8. Nyhuis PW, Gastpar M, Scherbaum N. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. *J Clin Psychopharmacol*. 2008; 28:593–595.
9. Karp JF, Butters MA, Begley AE, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. *J Clin Psychiatry*. 2014;75:e785–e793.
10. Skolnick P. The opioid epidemic: crisis and solutions. *Annu Rev Pharmacol Toxicol*. 2018; 58:143–159.
11. Stoll AL, Rueter S. Treatment augmentation with opiates in severe and refractory major depression. *Am J Psychiatry*. 1999; 156:2017.
12. Williams NR, Schatzberg AF. NMDA antagonist treatment of depression. *Curr Opin Neurobiol*. 2016;36:112–117.
13. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011;475:91–95.
14. Preskorn SH, Baker B, Kolluri S, et al. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol*. 2008; 28:631–637.
15. Pacheco Dda F, Romero TR, Duarte ID. Central antinociception induced by ketamine is mediated by endogenous opioids and μ- and δ-opioid receptors. *Brain Res*. 2014;1562: 69–75.
16. Singh JB, Daly EJ, Mathews M, et al. Approval of esketamine for treatment-resistant depression. *Lancet Psychiatry*. 2020;7: 232–235.
17. Klein ME, Chandra J, Sheriff S, et al. Opioid system is necessary but not sufficient for antidepressive actions of ketamine in rodents. *Proc Natl Acad Sci U S A*. 2020;117: 2656–2662.
18. Dadiomov D. Dissociating the clinical role and economic value of intranasal esketamine. *J Manag Care Spec Pharm*. 2020;26: 20–22.

Treatment of Opioid Use Disorder Attributed to Fentanyl With High-Dose Buprenorphine
A Case Report

To the Editors:

Synthetic opioid-related deaths are largely being driven by illicitly manufactured nonpharmaceutical fentanyl (NPF) and fentanyl analogs, including alpha-methylfentanyl, acetylfentanyl, butyryl fentanyl, and carfentanil.[1] The landscape of NPF use has been rapidly changing; in 2017, 59% of all US opioid-related deaths involved fentanyl, compared with 14% in 2010.[2] Treatment of high-potency opioid use disorders involving NPF poses challenges to clinicians, as current guidelines are supported by research that did not include participants using high-potency synthetic opioids. Earlier studies examining μ-opioid receptor availability in the setting of lower potency opioid use and treatment with buprenorphine contributed to the development of opioid agonist dosing guidelines.[3,4] Fentanyl and its analogs have a higher affinity for μ-opioid receptors and are significantly more potent than heroin, and thus may require higher doses of buprenorphine for effective treatment.[1] Limited information is available in the published literature to guide medical decision making regarding the treatment of high-potency opioid use disorders with buprenorphine.[5] We present a case of a patient with opioid use disorder attributed to NPF who was successfully inducted onto high-dose buprenorphine/naloxone while admitted to an inpatient facility and remains engaged in outpatient treatment post-discharge.

CASE REPORT

A 29-year-old man with a history of opioid use, social anxiety, and electronic cigarette use was admitted voluntarily to an addiction treatment facility for inpatient management of opioid use disorder. The patient reported a 9-year history of illicit opioid use, which initially involved the use of oxycodone tablets (up to 600–900 mg daily). In the 6 months before admission, he endorsed daily use of intranasal NPF. He denied using prescription or over-the-counter medications and denied using any substances aside from NPF and nicotine leading up to his admission. He had never received pharmacotherapy for opioid use disorder. At 30 hours from his last use of NPF, the patient registered a Clinical Opioid Withdrawal Scale score of 13. He provided informed consent to undergo buprenorphine/naloxone induction for maintenance treatment of severe opioid use disorder. During his admission, the dose of buprenorphine/naloxone was increased to address opioid withdrawal and cravings. Despite receiving 24 mg of buprenorphine per day, he continued to experience opioid withdrawal, for which he was given as-needed non-opioid medications (Table 1). A total daily buprenorphine dose of 32 mg was necessary to fully suppress his opioid withdrawal and cravings, and non-opioid medications were discontinued while on this high-dose regimen. He was discharged and referred to an addiction medicine specialist for office-based opioid treatment. At 6 months post-discharge, he continues to be prescribed 32 mg/8 mg of buprenorphine/naloxone daily by his outpatient provider, with no reported use of NPF or other illicit opioids.

