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ABSTRACT & COMMENTARY

Seniors Unsafe While Driving Under Influence of Opioids

By Seema Gupta, MD, MSPH

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Dr. Gupta reports no financial relationships relevant to this field of study.

SYNOPSIS: New and frequent opioid users 50-80 years of age who drove while on opioids increased their probability of an accident.

SOURCE: Monárrez-Espino J, Laflamme L, Rausch C, et al. New opioid analgesic use and the risk of injurious single-vehicle crashes in drivers aged 50-80 years: A population-based matched case-control study. *Age Ageing* 2016;45:628-634.

The treatment of pain in older adults presents unique challenges. Along with suffering from a number of chronic conditions for which multiple medications may be prescribed, the addition of another medication may place the patient at higher risk of drug-drug interactions. Existing morbidity, such as lower renal function, also may limit the choice of analgesics. Moreover, age-related changes, such as those in memory, cognition, and sensory functions, may deteriorate further with some analgesics, such as opioids, which can lower the ability of these patients to function independently. As the geriatric population in the United States grows, more older adults expect to lead an active life, which involves the ability to drive. As the nation endures an opioid epidemic in terms of addiction, morbidity, and mortality, optimizing drug therapy while adequately treating pain is an essential part of caring for an older patient. However, the potential impairment due to the use of opioids while driving remains an unsettled issue. Although some evidence-based literature reviews indicate opioids do not appear to be associated with intoxicated driving and are not associated with motor vehicle crashes, others have found an increased risk.[1,2] Some have suggested that relieving pain actually could improve cognitive functions. However, most evidence is not direct, and there remains a need for high-quality studies to produce more persuasive empirical evidence.[3]

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Monárrez-Espino et al conducted a population-based, matched, case-control study that included 4,445 Swedish drivers 50-80 years of age. These drivers had been involved in a single-car crash between 2005 and 2009 in which at least one person suffered an injury that required medical care. The 4,445 cases were matched 1:4 to 17,780 controls by sex, age, and residence. Study participants were considered new to opioid analgesics if they had received a prescription within one month before the crash. Regular or frequent users were those who received at least three prescriptions in the last six months, with at least one prescription within a month of the crash.

Researchers found that for the new opioid analgesic users, the risk was 100% higher compared with the risk in subjects of same age taking one or two non-opioid analgesics (adjusted odds ratio [OR], 2.0; 1.6-2.5). For the frequent opioid analgesic users, the risk was approximately 70% higher (OR, 1.7; 1.3-2.1) with three to four opioid dispensations, but no rising trend was observed with an increasing number of dispensations.

The authors asserted that the higher risk of crashing a motor vehicle associated with the new use of opioid analgesics possibly could be because of the lack of tolerance or adaptation to the pharmacological effects that could hinder driving abilities. However, the existing higher risk found in frequent users helped dismiss the notion that opioid-tolerant patients may not be at increased risk at all. Although some level of adaptation to the side effects may have developed in frequent opioid users, it is clear that the use of such medications while driving poses a safety risk.

■ COMMENTARY

According to the CDC, drug overdoses remained the leading cause of accidental death in the United States in 2015, increasing to 55,403 lethal overdoses, the equivalent of a Boeing-737 full of passengers crashing each day for the entire year.[4] Opioid use and addiction continues driving this rise, with prescription and illicit opioids causing 33,091 deaths in 2015. The rising mortality rates from overdoses underscores the morbidity from the national opioid epidemic, which has yet to peak. Evidence suggests abuse and misuse behaviors may be negatively associated with older age, and opioids may play a role in treatment of chronic pain in this population. However, opioid use among the elderly is associated with poorer mental health function, which may produce other consequences, such as falls and motor vehicle crashes.[5] Therefore, it is prudent to consider alternative treatment options and comorbid conditions as well as elderly patients' ability to understand the importance of managing opioid therapy responsibly prior to providing such a prescription.[6]

["Although some level of adaptation to the side effects may have developed in frequent opioid users, it is clear that the use of such medications while driving poses a safety risk."]

