Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (February 2020), 39, 135–137
DOI: 10.1111/dar.13017

BRIEF REPORT

High-dose buprenorphine for treatment of high potency opioid use disorder

MARLON DANILEWITZ[1,2] & MARK McLEAN[1,3]

[1]*British Columbia Centre on Substance Use, St. Paul's Hospital, Vancouver, Canada,* [2]*Department of Psychiatry, University of British Columbia, Vancouver, Canada, and* [3]*Department of Family Medicine, University of British Columbia, Vancouver, Canada*

Abstract

A 29-year-old woman presented to detox for treatment of an opioid use disorder with illicit fentanyl. While in detox, she was started on opioid agonist treatment with buprenorphine/naloxone. Unfortunately, she continued to have withdrawal symptoms despite being optimised to a dose of 32 mg. She was given additional PRNs of buprenorphine/naloxone to a total daily dose of 40 mg, which helped to alleviate her symptoms of withdrawal and cravings. She was stabilised on buprenorphine/naloxone 40 mg daily without any side effects and was discharged to a rehabilitation centre. [Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. *Drug Alcohol Rev* 2020;39:135–137]

Key words: opioid agonist therapy, buprenorphine, opioid use disorder, fentanyl.

Introduction

Over the last decades the prevalence and impact of opioid use disorders (OUD) have risen dramatically, reaching epidemic proportions in North America [1]. Treatment options for OUD include both pharmacologic and psychosocial options. Amongst medication strategies, buprenorphine has been identified as a first line therapy due to its therapeutic benefits in combination with optimal safety profile [2,3].

One factor implicated in the increasing number of non-fatal and fatal overdoses associated with opioids is the increased prevalence of use of high potency synthetic opioids [1]. At the same time, the current pharmacologic options for treating opioid use disorder are supported by research that primarily studied individuals with use disorders of lower potency opioids including oxycodone and heroin [4]. Product information from the maker of Suboxone, states that dosages higher than 24 mg/6 mg have not been demonstrated to provide any clinical advantage [5]. The results of these studies have informed clinical guidelines, leading to the identification of 32 mg and 24 mg as the daily maximum doses of buprenorphine/naloxone for treatment of OUD by the US Department of Health and Human Services and Health Canada, respectively [6,7].

Case

A 29-year-old homeless woman was seen at an inpatient medical detox centre in Vancouver, Canada. The woman had a 10-year history of illicit opioid use, which began with illicitly obtained oxycodone pills, shifting to smoking heroin and recently fentanyl. On average, in the weeks leading to her presentation, she reported smoking fentanyl multiple times a day with a total daily dose between 0.3 and 0.8 g, with her last reported use occurring the evening prior to admission.

In the past, she had been stabilised for significant periods of time on opioid agonist treatment. After 2 years of using illicit oxycodone, she reported a successful period on methadone maintenance treatment for almost 5 years on a daily dose of 80 mg. Subsequently, she sustained a relapse to heroin use and was later stabilised on buprenorphine/naloxone at a daily

Marlon Danilewitz MD, Addiction Medicine Fellow, PGY5 Psychiatry, Mark McLean MD MSc FRCPC, Physician Lead, Addiction Medicine Consult Team and Addiction Medicine Physician. Correspondence to Dr Marlon Danilewitz, University of British Columbia, Addictions Medicine Fellow BC Centre on Substance Use, Vancouver, BC, Canada. Tel: +778 988 8744; E-mail: marlondanilewitz@gmail.com

Received 11 June 2019; accepted for publication 31 October 2019.

dose of 8 mg/2 mg for several months, before relapsing to heroin and then transitioning to fentanyl use over the last 2 years. At admission, her urine was positive for cocaine and fentanyl, and her repeat urine 3 days into her admission was positive only for fentanyl, which was the most prevalent illicit opioid detected in urine drug screens in our region at that time [8].

