Evaluation of buprenorphine/naloxone dose and use of sedating supportive medication on treatment outcomes in veterans with opioid use disorder

Amber Kapuganti, PharmD, BCPP[1]
Traci Turner, PharmD, BCPP[2]
Christopher J. Thomas, PharmD, BCPS, BCPP[3]

Abstract

Introduction: This retrospective cohort study evaluated effects of buprenorphine/naloxone dose and concomitant use of selected sedating medications on treatment outcomes in patients with opioid use disorder.

Methods: Patients enrolled in the buprenorphine/naloxone clinic at the study institution from 2009 until April 2013 were included. There were no exclusion criteria. Part 1 assessed treatment failure within 6 months and time to treatment failure with buprenorphine doses >8 mg and ≤8 mg. Part 2 assessed for treatment failure within 6 months and time to treatment failure with use of selected sedating medications. Sedating medications were cyproheptadine, hydroxyzine, quetiapine, and trazodone. Treatment failure was defined as documentation of illicit opioid use per patient report, urine drug screen showing opioid use, or patient lost to follow-up.

Results: There were 132 patients included in this study, but 163 separate encounters due to multiple enrollments. Treatment failure was experienced within 6 months 51 times a patient was prescribed ≤8 mg (66.2%) and 26 times a patient was prescribed >8 mg (33.8%) ($P = .0005$). Average time to treatment failure was 5.1 months with ≤8 mg and 8.4 months with >8 mg. The 48% of patients who received sedating medications did not demonstrate any significant differences in treatment response at 6 months ($P = .2746$) or time to treatment failure ($P = .2209$).

Discussion: Doses of buprenorphine/naloxone >8 mg demonstrated better treatment response and prolonged time to treatment failure. Concomitant sedating medications did not have a statistically significant effect on treatment response or time to treatment failure.

Keywords: buprenorphine/naloxone, suboxone, dose, sedating, treatment failure

[1] (Corresponding author) Clinical Pharmacist, Outpatient Mental Health Clinic, Department of Veterans Affairs Medical Center, Chillicothe, Ohio, amber.kapuganti@va.gov, ORCID: http://orcid.org/0000-0001-6321-2113; [2] Clinical Pharmacist, Primary Care Mental Health Integration, Department of Veterans Affairs Medical Center, Chillicothe, Ohio, ORCID: http://orcid.org/0000-0001-9841-2967; [3] Mental Health Clinical Pharmacist and Pharmacy Practice Residency Director, Department of Veterans Affairs Medical Center, Chillicothe, Ohio, ORCID: http://orcid.org/0000-0003-1146-8891

Introduction

Per the *World Drug Report*[1] in 2016, an estimated 33 million people worldwide had an opioid use disorder. Opioid use disorder may lead to a multitude of problems, including infectious diseases, hypogonadism, gastrointestinal bleeding, cognitive impairment, respiratory depression, hyperalgesia, and death, due to overdose.[2] Additionally, there are concerns related to the incarceration and crime-related behavior often associated with

opioid use. Given the numerous medical and social risks of opioid use disorders, it is imperative that optimal treatment be provided. Treatment options include psychotherapy and medication. These programs may utilize several different medications, including methadone, buprenorphine, buprenorphine/naloxone, or naltrexone.

Methadone is a full opioid agonist that is commonly used in opioid agonist treatment due to its long half-life and potential for once-daily dosing. Due to QTc prolongation risks, methadone must be used cautiously when used concomitantly with other QTc prolonging agents and in patients with underlying cardiac conditions.[3-5] Use of methadone can be a challenge for patients based on limited accessibility, the burden of clinic visits, and safety concern related to risk of overdose during induction.

