Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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Exercise for Depression

Source: Cooney G, et al. *JAMA* 2014;311:2432-2433.

Common sense would predict that exercise might be beneficial for persons with depression, but since our simple intuitions have not always been confirmed by clinical data, it is nice to see data that say "Yes, your common sense was correct. Exercise is beneficial for depression."

Cooney et al reviewed clinical trials that compared exercise with either no treatment or a control for study subjects with depression. Because different clinical trials use different depression scales, results from different trials were converted to a single metric to standardize comparisons. To make the outcomes more clinically relevant, degree of change was quantified as small, moderate, or large.

Although not all trials found a favorable effect of exercise on depression — and one trial actually reported a detrimental effect — the meta-analysis of the data found an overall moderate, favorable effect of exercise compared to control, equivalent to an approximately 5-point reduction on the Beck Depression Inventory.

The data were not sufficient to distinguish a particular type (e.g., aerobic vs non-aerobic), intensity, or duration of exercise needed to achieve a favorable impact. Nonetheless, some national guidelines already include recommendations for exercise as a treatment for mild-to-moderate depression (NICE: National Institute for Health and Clinical Excellence Guideline from the United Kingdom). Patients might be more motivated to consider exercise as a respectable treatment if they understand that favorable results are supported by scientific data. ■

A Potential New Fix for Opioid-Induced Constipation

Source: Chey WD, et al. *N Engl J Med* 2014;370:2387-2396.

Most of the commonplace adverse effects associated with opioid analgesia, e.g., nausea, cognitive clouding, sedation, and pruritus, are transient. Constipation, unfortunately in addition to being one of the most common adverse effects of opioids, is also the most persistent. Mu receptors in the enteric nervous system (the colon has a brain, you say? Who knew!?) have a critical responsibility for controlling active propulsive activity of the colonic musculature: Activation of the mu receptor *suppresses* propulsive activity. Since all traditional opioids possess potent mu receptor agonist activity, suppression of colonic propulsive activity is routinely seen during opioid treatment, and the bowel does not appear to develop much tolerance to this effect.

Naloxegol is an oral mu receptor *antagonist* pending FDA approval in the United States. Because it is only effective at *peripheral* opioid receptor sites (e.g., colon) and not at *central* mu receptor sites (i.e., the CNS), it should not induce opioid withdrawal or reduce the efficacy of opioid analgesia. Data published from two randomized, double-blind, placebo-controlled clinical trials support the efficacy and tolerability of naloxegol. By intention-to-treat analysis, naloxegol provided a statistically significant and clinically meaningful sustained increase in frequency of bowel movements over a 12-week opioid treatment period compared to placebo. The drug was well tolerated. Although there are other mu receptor antagonists on the market — one is parenteral and the other is indicated only for postoperative ileus — it would be nice to have an orally active agent for patients treated with chronic opioids. ■

BP Lowering Effects of SGLT2 Inhibitors

Source: Oliva RV, et al. *J Am Soc Hypertens* 2014;8:330-339.

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are the newest class of agents available to treat diabetes. In the United States, only canagliflozin and dapagliflozin are FDA approved. SGLT2 inhibitors work by blocking the receptors in the proximal renal tubules from reabsorbing glucose back into circulation. As a result, glucose is excreted in the urine, calories are lost from the body, and we see not only reductions in plasma glucose and A1c, but reduced body weight and reduced blood pressure (BP).

To date, expert opinion has been that the BP reduction is a direct reflection of the diuresis associated with SGLT2 inhibition, but this continues to be debated. In any case, BP reduction is critical in diabetics, who suffer a greater burden of cardiovascular (CV) disease than non-diabetics and worse outcomes when CV events occur. Currently, less than 50% of diabetics with hypertension have attained BP control.

A meta-analysis of placebo-controlled

trials (n = 21 trials) with SGLT2 inhibitors found a mean change in systolic BP of approximately 4 mmHg. While at first glance this might seem small, remember that the patient populations selected for SGLT2 treatment were based on presence of diabetes, not hypertension, so the mean baseline BP levels in these trials would not reach the threshold for the diagnosis of hypertension.

