Drug Monitor

The Risks of Opioid Treatment for Veterans

Many veterans return home not only with physical health problems, but comorbid mental health problems, notably posttraumatic stress disorder (PTSD). On top of that, veterans with PTSD are at high risk for substance abuse, including misuse of prescription pain medications, such as opioids, say researchers from the San Francisco VAMC and the University of California at San Francisco, both in San Francisco, California; the Richard L. Roudebush VAMC and the Indiana University School of Medicine, both in Indianapolis, Indiana. Their study revealed that U.S. veterans of Iraq and Afghanistan with mental health diagnoses, especially PTSD, are highly likely to receive opioids for pain and just as likely to have adverse clinical outcomes—specifically, injuring themselves or others.

The main study population was 141,029 Iraq and Afghanistan veterans who received a diagnosis of new noncancer pain within 1 year of VA entry. Most veterans had 2 or more different pain diagnoses. Half received at least 1 mental health diagnosis; of those, 32% were diagnosed with PTSD.

Each veteran was followed up for 1 additional year from the initial pain diagnosis to evaluate whether he or she received an opioid prescription and whether he or she experienced an adverse clinical outcome during that year. Adverse clinical outcomes were categorized as accidents resulting in wounds or injuries, opioid-related accidents and overdose, alcohol- and nonopioid drug-related accidents and overdose, self-inflicted injuries, and violence-related injuries.

Of the veterans with pain diagnoses, 15,676 (11%) received prescription opioids for 20 or more consecutive days. Veterans with mental health diagnoses but not PTSD (eg, depression, anxiety, and traumatic brain injury) were significantly more likely to receive opioids for pain, compared with veterans without mental health diagnoses. Veterans with PTSD diagnoses were significantly more likely to be prescribed opioids than were veterans with non-PTSD mental health diagnoses. Of note, the researchers say, veterans with a drug use disorder and comorbid PTSD were more likely to be prescribed opioids than veterans with no mental health disorders (34% vs 7%).

Compared with veterans without mental health diagnoses, veterans with PTSD were more likely to be prescribed high doses of opioids (23% vs 16%), more than 1 type of opioid concurrently (20% vs 11%), and concurrent sedative hypnotics (41% vs 8%). They were also more likely to be prescribed opioids for longer than the median duration of 2 months and to obtain early opioid refills.

All the veterans with mental health disorders who were prescribed opioids had roughly double the risk of emergency department or inpatient admissions for alcohol-, drug-, and opioid-related accidents and overdoses; and self-inflicted and violence-related injuries. With the exception of wounds and injuries, the risk was highest among veterans with PTSD.

The researchers note that 2 other studies have also found higher rates of prescription opioid use in patients with PTSD, particularly those with the highest symptom severity scores. Other researchers have observed that patients with PTSD have dysregulation of the endogenous opioid system through lower pain thresholds and lower endogenous opioid levels. Treatment with opioids may cause or exacerbate substance abuse and worsen mental health problems.

Studies have shown that veterans with mental health problems tend to use VA primary care rather than specialized mental health treatment. In this study, 77% of opioids were prescribed by VA primary care clinicians. However, most VA primary care clinicians lack specialized training in the management of comorbid pain and PTSD, the researchers say. Faced with a patient in a "poorly differentiated state of mental and physical pain," with high-risk medical and psychiatric comorbidity, the physician may prescribe high-dose, high-risk opioids for the very patient who cannot handle them. Instead, the authors suggest, these patients may benefit from nonpharmacologic therapies and nonopioid analgesics, as well as integrated treatments that target both mental and physical pain simultaneously.

Source: Seal KH, Shi Y, Cohen G, et al. *JAMA.* 2012;307(9):940-947. doi: 10.1001/jama.2012.234.

The Effect of Weight on Vasopressin Therapy

The standard method of administering vasopressin by a fixed dose may be putting some patients at risk, say researchers from Sinai-Grace Hospital, Detroit, Michigan, and University of Michigan, Ann Arbor. Their retrospective study of 64 patients with septic shock demonstrates that a patient's weight may significantly alter the way the drug works. Some patients may not be receiving an optimum dose and are being exposed to either increased

risk of toxicity or ineffective therapy.

