide

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 Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

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.