3. Zacny J, Conley K, Galinkin J. Comparing the subjective, psychomotor and physiologic effects of intravenous buprenorphine and morphine in healthy volunteers. *J Pharmacol Exp Ther*. 1997;282(3):1187-1197.
4. Jensen M, Sjogren P, Upton RN, et al. Pharmacokinetic-pharmacodynamic relationships of cognitive and psychomotor effects in intravenous buprenorphine infusion in human volunteers. *Basic Clin Pharmacol Toxicol*. 2008;103(1):94-101.
5. Messinis L, Lyros E, Andrian V, et al. Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy. *Hum Psychopharmacol*. 2009;24(7):524-531.

http://dx.doi.org/10.1016/j.mayocp.2012.06.010

Buprenorphine Maintenance Therapy in Opioid-Addicted Health Care Professionals Returning to Clinical Practice

To the Editor: Hamza and Bryson[1] argue against health care professionals returning to clinical practice while taking buprenorphine, based on purported neurocognitive effects. Their argument is based on weak science and flawed assumptions. Studies examining neurocognitive effects associated with buprenorphine are mostly based on small, selected samples and frequently fail to account for preexisting neurocognitive function or to distinguish between short- and long-term effects (after development of full tolerance) of the drug. Most studies use weak, ie, nonrandomized study designs. None of the studies was based on health care professionals. These limitations preclude firm conclusions regarding the presence or absence of neurocognitive effects associated with buprenorphine.

More important, the impact of purported neurocognitive effects on job performance is not clear. Laboratory tests that show subtle effects cannot be extrapolated to real work performance. This would require direct measures of job task performance after long-term use of the drug—ideally using randomized study designs.

Furthermore, many factors affect neurocognitive performance. Examples include baseline ability, age, previous head injury, impaired sleep, chronic illness, viral infection, and many commonly prescribed medications (including those that are not controlled). Thus, even if buprenorphine is shown through scientifically valid studies to have meaningful effects on neurocognitive performance after long-term use, it would be wrong to single out health care professionals taking this medication. Rather, the same standards for evaluation of neurocognitive performance would have to be uniformly applied to all health care professionals regardless of the cause for any decrement in performance. It is doubtful that most health care organizations are prepared to undertake such mass neurocognitive screening given its high costs and uncertain benefit.

Kevin Fiscella, MD, MPH
Department of Family Medicine, Community and Preventive Medicine, and Oncology
University of Rochester
School of Medicine and Dentistry and Wilmot Cancer Center
Rochester, NY

1. Hamza H, Bryson EO. Buprenorphine maintenance therapy in opioid-addicted health care professionals returning to clinical practice: a hidden controversy. *Mayo Clin Proc*. 2012;87(3):260-267.

http://dx.doi.org/10.1016/j.mayocp.2012.04.008

In reply: We read with great interest the Letters to the Editor written in response to our article discussing the use of buprenorphine maintenance therapy in opioid-addicted health care professionals, and we are encouraged by the discussion that continues to evolve around this important issue. We are pleased that our review has generated so much conversation from those on the front lines of addiction medicine and welcome the opportunity to reply to the letters from Drs Earley, Newman, Selzer and Stancliff, and Fiscella.

Regarding the quality of research reviewed, Dr Fiscella asserts that our conclusions are based on "weak science and flawed assumptions," citing small sample size, nonrandomized study design, and failure to account for the possibility of preexisting neurocognitive deficits among other limitations as reasons to support his position that buprenorphine use should not preclude one from a return to clinical practice after treatment for substance abuse. Dr Fiscella also asserts that, because none of these studies were performed with actual health care professionals, any conclusions regarding the presence or absence of neurocognitive effects cannot be extrapolated to this group. Although we agree that the available studies have limitations, they hardly qualify as "weak science," and the concerns that he raises are not based in fact. Dr Fiscella claims that the studies were not randomized, yet the studies that we cited performed by Soyka et al in 2005[1] and 2008[2] and by Mintzer et al in 2004[3] did, in fact, use a randomized, double-blind design. Dr Fiscella claims that the studies fail to distinguish between long- and short-term maintenance therapy, but it is unclear what he means by this. The 2008 study by Jensen et al[4] evaluated single-dose effects, whereas the 2004 study by Mintzer et al[3] looked at dosage differences with study participants taking a particular dose for 7 to 10 days with performance assessment at 3 different time points, and the 2009 study by Messinis et al[5] evaluated participants who had been taking buprenorphine for 18 to 28 weeks. The results of these and the other studies included in our review, regardless of the design, are very consistent. Each of the peer-reviewed and published studies cited in our article reported similar disadvantageous effects on neurocognitive performance when patients were under the influence of buprenorphine. Whether undergoing short- or long-term therapy, healthy volunteers and recovering addicts alike demonstrated evidence of impairment. This in and of itself is troubling and, as was clearly stated in our article,[6] we believe that further studies need to be conducted that specifically examine the influence of buprenorphine on the ability of health care professionals to perform tasks directly related to their roles as clinicians.