Another commonly used agent is buprenorphine, a synthetic partial opioid agonist that binds the mu opioid receptor almost irreversibly with slow dissociation. Due to partial agonist activity, euphoric effects may be seen, but these are not as intense as those seen with full opioid agonists.[6] Buprenorphine has the potential to be improperly used through injection. This led to the invention of buprenorphine/naloxone since naloxone is an opioid antagonist that has no oral bioavailability but high bioavailability when injected.[3]

The opioid antagonist naltrexone is another option.[3] This agent is not addictive and does not cause physical dependence with use. Since it is not a controlled substance, there are fewer limitations on who can prescribe it. Certain patients may feel more comfort using a medication with no opioid agonist properties or may be drawn to the once-monthly injectable option. However, naltrexone use may not be appropriate in patients with comorbid pain diagnoses.

The buprenorphine/naloxone clinic at the study site was established in 2009. Before enrolling in the clinic patients must sign a consent form and opioid agreement and have lab work performed, including liver enzymes, hepatitis screening, pregnancy (if female), and urine drug screen (UDS). Patients are initially followed weekly for a few months, every other week for about 1 year, then monthly. At each follow-up visit patients must supply a UDS as use of illicit substances and benzodiazepines are not allowed. Use of benzodiazepines is not allowed due to concern for respiratory depression and death. Patients are given a warning for the first UDS showing use of illicit substances or benzodiazepines. If a second UDS shows use of illicit substances or benzodiazepines, the patient is discharged from the clinic. Patients are also expected to attend once-weekly group sessions and after-care appointments at the study site as well as 3 community support groups weekly.

To date, there have been no studies to determine the most efficacious dose of buprenorphine/naloxone in opioid agonist treatment. A study performed by Zubieta et al[7] showed a dose-dependent difference in receptor availability with use of buprenorphine, with 2 mg binding 36% to 50% of receptors and 16 mg binding 79% to 95%. Unfortunately, this study did not document receptor binding with other doses. Many of the early studies[8-10] comparing buprenorphine to placebo or other opioid agonist treatments assessed doses of 16 to 32 mg. With the information from Zubieta et al[7] showing a dose-dependent response between buprenorphine and receptor binding, it can be postulated that higher doses of buprenorphine/naloxone would result in fewer treatment failures. Therefore, part 1 of this study was to assess if there was a difference in treatment failure comparing doses ≤ 8 mg versus >8 mg. The cutoff of 8 mg was chosen because it was the middle point of the data of Zubieta et al[7] comparing 2 mg to 16 mg.

Part 2 of this study was to assess if use of concomitant sedating medications, particularly trazodone, hydroxyzine, cyproheptadine, or quetiapine, used any time during opioid agonist treatment affected treatment response. These medications may be prescribed for symptoms of insomnia, restlessness, anxiety, or mood disorders, which may be seen during the acute or postacute withdrawal period. One study by Amass et al[11] specifically examined the prescribing of ancillary medications during the withdrawal period. The most common symptoms reported by patients in their study included insomnia, anxiety and restlessness, and bone pain and arthralgias, which were treated with zolpidem, trazodone, lorazepam, oxazepam, or ibuprofen. Providing these medications during the acute withdrawal period helped patients successfully detoxify. Therefore, they concluded that the use of these adjunctive medications may have led to increased rates and extended periods of sobriety.[11]

Methods

This retrospective cohort study included all patients who were at least 18 years old and enrolled in the buprenorphine/naloxone clinic at the study site between 2009 and April 2013. There were no exclusion criteria. The Computerized Patient Record System was used to gather subject information including sex, age, race, psychiatric diagnoses, pain diagnoses, drug of choice, duration of opioid use, date enrolled in clinic, most recent dose of buprenorphine/naloxone, date the most recent dose was initiated, concomitant use of sedating medications, date of treatment failure, graduation from clinic, or if still being followed. The concomitant sedating medications assessed for included trazodone, hydroxyzine, cyproheptadine, and quetiapine as these were predetermined to be prescribed