The study was designed to determine the short-term effects of vasopressin on other vasopressor dosing requirements, and whether those are related to body weight. Secondary objectives included evaluation of blood pressure (BP) and heart rate after the start of vasopressin infusion. The primary outcome was the relationship between the change in catecholamine vasopressor dosing requirements at 0 h, 2 h, and 4 h (compared with baseline –1 h and vasopressin dosing adjusted for body weight (using the patient's actual weight).

Sixty patients were receiving norepinephrine monotherapy at the time of vasopressin initiation. Three were receiving norepinephrine with dopamine, epinephrine, or phenylephrine. One patient was on dopamine monotherapy.

Most of the patients received vasopressin at a dose of 0.04 U/min. Three patients received doses of 0.02 U/min, 0.03 U/min, and 0.033 U/min. The weight-adjusted dosing range of vasopressin in the patients was 0.229-0.871 µU/kg per minute—nearly a 4-fold difference, the researchers noted.

Changes in vasopressor dosing were significantly correlated with weight-adjusted vasopressin at 2 h and 4 h. Use of vasopressin was associated with significant increases in systolic BP, diastolic BP, and mean arterial pressure at each time point compared with baseline. Heart rate was significantly reduced at hours 2 and 4, when compared with the previous time point.

The researchers note that vasopressin is metabolized primarily in the liver and kidneys, does not bind to plasma proteins, and distributes widely through the extracellular fluid. Thus, they point out, the disposition of vasopressin in patients with varying weights, who receive aggressive fluid resuscitation, suggests that weight-adjusted vasopressin dosing may be an important consideration.

Source: Miller JT, Welage LS, Kraft MD, Alaniz C. *J Crit Care.* 2012;27(3):289-293. doi: 10.1016/j.jcrc.2011.06.018.

Diuretics and Cognitive Function in Elders

Potassium-sparing diuretics may have a neuroprotective effect in older patients, according to a post hoc analysis of the Ginkgo Evaluation of Memory (GEM) Study. Although the associations were modest, they were highly significant and selective, say researchers from Johns Hopkins University, Baltimore, Maryland; University of Washington, Seattle, Washington; Columbia University Mailman School of Public Health, New York, New York; University of California, Irvine, California; Wake Forest University, Winston-Salem, North Carolina; and University of Virginia, Charlottesville, Virginia.

Many trials have investigated the effects of antihypertensive medications on cognitive function—with "mixed results," the researchers say: Some showed angiotensin-converting enzyme inhibitors (ACE-I) and diuretics had protective effects; others showed no effects of ACE-Is, thiazide diuretics, or angiotensin II receptor blockers (AT2RBs). However, the researchers of the current study point out that those earlier studies could not specify the type of antihypertensive medications, and cognitive function was often a secondary endpoint.

This study is an extension of earlier work, in which the researchers observed that diuretic and ACE-I use for more than 3 years was selectively associated with reduced incidence of impairment in memory and executive function.

Of the 2,707 participants aged ≥ 75 years included in the analysis, 53% reported using antihypertensive medications. Of those, 17% were using a diuretic, 11% an ACE-I, 2% an AT2RB, and 21% other antihypertensives.

Diuretic use was associated with better verbal learning and memory when compared with the nondrug group. No association was found between loop or thiazide diuretics and cognitive functions. However, when diuretics were classified according to potassium-sparing and potassium-nonsparing, potassium-sparing diuretics were found to better enhance performance on verbal learning and memory.

By contrast, the researchers found no differences in any of the 6 cognitive outcomes between participants receiving either ACE-Is or AT2RBs and participants not receiving those drugs when compared with the nondrug or the "other antihypertensive drug" groups.

Source: Yasar S, Lin F-M, Fried LP, et al; Gingko Evaluation of Memory (GEM) Study Investigators. *Alzheimers Dement.* 2012;8(3):188-195. doi: 10.1016/j.jalz.2011.03.010.

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