Drs Selzer and Stancliff seem to suggest that we chose to include only poorly designed studies to support our conclusion that caution should be used when prescribing buprenorphine in this population. In fact, we reviewed all of the published literature on the topic and came to the same conclusion as Drs Selzer and Stancliff did: the literature on the topic of the cognitive effects of buprenorphine is limited and more research is needed. This view is shared by Dr Earley and others, who echo the need for more definitive research. Weakness in the existing literature

should underscore the need for caution, not serve as a call to press forward. We challenge Drs Selzer and Stancliff and others who are actively involved in the treatment of addicted health care professionals to design and conduct better studies to fill the current knowledge gap. Until then, we stand by our recommendation that caution should be the default position.

Regarding our study design, Drs Selzer and Stancliff suggest that our skills in engaging the representatives of the various professional health programs is somewhat lacking. Although Drs Selzer and Stancliff responded to our initial e-mail query immediately and shared their program's policies and practices without hesitation, this was unfortunately not the case with representatives from every program. Multiple attempts were made to obtain this information, but when these attempts were (in some cases) met with referral to legal counsel, we took this as an indication that the programs did not wish to share their policies. Regarding "secretive practices," these actions speak for themselves. If the table we composed is not clear enough, perhaps this is due to the constraints inherent with concisely describing the various and sundry policy statements from 51 different locations. It would seem that this is further evidence that the time has come to introduce a single set of policies shared by all states and districts.

The comment of Drs Selzer and Stancliff that "much in this article is informed by bias rather than science" deserves a direct reply. The use of the word bias in this context implies that a conflict of interest exists and that one or both of us may stand to benefit in some way from the decreased use of buprenorphine in the (relatively small) population of health care professionals who are maintained with this drug. Because the ability to prescribe this drug is the source of considerable income for some, we feel the need to strongly reaffirm that this is not the case with us. Neither of us has any interest, financial or otherwise, in the promotion or detraction of buprenorphine's use in the treatment of persons addicted to opioids. According to the Drug Addiction Treatment Act, the ability to prescribe buprenorphine for the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements and who have notified the Secretary of Health and Human Services of their intent to prescribe this product for the treatment of opioid dependence. Physicians must become certified to prescribe buprenorphine[7,8] for treatment of opioid dependence, after which they are assigned a unique identification number that must be included on every prescription written for this purpose. We are not certified to prescribe this drug and do not benefit from its use in any manner. We agree that buprenorphine has a legitimate use in addiction treatment, but, as pointed out by Dr Earley, it hardly makes sense to use it in this population of health care professionals when the proven track record of abstinence-based therapy is so strong.

Regarding our conclusions, Dr Fiscella proposes that even if buprenorphine is found to have significant neurocognitive effects, it would be "wrong" to disallow its use in health care professionals who wish to practice clinically. He even goes so far as to suggest that to require neurocognitive testing before return to clinical practice would be cost prohibitive. This assertion is irrational, is dangerous, and minimizes the important role that health care workers have in our modern health care system. If we do not allow an individual under the influence of opioid maintenance therapy to pilot a plane or drive a school bus or tractor trailer, why then is it wrong to suggest that we should take a closer look at the practice of allowing a surgeon or an anesthesiologist to perform surgery or provide anesthesia while taking buprenorphine? We believe it is both self-serving for the medical practitioner in recovery and somewhat irrational from a neurophysiologic perspective to argue that an individual who is managing addiction and requires opioid maintenance therapy should not be held to the same high standards as workers in other safety-sensitive positions.