DISCUSSION

The effect of opioid addiction on American society has been substantial. The addition of buprenorphine products to the addiction provider's armamentarium has been of critical importance in combating the opioid epidemic. Indeed, it is for this reason that buprenorphine has been designated as an essential medication by the World Health Organization. With the passage of the Drug Addiction Treatment Act of 2000, qualified providers can prescribe buprenorphine in office-based settings, thereby freeing opioid agonist therapy from the requirement that it be dispensed in licensed opioid treatment programs (OTPs). An effect of this change in the law has been the expansion of the number of individuals with opioid addiction who have access to this evidence-based therapy in outpatient settings.

Buprenorphine is a semisynthetic opioid that is derived from thebaine, an alkaloid of the opium poppy. Buprenorphine functions as a high-affinity, low-efficacy μ-opioid receptor agonist as well as a high-affinity κ-opioid receptor antagonist, and it also binds to δ-opioid receptors and opioid receptor–like 1 receptors.[6] Maintenance doses of buprenorphine range from 4 to 24 mg per day. The maximum daily dose of buprenorphine recommended by the Food and Drug Administration (FDA) is 24 mg, and previous research demonstrated that dosages higher than 24 mg per day have not provided a clear therapeutic benefit on account of the ceiling effect associated with the partial agonist actions of buprenorphine.[7] This dosing recommendation has been echoed in Treatment Improvement Protocol 63: Medications for Opioid Use Disorder (published by the Substance Abuse and Mental Health Services Administration in 2020), which offers the recommendation that patients not responding to doses of buprenorphine at the upper limit approved by the Food and Drug Administration (ie, 24 mg per day) should be considered for methadone treatment. It is important to note, however, that the data relied on in determining these buprenorphine dosing guidelines did not include subjects using high-potency opioids, such as NPF. In their study published in 1996, Compton and colleagues[8] indicated that higher doses of buprenorphine may be required to stabilize certain patients. Also, there is a suggestion that the

TABLE 1. COWS Scoring, Total Daily Dosing of Buprenorphine/Naloxone, and Adjunctive Therapies

Day	COWS, AM	COWS, PM	Buprenorphine/Naloxone, Total Daily Dose, mg	Baclofen 10 mg PRN, No. Doses	Clonidine 0.1 mg PRN, No. Doses	Dicyclomine 20 mg PRN, No. Doses
0	13	12	8	3	2	3
1	6	5	8	1	2	1
2	9	2	8	3	2	4
3	15	8	20	3	2	3
4	9	7	20	3	3	3
5	9	3	24	2	1	2
6	3	6	24	2	2	2
7	3	3	32	0	1	0
8	1	3	32	1	1	0
9	0	1	32	0	0	0
10	1	-	16*	0	0	0

*Patient received AM dose of buprenorphine/naloxone before discharge.
COWS, Clinical Opioid Withdrawal Scale; PRN, as needed.

severity of opioid addiction may correspond to a higher dose of buprenorphine being necessary to effectively treat opioid use disorder.[9] Indeed, it is noted in the literature that patients using high doses of opioids require 90% μ-opioid receptor occupancy (corresponding to 5–6 ng/mL plasma concentration of buprenorphine) for optimal therapy, and not 70% (2–3 ng/mL plasma concentration) that is typically necessary for treatment of opioid use disorder associated with lower potency opioids; patients may need 32 mg of buprenorphine per day to achieve 90% receptor occupancy.[4,10] Given that the potency of NPF and its analogs is several times greater than the potency of heroin or oxycodone,[11] it is possible higher doses of buprenorphine may be needed to fully suppress cravings and withdrawal. Furthermore, research has revealed that 32 mg of buprenorphine produced no greater respiratory depression than 16 mg, and there is evidence that use of high-dose buprenorphine (32 mg per day) may induce less euphoria than lower doses (8–16 mg), which is relevant from an abuse potential standpoint.[12]

