Clinical Briefs in Primary Care

Evidence-based updates in primary care medicine

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Opioid-induced Nausea and Vomiting

SOURCE: Raffa RB, Colucci R, Pergolizzi JV. *Postgrad Med* 2017;129:698-708.

Opioids are highly effective when administered for appropriate indications. Unfortunately, opioid-induced nausea and/or vomiting (OINV) can limit opioid effectiveness. In the immediate postoperative period, OINV can stress wound integrity and prolong hospital stay. In the outpatient setting, some patients are faced with the dilemma of accepting lesser levels of pain control in exchange for less OINV as they consider whether they should decrease their opioid dosing schedule.

A commonly recommended suggestion to reduce OINV is to take the medication with food. Unfortunately, this recommendation rests on historical dogma rather than well-established data. Raffa et al examined studies about OINV to discern whether administration of opioids with food is effective.

The amount and quality of the literature available was quite limited. While some studies reported complete pharmacokinetics and pharmacodynamics of opioids with and without food, the relationship between opioid plasma levels and symptoms often is omitted. Although no consistent relationship between OINV and the fed/fasting state was ascertained definitively, the data reviewed suggested that, if anything, high-calorie, high-fat meals tend to exacerbate OINV. Since much of the trial data found that feeding elevates the maximum plasma opioid dose in some patients, and OINV appears to be related to opioid blood levels, it would make sense that feeding might worsen OINV in susceptible individuals.

Currently, methods to address OINV include antiemetics, reduced opioid dose, and switching between opioids to identify agents with less potential to induce OINV. Taking opioids with food was not demonstrated to reduce OINV. ■

The Long-term Picture After Bariatric Surgery

SOURCE: Adams TD, Davidson LE, Litwin SE, et al. *N Engl J Med* 2017;377:1143-1155.

While often viewed as a last-resort treatment of obesity, bariatric surgery actually is the only intervention demonstrated to improve obesity-related mortality. Strict criteria for payment by insurers and costs that are inaccessible to most of the uninsured have restricted the population who could benefit from bariatric surgery.

Adams et al enhanced the somewhat sparse literature on long-term outcomes with bariatric surgery. Their 12-year prospective follow-up of patients with severe obesity included a bypass surgery group (n = 418), a group intended for surgery (n = 417) but who ultimately did not undergo surgery (e.g., for lack of insurance coverage), and a matched group of severely obese patients not seeking surgical treatment. Favorable impact was sustained over the 12-year observation period. Overall weight loss at 12 years was 35 kg (bariatric surgery) vs. 2.9 kg (intended surgery) and 0 kg (no surgery). For diabetics at the time of bariatric surgery, diabetes remained in remission for more than half of patients at 12 years. The likelihood of new-onset diabetes over 12 years of follow-up among those not diabetic at baseline was reduced by > 90%. The benefits of bariatric surgery are substantial, prompt, and enduring. ■

Is It Safe to Use PPIs Long Term?

SOURCE: From the Medical Letter on Drugs and Therapeutics. *JAMA* 2017;318:1177-1178.

Proton pump inhibitors (PPIs) are among the most widely used medications in the United States, thanks to a generally favorable combination of efficacy, tolerability, and safety. Because such a large portion of the adult population uses PPIs, even if a small fraction experiences an adverse effect, it becomes a potentially important issue.

Probably the most concerning adverse effect of PPIs is increased fracture risk. Although not all individual studies confirmed increased fracture risk from PPIs, a meta-analysis of 18 trials indicated a 26-33% increased risk. Since PPIs are not associated with osteoporosis, the mechanism by which PPIs incur increased fracture risk is unknown.

The FDA sent a warning letter to clinicians about another potentially serious adverse effect of PPIs: hypomagnesemia. To date, only long-term use has been associated with hypomagnesemia, and the

mechanism is unknown. The severity of consequences ranges from simple fatigue to serious events like seizures and arrhythmias. Monitoring magnesium levels may be appropriate, especially in patients also receiving magnesium-depleting medications (e.g., diuretics).