We strongly disagree with Dr Fiscella's assertion that the absence of direct evidence should be a reason to continue the practice of allowing health care professionals to practice while maintained with buprenorphine until it is deemed unsafe. Lack of evidence of effect is not the same as lack of effect. In the interest of patient safety we believe that the more conservative and thoughtful approach would be to first conduct appropriate investigations to determine whether the practice is safe before allowing an individual to practice while taking this drug. Given the extremely high success rates of abstinence-based recovery programs for health care professionals, as pointed out by Dr Earley, we believe that asking a trained nurse or physician to discontinue opioid maintenance therapy before returning to clinical practice is hardly draconian. We find it difficult to accept the assertion that individuals have some form of right to return to clinical practice under the influence of this drug when to do so has the potential to significantly affect patient safety.

Unfortunately, it appears that Dr Newman has missed the point of our review altogether. He suggests that we somehow "reject" the use of buprenorphine when it comes to colleagues who want and need the help of this drug, but this is not at all the case. What we reject is the assertion that buprenorphine is some kind of "magic bullet" that has no negative or unintended effects. We accept that for some people maintenance therapy is the only option and that there will always be some patients who are unable to abstain from drugs of abuse without it, but just because a therapy works doesn't mean it is without adverse effects. He points out that maintenance treatment of addiction has been strongly endorsed by the highest governmental authorities, yet fails to point out that these same authorities limit the activities that may be performed by patients while they are undergoing this very same maintenance therapy. Are we then to accept that providing medical care requires less attention to detail than driving a bus?

Dr Newman believes that our recommendation that health care professionals maintained with buprenorphine not be allowed to return to clinical practice until it is determined that they are not cognitively impaired is unreasonable, but he fails to acknowledge that this is the majority position of the individual physician health programs and nursing programs we queried. Dr Newman suggests that we might very well extend this policy to those taking benzodiazepines, opioids, or other medications for reasons other than maintenance therapy, as if the indication for

which a drug is prescribed somehow lessens its effect. Although this statement may have been made tongue-in-cheek, we do not believe that it is an unreasonable policy to promote when the outcome can only increase patient safety. We therefore stand by our recommendation that when the patient is an individual whose job performance has the potential to adversely affect others, it is reasonable to make sure he/she is not impaired before returning to work.

Ethan O. Bryson, MD
Department of Anesthesiology
Mount Sinai Hospital
New York, NY

Heather Hamza, CRNA, MS
Department of Anesthesiology
Los Angeles County Medical Center at the University of Southern California
Los Angeles

1. Soyka M, Hock B, Kagerer S, Lehnert R, Limmer C, Kuefner H. Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients. *J Clin Psychopharmacol*. 2005;25(5):490-493.
2. Soyka M, Lieb M, Kagerer S, et al. Cognitive functioning during methadone and buprenorphine treatment: results of a randomized clinical trial. *J Clin Psychopharmacol*. 2008;28(6):699-703.
3. Mintzer MZ, Correia CJ, Strain EC. A dose-effect study of repeated administration of buprenorphine/naloxone on performance in opioid-dependent volunteers. *Drug Alcohol Depend*. 2004;74(2):205-209.
4. Jensen ML, Sjogren P, Upton RN, et al. Pharmacokinetic-pharmacodynamic relationships of cognitive and psychomotor effects in intravenous buprenorphine infusion in human volunteers. *Basic Clin Pharmacol Toxicol*. 2008;103(1):94-101.
5. Messinis L, Epameinondas L, Andrian V, et al. Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy. *Hum Psychopharmacol*. 2009;24(7):524-531.
6. Hamza H, Bryson EO. Buprenorphine maintenance therapy in opioid-addicted health care professionals returning to clinical practice: a hidden controversy. *Mayo Clin Proc*. 2012;87(3):260-267.
7. Buprenorphine: Physician and Treatment Locator. SAMHSA Web site. http://buprenorphine.samhsa.gov/bwns_locator/. Accessed June 11, 2012.
8. Suboxone (buprenphine). Getting certified. http://www.suboxone.com/hcp/certification/Default.aspx. Accessed June 11, 2012.

