Case in Point

Safe Use of Buprenorphine/Naloxone in a Veteran With Acute Hepatitis C Virus Infection

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As the number of veterans with multiple injuries and hepatitis C virus increases, these clinicians address concerns regarding the best course of treatment while considering opioid abuse disorders, liver safety, and mental health disorders.

Prescription opioid use disorders are the fastest growing type of drug use disorders in the United States.[1] All federal practitioners are treating increasing numbers of returning Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans. A number of these veterans have sustained multiple combat injuries, and their injury-related painful conditions have made them candidates for opioid therapy.

Edlund and colleagues[2] studied the risk factors for opioid abuse and dependence among veterans using opioids for chronic noncancer pain and found mental health disorders to be a more significant risk factor than nonopioid substance abuse. They also found that young men who had had a larger supply of prescription opioids dispensed were at higher risk for opioid abuse/dependence. Similar studies in nonveteran populations have had consistent results,[3,4] thus making these young returning veterans a vulnerable population.

Hepatitis C virus (HCV) seropositivity is prevalent among people with opioid addictions. An estimated 4 to 6 million people are infected with HCV in the United States, with at least 60% of them being addicted to opioids.[5] Thus, liver safety is of prime concern in this population.

In the United States, buprenorphine/naloxone has been in use for managing opioid dependence disorders since 2002.[6] The unique pharmacologic profile of this medication makes it an ideal treatment option in some ways. Given its safety, efficacy, and convenient use in comparison with methadone, it is now increasingly being used for first-line management in opioid dependence.[7] However, safety concerns have been raised for patients with liver dysfunction. In early reports on adverse effects of buprenorphine, increases in both aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were statistically higher in patients with preexisting HCV infection than in patients without such a history.[8] The increase in AST was dose related.[8] Buprenorphine has caused liver dysfunction in patients with HCV infection, particularly after intravenous administration.[9,10]

In a case series, 4 patients who were identified as having acute HCV infection at screening for treatment tolerated buprenorphine well, despite markedly elevated initial transaminase levels.[11] The investigators in that series even noted an improvement in the transaminases—suggesting that abnormal liver function tests and acute HCV infection should not preclude treatment with buprenorphine.

In a recent report on liver safety and HCV data from a trial involving adolescent and young adult patients who were undergoing treatment with buprenorphine—a trial completed through the National Institute on Drug Abuse (NIDA) Clinical Trials Network—investigators found that 28 of the 152 patients were HCV-positive at baseline, and 4 of the 28 seroconverted within 12 weeks.[12] Although HCV status was a significant predictor of transaminase elevation, no evidence of hepatotoxicity of bu-

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prenorphine was found in the exploratory analysis. This finding suggests that stabilization with buprenorphine may decrease the incidence of transaminase abnormalities associated with HCV in opioid-dependent young people.

In this article, we report the case of a 27-year-old OIF veteran who was in the U.S. Army 82nd Airborne Division from 2001 to 2004. While serving as a gunner in Iraq for 10 months, he was subjected to bomb and rocket-propelled grenade explosions, a vehicle accident, and a fall. This veteran had a history of multiple fractures, including fractures of both wrists, the left clavicle, and the left humerus.

In September 2009, he presented to the Buprenorphine Clinic at the VA Medical Center in Salem, Virginia, with a history of prescription pain pill (oxycodone, acetaminophen/hydrocodone, acetaminophen/oxycodone) abuse of more than 5 years' duration. He used these pills on and off and then continually for 1 year after the most recent wrist fracture.

He also had a history of short-term intravenous heroin use. In addition, he had a history of heavy drinking while in the service and sporadic current drinking, daily use of marijuana in the teen years, experimental use of hallucinogens and amphetamines, and current abuse of benzodiazepines. His history included re-experiencing, hypervigilance, and constant anxiety—consistent with subthreshold posttraumatic stress disorder (PTSD). Overlapping depressive symptoms were also present. There was no history of psychiatric hospitalization or suicide attempts. The patient had a family history of alcohol and substance use (both parents were alcoholics). He was single, never married, unemployed, and living with grandparents at the time of presentation. He had been started on citalopram 20 mg/d for anxiety symptoms by his primary care physician 2 weeks before presenting to the Buprenorphine Clinic.

Table. Enzyme levels and viral markers at baseline and follow up

Liver enzymes/viral markers	Baseline	1 month	6 months
Aspartate aminotransferase, U/L	166	69	26
Alanine aminotransferase, U/L	73	40	26
Hepatitis C virus antibody	Reactive	Not done	Not done
Hepatitis C virus genotype	Not done	1	Not done
Hepatitis C virus RNA	Not done	9120	Undetectable

Through routine baseline laboratory investigations before enrollment in the clinic, the patient was found to be positive for HCV antibody. He stated that he had never been tested for HCV infection and that he suspected he had contracted it during intravenous heroin use. The only symptom of acute HCV infection was abdominal pain.

Three months after starting buprenorphine, the patient was seen in the gastroenterology clinic for management of acute HCV infection. Ribavirin and pegylated interferon were started, but he could not tolerate them and discontinued them after 1 week. The abdominal pain gradually subsided. For more than 1 year afterward, he was maintained on buprenorphine 16 mg/naloxone 4 mg and received citalopram 20 mg/d for anxiety and depressive symptoms. He continued to do well. He was adherent, remained abstinent, and was working full-time. With use of buprenorphine, he noted mild improvement in pain.

DISCUSSION

In our patient's case, we see safe use of buprenorphine in the setting of acute HCV infection and, in fact, lowering of transaminases (see Table). It is important for primary care physicians and addiction psychiatrists who are treating patients in these populations to be aware of the current physician clinical support system (PCSS) guidelines for buprenorphine based on observational studies.[13] Recommended in these guidelines are obtaining complete liver and HCV laboratory test results at baseline (before starting treatment with buprenorphine), periodically monitoring liver function tests, looking for signs of hepatotoxicity, and, if hepatotoxicity develops, considering a lower dose or discontinuing buprenorphine and consulting with gastroenterology or hepatology. Following these guidelines would ensure that patients with abnormal liver function and acute HCV infection are not excluded from treatment.

Family and personal history of nonopioid drug use, combat-related trauma, use of narcotic pain medications, and subsyndromal PTSD all contributed to this patient's opioid dependence. This situation again raises concerns of whether it is justified to use narcotic pain medications to manage noncancer-related pain conditions, particularly in young people. In addition, use of buprenorphine for comorbid opioid dependence and pain syndromes may be preferable to use of pure opioid agonists. Limited evidence exists to sup-

port use of sublingual buprenorphine for pain conditions, though sublingual buprenorphine has been found useful in opioid-induced hyperalgesia in human pain models.[14]

Large, multicenter studies are needed to fully understand the nature and impact of comorbidities in OEF/OIF veterans. The VHA and the National Institutes of Health are collaborating to investigate several of these questions, and a study funded by NIDA through the Central Arkansas Veterans Healthcare System and the University of Arkansas is being conducted on opioid use among OEF/OIF veterans.[1]

Author disclosures

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