This case highlights the need for additional investigation into the effectiveness of buprenorphine doses exceeding 24 mg per day in treating opioid use disorder attributed to NPF. We concede that without a control for this case, the decrease in withdrawal symptoms could be attributed in part to the effect of time from last opioid use, because it is difficult to ascertain the degree to which the higher dose of buprenorphine was directly responsible for alleviating withdrawal. Nevertheless, if high-dose buprenorphine is effective in stabilizing patients, then the recommendation calling for patients not fully responding to buprenorphine 24 mg per day to be transitioned to methadone warrants reconsideration. Although the benefits of methadone therapy for opioid use disorder are beyond dispute, there are important advantages to buprenorphine over methadone. Buprenorphine, unlike methadone, can be prescribed in office-based practice and does not require enrollment in an OTP. Many individuals do not have easy access to OTPs, or they lack the ability to comply with OTP requirements (such as daily dosing visits). Also, many patients are better suited for buprenorphine therapy based on their medical/cardiac history or because of potential drug-drug interactions. Although we acknowledge that the potential for diversion increases with higher doses of buprenorphine being prescribed, strategies exist to mitigate this risk, such as prescribing combination buprenorphine/naloxone and not the buprenorphine monoproduct, utilizing random pill/film counts, and conducting opioid confirmation testing. Expecting individuals with opioid use disorder attributed to NPF to switch to a medication (methadone) that may not be accessible or in their best medical interest without first conducting a robust study of the utility of high-dose buprenorphine seems imprudent, because it may result in a group of patients being excluded from receiving a potentially beneficial and life-saving treatment.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest. Written consent was obtained from the patient.

Received July 25, 2020; accepted after revision September 27, 2020.

Michael H. Baca-Atlas, MD, FASAM
Department of Family Medicine
University of North Carolina
School of Medicine
Chapel Hill, NC

Joseph B. Williams, MD, FASAM
Department of Psychiatry
University of North Carolina
School of Medicine
Chapel Hill, NC
joseph_williams@med.unc.edu

REFERENCES

1. Armenian P, Vo KT, Barr-Walker J, et al. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. *Neuropharmacology.* 2018;134(Pt A): 121–132.
2. National Institute on Drug Abuse. Drug Facts – Fentanyl. 2019. Published online February 2019. Available online at: https://www.drugabuse.gov/publications/drugfacts/fentanyl. Accessed 09/09/2020.
3. Hillhouse M, Canamar CP, Doraimani G, et al. Participant characteristics and buprenorphine dose. *Am J Drug Alcohol Abuse.* 2011;37:453–459.
4. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend.* 2014;144:1–11.
5. Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. *Drug Alcohol Rev.* 2020;39: 135–137.

6. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med*. 2019;13:93–103.
7. Ciraulo DA, Hitzemann RJ, Somoza E, et al. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. *J Clin Pharmacol*. 2006; 46:179–192.
8. Compton PA, Wesson DR, Charuvastra VC, et al. Buprenorphine as a pharmacotherapy for opiate addiction: what dose provides a therapeutic response? *Am J Addict*. 1996;5: 220–230.
9. Fareed A, Vayalapalli S, Casarella J, et al. Treatment outcome for flexible dosing buprenorphine maintenance treatment. *Am J Drug Alcohol Abuse*. 2012;38:155–160.
10. Stanciu CN. The state of opioid medication assisted treatment (MAT). *J Alcohol Drug Depend*. 2018;6:e141.
11. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. *N Engl J Med*. 2017;377: 391–394.
12. Walsh SL, Preston KL, Stitzer ML, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther*. 1994;55:569–580.

Memantine for Behavioral Symptoms of Hepatic Encephalopathy Associated With Alcoholic Cirrhosis
A Case Report

To the Editors:

Hepatic encephalopathy (HE) is associated with severe liver damage such as fulminant hepatitis, cirrhosis, or portosystemic shunt. Although detailed mechanisms of brain neural dysfunction caused by liver failure remain unknown, it has been considered that ammonia metabolism is inhibited in liver failure, and excessive ammonia toxicity may lead to the onset of HE.[1] Patients with HE show a variety of neuropsychiatric abnormalities such as disorientation, mood disorder, personality change, and confusion. These behavioral symptoms of HE are often improved by treatment for HE itself, and there is no evidence-based treatment for aggression as a sequela.[2]

Memantine, a noncompetitive *N*-methyl-D-aspartate glutamatergic receptor (NMDAR) antagonist, is widely used for the treatment of Alzheimer disease (AD). Alzheimer disease is believed to be a neurodegenerative disease associated with neurocytotoxicity caused by excessive glutamate. The clinical effects of memantine are thought to be related to inhibition of NMDARs.[3,4] Recent studies suggest that hyperactivity of glutamatergic neural function also exists in alcohol dependence and HE.[5–7] It has been suggested that glutamate concentration in cerebrospinal fluid may be positively correlated with human aggression.[8] It has also been reported that memantine improves hyperammonemia-associated encephalopathy and acute HE[9] in rats, but not in humans.