http://dx.doi.org/10.1016/j.mayocp.2012.06.006

Why Vitamin D Status Should Be Checked in Patients With Nonalcoholic Fatty Liver Disease

To the Editor: In an excellent clinical vignette in the January 2012 issue of *Mayo Clinic Proceedings*, Nelsen et al[1] discussed the diagnosis and management of patients with nonalcoholic fatty liver disease (NAFLD). We suggest that in patients with this hepatic manifestation of the metabolic syndrome, vitamin D status should also be considered.

In addition to its traditional calcium-related effects on the skeleton, vitamin D deficiency has now been recognized to exert nonskeletal adverse effects on several other organ systems. Hypovitaminosis D is highly prevalent in the United States and around the world. In particular, it reaches a peak of 75% in patients with metabolic syndrome.[2] In this setting, it has been found that patients with biopsy-proven NAFLD had a significantly higher prevalence of hypovitaminosis D (defined as a serum vitamin D concentration of ≤37.5 nmol/L) and markedly lower 25-hydroxyvitamin D (25[OH]D) levels (the best estimates of overall vitamin D status level) than matched controls.[3] The 25(OH)D concentrations were lower in individuals with nonalcoholic steatohepatitis than in those with simple steatosis and inversely associated with the severity of liver histology among NAFLD patients, after adjustment for a broad spectrum of potential confounders. Interestingly, a strong independent association between low 25(OH)D levels and NAFLD has also been found in a population of adults without signs of severe liver damage.[4] This association was independent of diabetes, dyslipidemia, and insulin resistance.

Although the cross-sectional design of these studies[3,4] does not allow establishment of a causative nature of the associations between hypovitaminosis D and NAFLD, the linear inverse correlation between serum 25(OH)D levels and the degree of NAFLD suggests that vitamin D may exert a dose-dependent effect of fat accumulation in hepatocytes. Several mechanisms may explain a causal role of vitamin D deficiency in the development of NAFLD and nonalcoholic steatohepatitis. In fact, vitamin D is capable of reducing free fatty acid–induced insulin resistance both in peripheral tissues and in hepatocytes.[4] Moreover, vitamin D exerts an immunomodulatory action by suppressing fibroblast proliferation and collagen production,[5] which may be particularly important in the evolution to cirrhosis.

Therefore, although intervention trials are warranted to evaluate whether vitamin D supplementation may be a means to prevent and/or treat patients with NAFLD, we believe that vitamin D status should be checked in individuals with liver steatosis.

Luca Mascitelli, MD
Comando Brigata Alpina "Julia"
Medical Service
Udine, Italy

Mark R. Goldstein, MD, FACP
Fountain Medical Court
Bonita Springs, FL

William B. Grant, PhD
Sunlight, Nutrition, and Health Research Center
San Francisco, CA

1. Nelsen EM, Newman DB, Sweetser S. 52-Year-old man with liver enzyme abnormalities and elevated ferritin level. *Mayo Clin Proc*. 2012;87(1):94-97.
2. Pinelli NR, Jaber LA, Brown MB, Herman WH. Serum 25-hydroxy vitamin D and insulin resistance, metabolic syndrome, and glucose intolerance among Arab Americans. *Diabetes Care*. 2010;33(6):1373-1375.
3. Targher G, Bertolini L, Scala L, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis*. 2007;17(7):517-524.
4. Barchetta I, Angelico F, Del Ben M, et al. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. *BMC Med*. 2011;9:85.
5. Artaza JN, Norris KC. Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. *J Endocrinol*. 2009;200(2):207-221.

http://dx.doi.org/10.1016/j.mayocp.2012.02.026

In reply: Vitamin D and its relationship to nonalcoholic fatty liver disease (NAFLD) has become of recent interest as studies have linked low serum 25(OH)D levels with NAFLD. The potential therapeutic role of vitamin D supplementation in NAFLD is an intriguing concept given its