SGLT2 inhibitors do not work to reduce glucose in persons with significant CKD (GFR < 45-60 mL/min) because they are dependent on good glomerular filtration rates to induce meaningful amounts of urinary glucose excretion. It is heartening to see a class of diabetic pharmacotherapy that not only produces improved glycemia, but also is associated with weight reduction and lower systolic BP. ■

Perioperative Cardiovascular Adverse Events in Stroke Survivors

Source: Jørgensen ME, et al. *JAMA* 2014; 312:269-277.

Once a person has experienced a stroke, risk for future cardiovascular events remains substantially elevated compared to a healthy population.

The perioperative period is known to be a time of increased risk for major adverse cardiovascular events (MACE), and it would be valuable to know the interval after which surgical procedures could be performed with minimum risk of MACE for stroke survivors: Is an operation safe 3 months after a stroke? 6 months? 1 year?

Jørgensen et al evaluated data from the Danish Nationwide Cohort Study (n = 481,183 elective noncardiac surgeries in adults) to examine the relative risk for MACE in the general population vs stroke survivors. Even distant from the event, risk for MACE was greater in stroke survivors compared to the healthy population (odds ratio [OR] = 1.46). Additionally, the risk of perioperative MACE was greatest in the time period most proximate to the stroke: OR was as high as 14.2 if surgery occurred within 3 months of stroke, reduced to 4.85 in the 3-6 months post-stroke interval, and reduced further to an OR of 2.47 if surgery was performed at least 12 months post-event. These data should provide impetus to advise stroke survivors that unless there is some urgency to an elective procedure, cardiovascular outcomes are best when elective surgery is performed at least 12 months from the date of the index event. ■

PSA Screening: Game Over? Well, Maybe

Source: Barton MK. *CA Cancer J Clin* 2014;64:221-222.

In 2008, the United States Preventive Services Task Force (USPSTF) guideline made one of the first steps toward reducing the number of persons screened for prostate cancer by indicating the lack of value for persons ≥ 75 years. Four years later, their recommendations were updated into a guideline that advised *not* performing prostate cancer screening on any men, since benefits could not be confirmed to outweigh risks. So, game over?

A study performed under the leadership of faculty from the University of Chicago department of urologic surgery analyzed data from the National Health Interview Survey, an ongoing interview done annually on 87,500 people in the United States. The subgroup chosen for analysis in this report focuses on men in two age groups: 65-74 years and ≥ 75 years. Results of these populations when queried in 2005 and 2010 were compared.

Was the 2008 caveat issued by the USPSTF heeded? For men aged ≥ 75 years, investigators found no meaningful difference in the rates of prostate cancer screening comparing results from 2005 interviews (36% screened) and 2010 interviews (34% screened). The majority of these men reported that their physician had advised them to undergo the screening, with only about 25% of men reporting any discussion of potential disadvantages of prostate cancer screening.

Guidelines are only guidelines: That is, it is the artful application of clinical judgment to science that should produce therapeutic wisdom. Nonetheless, clinicians should always carefully examine their process when acting in a way that is directly countercurrent to major national guidelines. ■

AF is Responsible for Even More Strokes

Source: Gladstone DJ, et al. *N Engl J Med* 2014;370:2467-2477.

Atrial fibrillation (AF) is the most potent predictive factor for risk of stroke. The good news is that stroke risk in AF patients can be reduced by more than two-thirds with use of currently available antithrombotic medications, while incurring only a minor risk (< 1.0%/yr) of central nervous system bleed.

I guess the reason we use the words "idiopathic" and "cryptogenic" is because it is difficult for us to say "We just don't know." But package the answer in whichever jargon you like, cryptogenic stroke is an important public health issue, since approximately 25% of ischemic strokes are ultimately so-classified.

Before labeling a stroke cryptogenic, an evaluation for underlying pathology is generally performed, which includes scrutiny for AF, since that is so frequently a culprit and so importantly remedied. If AF was not detected in the proximate temporal vicinity of the stroke, can an "innocent" verdict be rendered as far as AF is concerned?

Sometimes, apparently not. Gladstone et al report on the results from cryptogenic stroke/TIA patients (n = 572), half of whom were randomized to 30-day post-event cardiac rhythm monitoring. AF of at least 30 seconds duration was identified in 16.1% of the patients who were monitored.

AF is responsible for a significant number of stroke patients who would not otherwise enjoy the benefits of anticoagulation. More routine inclusion of longer monitoring will help to identify these patients. ■

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