At admission, she presented with significant withdrawal symptoms, and after discussion with the patient, she elected for a trial of buprenorphine/naloxone given the greater ease in obtaining carries and improved safety profile. Given her presentation with elevated withdrawal symptoms, it was decided to pursue a traditional induction protocol for stabilising the patient. On induction day 1, she received a total of 16 mg buprenorphine/naloxone in divided doses, and the intensity of her withdrawal decreased from 14 at the start of the day to 12 after her final dose. On induction day 2, she was administered 16 mg of buprenorphine/naloxone with additional PRNs of buprenorphine/naloxone, reaching a total 30 mg of buprenorphine/naloxone, which decreased her withdrawal, yielding a significant reduction in her Clinical Opiate Withdrawal Scale (COWS) score from 11 at the start of the day to 5 after her final dose. On induction day 3, her dose was increased to 24 mg of buprenorphine/naloxone with additional PRNs, in total receiving 32 mg buprenorphine/naloxone on day 3, helping to further alleviate her withdrawal, and which was associated with her COWS score decreasing from 7 to 2 over the day. On day 4, her dose of buprenorphine/naloxone was consolidated to a dose of 32 mg. While her dose of buprenorphine/naloxone had been optimised, she continued to experience significant withdrawal symptoms, and her COWS score rose post-dose from 4 to 6. Given the patient's withdrawal symptoms, a decision was made in collaboration with the patient to offer her two additional 4 mg buprenorphine/naloxone doses. After each dose, she continued to report feeling better. In total on day 4 she received a total of 40 mg of buprenorphine, which along with symptomatic improvement was associated with her final COWS score decreasing to 3. From that time forward, she continued to receive a daily total of 40 mg of buprenorphine, noting an improvement in withdrawal symptoms, most chiefly joint aches, flushing sensations, and cravings and with a 40 mg dose of buprenorphine. Ultimately, she was discharged to a rehabilitation centre on a dose of 40 mg of buprenorphine/naloxone daily.

Discussion

The case highlights the management of a woman with severe OUD, including use of fentanyl. Her case is unique in that she continued to demonstrate symptoms of opioid withdrawal on the Canadian maximum daily dose of 24 mg buprenorphine/naloxone and the US maximum dose of 32 mg buprenorphine/naloxone. To address her ongoing withdrawal symptoms, her dose of buprenorphine/naloxone was then increased to 40 mg daily to help manage her withdrawal symptoms and cravings. She was stabilised on 40 mg buprenorphine/naloxone without any adverse events.

The current research on opioid replacement reflects studies involving populations that were primarily using heroin [4]. The determination of the maximum daily dosage of buprenorphine/naloxone does not reflect the current state among opioid users in many regions across North America. The rapid rise in mortality rates attests to the significance of this change in the opioid use landscape [1,9]. Fentanyl is a synthetic μ opioid receptor full agonist that is associated with strong analgesic and euphoric effects. Modifications to fentanyl's piperidine ring has allowed for the development of potent derivatives including carfentanil and lofentanil [10]. Experts note that fentanyl and carfentanil are 50 and 5000 times as potent as heroin respectively [11]. A factor in the increased potency of fentanyl and other synthetic opioids is their higher binding affinity in comparison to prescription opioids like oxycodone, possibly contributing to the potential need for higher doses of buprenorphine/naloxone [12]. As a result of the change in drug landscape clinicians have been employing new strategies to help patients including non-traditional and rapid induction protocols among other strategies [13]. The case under discussion highlights this shift in drug patterns. The patient's previous drug use patterns consisted of daily usage of oxycodone and heroin, and during this pattern of use she had been stabilised on a low dose of buprenorphine/naloxone of 8 mg/2 mg.

Research has demonstrated the need for flexible dosing of buprenorphine/naloxone. In particular, doses above 16 mg of buprenorphine/naloxone have been found to be superior to lower doses for reduction in cravings and illicit opioid use, and retention in treatment [14]. Experts suggests that factors including pain, and severity of opioid use may correlate with need for higher doses [15]. Buprenorphine/naloxone has been regarded as partial agonist at the μ receptor, stemming from studies demonstrating its ceiling effect on respiratory depression. Research has also outlined the significant inter-subject variability in buprenorphine plasma levels, especially at higher doses [12].