When other options (non-pharmaceutical and pharmaceutical) already have been considered and a clinical decision is made to prescribe opioids, it may be reasonable to recommend that elderly patients consider refraining from driving when starting an opioid medication. For those already on maintenance opioid treatments, the study shines the light on the opportunity to take a case-by-case approach when considering the potential risk of an impaired driver while taking an opioid. ■

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BRIEF REPORT

Pulmonary Embolism Common Cause for Syncope in Hospitalized Patients

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports he is a consultant for Procter & Gamble.

SOURCE: Prandoni P, Lensing AW, Prins MH, et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. *N Engl J Med* 2016;375:1524-1531.

Syncope is a chief complaint for which neurologists often are consulted. In most cases, the neurological concern is possible stroke or an epileptic seizure. However, a variety of cardiopulmonary problems are most often the underlying cause of syncope, including cardiac arrhythmias and pulmonary embolism. The investigators of this study reviewed the clinical records of 560 patients (mean age of 76 years) who were admitted to the hospital with syncope. Diagnosis of pulmonary embolism was ruled out in 330 of the 560 patients on the basis of a negative D-dimer assay and low pretest clinical probability. Of the remaining 230 patients, pulmonary embolism was identified in 97 (42.2%). In the entire cohort, prevalence of pulmonary embolism was 17.3% and there was evidence of an embolus in a main pulmonary or lobar artery larger than 25% of the total area of both lungs in 61 patients. Based on this careful and detailed review of clinical features of patients with syncope, it appears that pulmonary embolism may be one of the most common causes, and should be considered by all physicians who are evaluating such patients, including neurologists. ■

BRIEF REPORT

Dental Care May Reduce Risk of Pneumonia

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Doll M, Kelly K, Ratliff S, et al. Access to dental care and the risk of pneumonia: The importance of healthy teeth. IDWeek Thursday afternoon poster session, Oct. 27, 2016; New Orleans.

Dentists have seized on data presented at IDWeek in New Orleans in October, and for good reason. It is generally believed that dental care is important to overall good health, nutritional status, and a reduction in certain kinds of infection. Indeed, data derived from the 2013 Medical Expenditure Panel Survey (MEPS) found that a lack of routine dental care may be associated with an increased risk of pneumonia.

MEPS is administered by the Agency for Healthcare Research and Quality and evaluates national data on healthcare utilization and cost, with data garnered from individual households.

Data from the 2013 survey included questions regarding the number of annual dental visits, the frequency of dental check-ups, and the presence of dental insurance during the previous two years. In addition, the survey identified 441 individuals

diagnosed with at least one episode of pneumonia in 2013 (1.68% of the sample).

In simple and bivariate logistical analyses, Caucasian race, older age, a perception of general poor health, a lack of dental insurance, and a lower frequency of dental visits were each significantly associated with an increased risk of pneumonia. Individuals with no routine dental check-ups in the previous two years had an 86% increased risk of pneumonia compared to those with two or more routine annual dental check-ups (confidence interval, 1.30-1.65; $P = 0.0008$). In a complex multivariate model, an increased frequency of routine dental check-ups remained significantly associated with a lower risk of pneumonia. Interestingly, while the presence of dental insurance was strongly associated with the frequency of dental check-ups, dental insurance did not appear to affect the risk of pneumonia in the final statistical model. ■

BRIEF REPORT

Cardiorespiratory Fitness May Stave Off the Development of Depression

By David Kiefer, MD

Clinical Assistant Professor, Department of Family Medicine, University of Wisconsin; Clinical Assistant Professor of Medicine, Arizona Center for Integrative Medicine, University of Arizona, Tucson

Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: Lower cardiorespiratory fitness increases the risk of developing depression in adults.

SOURCE: Schuch FB, Vancampfort D, Sui X, et al. Are lower levels of cardiorespiratory fitness associated with incident depression? A systematic review of prospective cohort studies. *Prev Med* 2016;93:159-165.