Here, we report a case of a 70-year-old male patient with aggressive behavior as a sequela of HE. The patient was treated successfully with memantine.

CASE REPORT

A 70-year-old man was admitted to our neurology ward with impaired consciousness. The patient typically had a mild temperament but began drinking excessively after retirement. Despite a diagnosis of alcoholic cirrhosis at age of 63 years, he continued drinking excessively until the point of admission.

On admission, he had a temperature of 39°C, and his Glasgow Coma Scale score was 5 (eyes, 4; verbal, T; motor, 1). Laboratory tests revealed inflammatory activity and elevated levels of liver enzymes. A fluid-attenuated inversion recovery magnetic resonance imaging brain scan exhibited symmetrical high-signal abnormalities in the bilateral hippocampus, insular cortex, inferior frontal lobe, thalamus, midbrain, and cerebellar cortex (Fig. 1). In addition, symmetrical high-signal abnormalities in the pallidus on T1-weighted images were identified before hospitalization. An electroencephalogram revealed generalized slow waves and occasional triphasic waves.

The patient was diagnosed with progressive HE. He was treated with Aminoleban, antibiotics, and antiepileptic drugs including topiramate. His conscious state gradually improved, and his convulsive symptoms were controlled by treatment with these drugs. After a 2-month admission, he recovered and was transferred to another hospital for rehabilitation. However, he developed a sequela of aggression associated with his HE and could not continue the rehabilitation program.

After discharge, he was admitted to the psychiatric ward of our hospital. On admission, he was disoriented and could not follow instructions. He resisted treatment and was hostile toward others. Because of his aggressive behavior and agitated state, his cognitive function could not be assessed with the revised Hasegawa Dementia Scale or Mini-Mental State Examination. He was somnolent at night; however, during the daytime, he was angry and agitated by trivial events. At these times, he was violent to the point of throwing items.

On admission, we discontinued 200 mg/d of topiramate because of the possibility of worsening aggression. We started valproic acid treatment and eventually increased the dose to 600 mg/d while monitoring liver function. However, his aggression did not improve.

On day 28, we received consent for the use, and memantine treatment was started at 5 mg/d, later increasing the dosage to 20 mg/d. Throughout treatment, his psychiatric symptoms gradually improved and he became calm. His mood stabilized, and he responded positively to family visitations. However, his impaired cognitive function did not improve. On day 56, he was discharged. Because the patient had cognitive dysfunction associated with HE, we obtained verbal informed consent from his wife to publish this case report.

DISCUSSION

To our knowledge, this is the first case report in which memantine reduced

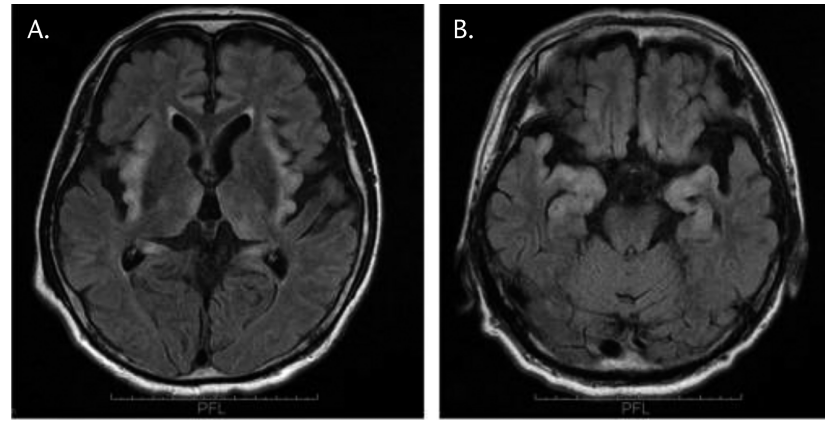

FIGURE 1. Fluid-attenuated inversion recovery—magnetic resonance imaging brain scan exhibited symmetrical high-signal abnormalities in the bilateral hippocampus, insular cortex, inferior frontal lobe, thalamus, midbrain, and cerebellar cortex.