Other rare but important adverse effects reported include acute kidney injury, chronic kidney disease, reduced vitamin B12 levels, iron deficiency, community-acquired pneumonia, and *Clostridium difficile* infection. The risk:benefit relationship of PPIs is favorable for most patients, but clinicians should remain vigilant for adversities noted above. ■

Menopausal Hormone Replacement

SOURCE: Manson JE, Aragaki AK, Rossouw JE, et al. *JAMA* 2017;318:927-938.

Hormone replacement therapy (HRT) reached its peak in the late 1990s based on observational data that suggested improvements in cardiovascular health, cognition, genitourinary health, and other factors. That changed drastically following the HERS trial and the Women's Health Initiative (WHI), both of which found not only no cardiovascular benefit associated with HRT but increased adversities such as breast cancer and venous thrombosis.

Women were enrolled in the WHI from 1993-1998, and have been followed through 2014, so clinicians can look at the long-term effects of their treatments for the six or seven years they participated in the trial through that date. There was no difference in all-cause mortality or cancer-related mortality between treated and untreated patients over 18 years of follow-up. It has been noted that younger women (age 50-59 years) in the WHI had a favorable outcome for all-cause mortality during the trial. This trend continued through the 18-year follow-up (hazard ratio for mortality, 0.87; confidence interval, 0.76-1.00).

For women who currently use or have used hormone replacement for menopausal symptoms, these data should be reassuring that their symptom relief does not come at a cost of increased total or cancer-related mortality. ■

More Good News for GLP-1 RA in Type 2 Diabetes

SOURCE: Mann JFE, Ørsted DD, Brown-Frandsen K, et al. *N Engl J Med* 2017;377:839-848.

Since 2008, the FDA has required all new diabetes medications to provide evidence of cardiovascular (CV) safety. The good news is that several classes of agents have demonstrated not only CV safety, but even efficacy in reducing CV events and (in some cases) all-cause mortality.

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) liraglutide, the sodium-glucose co-transporter-2 inhibitors empagliflozin and canagliflozin, and the dopamine agonist bromocriptine have demonstrated beneficial effects on CV outcomes. Whether these results will be revealed as a class effect remains to be determined.

Alongside the favorable CV data, there is good news in relation to renal endpoints in some of these same trials, the most recent of which is reported from the liraglutide CV safety trial (LEADER). Renal outcomes showed favorable effects of liraglutide compared to placebo, primarily driven by a reduction in the number of patients who developed new macroalbuminuria (> 300 mg urinary albumin/24 hours). Similarly, the rate of decline in renal function, as measured by glomerular filtration rate, was statistically significantly less in patients treated with liraglutide than placebo.

Reductions in microvascular disease (early nephropathy, in the case of type 2 diabetes) has been a major justification for management of glucose for several decades. It is reassuring to confirm that the risk for more advanced nephropathy is ameliorated by use of liraglutide. ■

A Link Between *Demodex* Mites and Rosacea

SOURCE: Chang YS, Huang YC. *J Am Acad Dermatol* 2017;77:441-447.e6.

Rosacea is a common dermatologic disorder of uncertain etiology that often is refractory to therapy. Although numerous interventions have been tried, no cure for rosacea is at hand. Antibiotics (e.g., tetracyclines, metronidazole), beta-blockers (e.g., propranolol), alpha-beta-blockers (e.g., carvedilol), systemic steroids, and calcineurin inhibitors (e.g., tacrolimus) have demonstrated some degree of success, but many patients must rely on polypharmacy for adequate symptom control.

An association of the *Demodex* mite and rosacea has been recognized for more than 50 years. Indeed, antiparasitic medications (ivermectin, permethrin) recently have been shown to produce a favorable effect on rosacea. To better delineate the *Demodex*-rosacea relationship, Chang and Huang performed a meta-analysis of studies comparing the prevalence of *Demodex* and the *Demodex* density (intensity of mite colonization) in patients with rosacea vs. controls. Patients with rosacea were nine times more likely to be infested with *Demodex* than controls. Similarly, *Demodex* density was statistically significantly higher in rosacea patients.

The role of *Demodex* in rosacea appears to be well demonstrated. Since eradication of *Demodex* is insufficient to resolve rosacea, other pathophysiologic pathways also must be involved. ■

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