Using a systematic review research methodology, Schuch et al saved clinicians the task of having to review individual clinical trials themselves. The authors justified exploring cardiorespiratory fitness (CRF), which they defined as "… the ability of the circulatory and respiratory systems to supply oxygen to working muscles during sustained physical activity, typically expressed as mL O_2/kg-1/min-1 … ," because of some prior work supporting its effect on human health as being as great or greater than the more generic variable, physical activity (the authors provided some references to this effect). In this review, the researchers found three CRF clinical trials, and used two of them to generate data for this analysis; the third study did not include a hazard ratio (HR), precluding its inclusion in the pooling of data. The adult study participants did not have a mental health condition diagnosed at baseline. In addition, the clinical trials were prospective in design, and had at least one year of follow-up. Studies also had to have the primary outcome as either the risk (odds) of developing depression, or "… the association between cardiorespiratory fitness and depression or depressive symptoms."

Overall, the pooled analysis included data on 1,131,330 people. A higher risk ($P < 0.001$) of developing depression was demonstrated in those adults with low CRF (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.61-1.91) and medium CRF (HR, 1.29; 95% CI, 1.20-0.138). The authors interpret these results as evidence that "…interventions that specifically target CRF might also promote positive mental health outcomes." However, there are caveats. This is merely an observation study, so causation can't be implied; for example, we are not able to say that low CRF *causes* depression. Furthermore, few details were provided of the methods that CRF was measured, other than the fact that the studies did not use the "gold standard" VO_{2max}. Future studies that standardize this measurement would do much to help clinicians know exactly what to tell patients about how long, what type, and how intense exercise would benefit their mental health. Obviously, more studies are needed (just two were included here), but the number of patients studied in this analysis was impressive. In addition, the authors did not include the results of the high CRF groups, so any implication that more exercise leads to a lower risk of depression would be merely conjecture. Going forward, there is little reason for clinicians not to help patients move (pun intended) away from being in the low and medium CRF groups, no matter how that is defined, and it may also benefit their mental health. ■

ABSTRACT & COMMENTARY

Diabetes and Vitamin C Deficiency May Be Common

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Low levels of vitamin C were noted in seven of 11 patients with diabetes, including six of seven with lower extremity ulcers. Vitamin C repletion appeared to help heal these ulcers.

SOURCE: Christie-David DJ, Gunton JE. Vitamin C deficiency and diabetes mellitus — easily missed? *Diabet Med* 2016 Nov 18. [Epub ahead of print].

In this retrospective study, 11 patients with diabetes from a clinic in Sydney, Australia, with either nonhealing foot ulcers or who were suspected by history to have a poor diet were studied. Seven patients had nonhealing ulcers of their lower extremities, and four other patients without ulcers were suspected of having vitamin deficiency. In the group of 11 patients tested, the median vitamin C level was 19 umol/L (normal > 40 umol/L). Six of seven patients with lower extremity ulcers had low vitamin C levels compared to only one of four who did not have an ulcer and had low levels. All of these patients were treated with vitamin C 500-1,000 mg daily. Five of six patients with ulcers who were vitamin C-deficient healed their ulcers, and the remaining ulcer patient who was found to be zinc-deficient (but not vitamin C-deficient) healed after zinc repletion.

■ COMMENTARY

While this is a very small, non-randomized, observational study, I found the results intriguing. We all learned in medical school how important vitamin C is for wound healing and maintaining tissue integrity, but most of us practicing in the developed world probably do not even think of some of the subtler manifestations of scurvy. Although this small study does not describe well the presence or absence of traditional risk factors for lower extremity ulcers in these 11 patients with diabetes (vascular disease and neuropathy), the prevalence of vitamin C deficiency in this small cohort of patients is striking. I confess to not even considering vitamin C (or other micronutrient) deficiency in most of the generally obese diabetic patients I see in the hospital and clinic for diabetic ulcers and foot infections, but I will definitely do so in the future. Clearly a larger prospective, randomized study of assessment and repletion of vitamin C (and other micronutrients) in diabetic patients with foot ulcers would be welcome. ■

PHARMACOLOGY UPDATE

Crisaborole Ointment (Eucrisa)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a topical boron-containing phosphodiesterase 4 (PDE-4) inhibitor, crisaborole, for the treatment of atopic dermatitis. This PDE-4 subtype shows anti-inflammatory properties as do two other members of this class are roflumilast for COPD and apremilast for psoriasis. Crisaborole is marketed as Eucrisa.