One challenge for dosing buprenorphine/naloxone above 32 mg involves ingestion due to the challenge of dissolving the entire dose under the tongue at the same

time. In our case, the patient did not complain of any such difficulty. Strategies to optimise the task of dissolving the tablet include moistening the mouth prior to ingestion and dividing the dose into multiple ingestions. Alternatively, different formulations of buprenorphine/naloxone including a sublingual film, which may decrease concerns regarding ingestion. It is possible that the patient could have been stabilised on a lower dose of buprenorphine/naloxone if more time had been given before further titrating her dose, given the long half-life of buprenorphine. However, recent research has demonstrated that higher initial starting doses of buprenorphine are helpful in improving retention in treatment and decreasing illicit substance use [4,16,17]. Ultimately, dosing buprenorphine/naloxone at high doses should proceed with caution given concerns for sedation and other side effects. Case reports have also raised the theoretical concern for hepatoxicity in high dose buprenorphine based of the correlation of individuals who injected buprenorphine and ensuring liver toxicity. At the same time, these reports have been limited to individuals with concurrent hepatitis C [18].

The patient's response to a higher dose of buprenorphine/naloxone on successive days suggests that her clinical picture was more in keeping with withdrawal from fentanyl. On day 5, her level of withdrawal decreased smoothly from a COWS score of 4 to 1 when her dose of buprenorphine/naloxone was titrated to 40 mg.

Conclusion

This case reflects the new norm among illicit opioid users of illicit fentanyl. At the same time, the current opioid epidemic requires greater reflection on current OUD practice guidelines. The success of our patient on buprenorphine/naloxone at 40 mg highlights need for greater research into the therapeutic use of buprenorphine/naloxone at doses above 32 mg in the wake of changing population opioid use patterns.

References

[1] Rudd RA, Seth P, David FSL. Increases in drug and opioid-involved overdose deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–52.

[2] Busse JW, Craigie S, Juurlink DN *et al*. Guideline for opioid therapy and chronic noncancer pain. CMAJ 2017;189:E659–66.

[3] British Columbia Centre on Substance Use. A Guideline for the clinical management of opoid use disorder. Available at: http://www.bccsu.ca/care-guidance-publications/. Vancouver, British Columbia: British Columbia Centre on Substance Use, 2017.

[4] Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014;2:CD002207.

[5] Fda, Cder. Initial REMS approval: 08/2010 Most recent modification: 04/2014 NDA 22–410 SUBOXONE ® (buprenorphine and naloxone) sublingual film CIII Buprenorphine (opioid partial agonist-antagonist) Naloxone (opioid antagonist). 2014. Available at: www.SuboxoneFilmREMS.com (accessed 12 October 2018).

[6] 3TC. Product Monograph, 2013. doi:https://doi.org/10.1182/blood-2010-06-289280

[7] Lewis RL, Chou YL. Group Technology Coding System for Die Casting. Trans - SDCE Int Die Cast Expo Congr (Society Die Cast Engine. 1987.

[8] Tupper KW, McCrae K, Garber I, Lysyshyn M, Wood E. Initial results of a drug checking pilot program to detect fentanyl adulteration in a Canadian setting. Drug Alcohol Depend 2018;190:242–5.

[9] Tomassoni AJ, Hawk KF, Jubanyik K *et al*. Multiple fentanyl overdoses — New Haven, Connecticut, June 23, 2016. MMWR Morb Mortal Wkly Rep 2017;66:107–11.

[10] Vardanyan RS, Hruby VJ. Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications. Future Med Chem 2014;6:385–412.

[11] Volkow ND, Collins FS. The role of science in addressing the opioid crisis. N Engl J Med 2017;377:391–4.

[12] Volpe DA, Tobin GAMM, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011;59:385–90.

[13] Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. Am J Addict 2019;28:262–5. d

[14] Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. J Addict Dis 2012;31:8–18.

[15] Fareed A, Vayalapalli S, Casarella J, Drexler K. Treatment outcome for flexible dosing buprenorphine maintenance treatment. Am J Drug Alcohol Abuse 2012;38:155–60.

[16] Zanto TP, Hennigan K, Östberg M, Clapp WC, Gazzaley A. Predictive knowledge of stimulus relevance does not influence top-down suppression of irrelevant information in older adults. Cortex 2011;46:564–74.

[17] Jacobs P, Ang A, Hillhouse MP *et al*. Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories. Am J Addict 2015;24:667–75.

[18] Peyriere H, Tatem L, Bories C, Pageaux G-P, Blayac J-P, Larrey D. Hepatitis after intravenous injection of sublingual buprenorphine in acute hepatitis C carriers: report of two cases of disappearance of viral replication after acute hepatitis. Ann Pharmacother 2009;43:973–7.