INDICATIONS

Crisaborole is indicated for topical treatment of mild to moderate atopic dermatitis in patients ≥ 2 years of age.[1]

DOSAGE

The recommended dose is topical application (a thin layer) twice daily to affected area. Crisaborole is available as a 2% ointment.

POTENTIAL ADVANTAGES

Crisaborole provides a non-corticosteroid for the treatment of atopic dermatitis. It has low systemic exposure and is metabolized quickly to its inactive metabolites.[1]

POTENTIAL DISADVANTAGES

Crisaborole currently is not indicated for use on children < 2 years of age. The safety of long-term application has not been determined.

COMMENTS

Crisaborole's anti-inflammatory action is believed to be due to its inhibition of PDE-4, which is the predominant cyclic AMP degrading enzyme.[2] PDE-4 is overactive in inflammatory cells in patients presenting with atopic dermatitis.[3]

The efficacy and safety of crisaborole were evaluated in two identically designed, vehicle-controlled, double-blind, randomized studies.[1,4] Subjects (n = 1,511) with mild (38.5%) and moderate (61.5%) atopic dermatitis were randomized 2:1 to crisaborole or vehicle twice daily for 28 days.

The primary efficacy endpoint, assessed at day 29, was the proportion of subjects who achieved success. Success was defined as an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with a 2-grade or more improvement from baseline. ISGA was a 4-point scale based on the degree of erythema, induration/papulation, and oozing/crusting.

Success rates were 32.8% for study one and 31.4% for study two compared to 25.4% and 18.0%, respectively, for vehicle-placebo. Improvement was seen by day eight, and a higher proportion of subjects on crisaborole showed greater reduction in erythema, exudations, excoriation, induration/papulations, and lichenification.[4] Crisaborole is well tolerated, with burning and stinging at the application site reported in 4% of subjects, compared to 1% for the vehicle.

There are no published comparative trials comparing crisaborole and topical corticosteroids or calcineurin inhibitors (i.e., pimecrolimus, tacrolimus) at this time.

CLINICAL IMPLICATIONS

Atopic dermatitis is a common, chronic, pruritic, inflammatory skin disorder. The mainstay topical anti-inflammatory pharmacologic therapy is topical corticosteroids.[5] Topical calcineurins are alternatives to corticosteroids if the latter was ineffective and caused adverse effects (e.g., atrophy).

Crisaborole is the first topical PDE-4 inhibitor to be approved for atopic dermatitis. It seems to be effective and well tolerated. It provides an alternative to topical corticosteroids and calcineurin inhibitors for atopic dermatitis in children (≥ 2 years of age) and adults.

Relative effectiveness to existing agents remains to be determined. The cost is not available at this time. ■

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Clinical Briefs

By Louis Kuritzky, MD

Dietary Supplement Trends, 1999-2012

SOURCE: Kantor ED, Rehm CD, Du M, et al. Trends in dietary supplement use among US adults from 1999-2012. *JAMA* 2016;316: 1464-1474.

According to results from in-home interviews with 37,859 U.S. adults, 52% reported use of a supplement within the 30 days prior to the interview. Included under the canopy of "supplements" were multivitamins, fish oil, and individual supplements (such as vitamin D). Of concern (depending on your personal philosophical-scientific position on the issue), the use of supplements has remained essentially stable during the 1999-2012 interval.

Although some major players have declined over the past decade (multivitamin/multimineral use decreased from 37% to 31%), others have increased substantially: fish oil use increased from 1.3% in 1999 to 12% in 2012, and vitamin D increased from 5.3% to 19%. The authors reported that approximately 25% of supplement use had been recommended by a health-care provider.

With the exception of folate supplementation for women, support for the benefits of supplements, in the absence of predefined deficiency, is scant.

The item that provided me that greatest reason for pause was not in the article itself but an editorial about this article in the same issue of *JAMA*, which I believe deserves to be quoted in full (reader discretion is advised): "... even after high-quality studies that show no meaningful clinical differences between supplements and placebos are published, the law provides [supplement] manufacturers latitude to continue advertising their products based on earlier, low-quality data. For example, Ginkgo biloba continues to be sold 'to support mental sharpness' despite a large, high-quality, NIH-funded study that found evidence to the contrary."

I am already reasonably supple. In the absence of strong evidence, I will continue to eschew supplements. ■

New Tools for Glucose Monitoring

SOURCE: Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: A multicentre, non-masked, randomised, controlled trial. *Lancet* 2016;388:2254-2263.

The inconvenience of frequent finger-stick testing to assess control of diabetes is particularly problematic for type 1 diabetics. The FreeStyle Libre (trade name) is a sensor the size of a human hair that is inserted in the skin of the upper arm and attached to a patch that records glucose readings over eight hours. The reading device can be downloaded and has the capacity to store up to 90 days of readings. Does the FreeStyle Libre outperform traditional fingerstick methodologies?

To test this hypothesis, Bolinder et al randomized participants with already well-controlled type 1 diabetes (n = 328) to use the "flash glucose monitoring system" or typical finger-stick monitoring. The primary outcome of the trial was amount of time in hypoglycemia during six months of follow-up. Time in hypoglycemia was reduced by 38% with the Freestyle Libre device, compared to "traditional" methods. A small number of participants (n = 10) experienced local reactions at the site of insertion of the sensor.

The device recently received FDA approval. A FreeStyle Libre "starter kit" currently is advertised at $359. ■

Placebo for Osteoarthritis Pain

SOURCE: Dieppe P, Goldingay S, Greville-Harris M. The power and value of placebo and nocebo in painful osteoarthritis. *Osteoarthritis Cartilage* 2016;24:1850-1857.

Terminology about placebo, according to Dieppe et al, might be more useful if divided into placebo response ("a change seen in response to a sham intervention") and placebo effect ("the difference between doing nothing ... and giving a sham treatment"). The authors chose to focus on the symptomatic improvements that can occur for patients simply as a result of an encounter with a health professional.

By comparing pain reduction achieved in placebo groups of randomized, controlled osteoarthritis trials with treatment arms that received no treatment (not even placebo), the authors determined that an effect size of about 0.5 is seen with placebo, comparable to that seen with many "active" interventions. Context also may be important. For instance, injection placebos were particularly powerful.

The physiologic underpinnings of placebo response for pain indicate it is not "imaginary." For instance, the pain reduction of placebo can be blocked by pre-administration of naloxone, suggesting that such responses may be reflective of activation of endogenous endorphins.

The authors concluded that positive placebo response from patients occurs most fruitfully when patients feel safe, calm, and validated by their clinician. ■

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CME QUESTIONS

1. **Researchers found that compared to the risk in patients of the same age taking one or two non-opioid painkillers, new opioid users demonstrated an approximately ___ increased risk for motor vehicle crash.**
   a. 50%
   b. 70%
   c. 100%
   d. 200%

2. **Which of the following is an association with low cardiorespiratory fitness?**
   a. A 33% lower risk of developing depression
   b. A 76% higher risk of developing depression
   c. A 76% lower risk of worsening depression
   d. A 76% higher risk of depression resolving

3. **Pulmonary embolism appears to be one of the most common causes of syncope.**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

A Healthy Lifestyle May Halve the Genetic Risk of Coronary Disease

Do Antipsychotics Help with Delirium?