TABLE 1: Comparison of demographic characteristics between groups

Demographic Characteristic	Dose ≤8 mg	Dose >8 mg	P Value	Sedating Medication	No Sedating Medication	P Value
Sex, No. (%)						
Male	79 (94.0)	78 (98.7)	.2114	84 (97.7)	72 (94.7)	.4228
Female	5 (6.0)	1 (1.3)		2 (2.3)	4 (5.3)	
Race, No.						
White	82	77	1.0	84	75	1.0
Black	2	2		2	2	
Mean age, y	37.5	38.7		37.7	38.9	
Comorbid psychiatric diagnosis, No. (%)						
Yes	76 (90.5)	70 (88.6)	.7997	79 (91.9)	66 (85.7)	.2237
No	8 (9.5)	9 (11.4)		7 (8.1)	11 (14.3)	
Pain diagnosis, No. (%)						
Yes	60 (71.4)	69 (87.3)	.0198	70 (81.4)	59 (76.6)	.5629
No	24 (28.6)	10 (12.7)		16 (18.6)	18 (23.4)	
Concomitant sedating medication, No. (%)						
Yes	40 (47.6)	46 (58.2)	.2098			
No	44 (52.4)	33 (41.8)				

most often for patients followed in this clinic. Treatment failure included documentation per patient report, UDS showing illicit substance use, or patient being lost to follow up. Graduation from the clinic was defined as patient and physician choosing to taper buprenorphine/naloxone due to maintained sobriety and desire to discontinue medication. This study was approved by the University of Cincinnati Institutional Review Board and Veterans Affairs Research and Development Committees.

Outcomes

The primary outcome for part 1 was to compare the incidence of treatment failure within 6 months between patients prescribed ≤8 mg versus >8 mg with a secondary outcome to assess overall time to treatment failure. The primary outcome for part 2 was to compare the incidence of treatment failure within 6 months between patients prescribed concomitant supportive medications versus those who were not; a secondary outcome was to assess overall time to treatment failure.

The primary outcome of treatment failure at 6 months was assessed using the Fisher exact test. The secondary outcome for time to treatment failure comparing doses was calculated using a paired t test. The secondary outcome for time to treatment failure with sedating medications was assessed using analysis of variance. A preset alpha of 0.05 was used. Using a 95% confidence interval and assuming a dropout rate of 70% ± 10%, it

was calculated that 29 patients would need to be included in each arm to reach statistical significance.

Results

There were 132 patients included in the study but 163 encounters due to multiple enrollments in the clinic. The majority of patients were white men with an average age of 38 years who had comorbid psychiatric and/or pain diagnoses. All baseline demographics were similar except that there was a larger proportion of patients in the >8 mg dose group who had comorbid pain (Table 1).

We found that 51 of the 84 times a patient was prescribed ≤8 mg (66.2%) and 26 of the 79 times a patient was prescribed >8 mg (33.8%) treatment failure was experienced within 6 months ($P=.0005$). The average time to treatment failure was 5.1 months in those receiving ≤8 mg compared with 8.4 months in those receiving higher doses ($P=.0251$; Table 2).

Furthermore, 37 of the 86 times a patient was prescribed a supportive medication with sedating features (48.1%) and 40 of the 77 times a patient was not prescribed a supportive medication with sedating features (51.9%) treatment failure was experienced within 6 months. The average time to treatment failure in patients receiving any of the 4 sedating medications evaluated in this study was 6.8 months compared with 5.3 months for those not receiving a sedating medication (Table 2).

TABLE 2: Patient outcomes

Outcome	Dose ≤8 mg	Dose >8 mg	P Value	Sedating Medication	No Sedating Medication	P Value
Treatment failure within 6 mo, No. (%)						
Yes	51 (66.2)	26 (33.8)	.0005	37 (48.1)	40 (51.9)	.2746
No	33 (38.4)	53 (61.6)		49 (57.0)	37 (43.0)	
Treatment failure at any time, No. (%)						
Yes	65 (58.0)	47 (42.0)	.0179	59 (52.2)	54 (47.8)	.8662
No	19 (37.3)	32 (62.7)		27 (54.0)	23 (46.0)	
Graduated from clinic, No. (%)						
Yes	5 (45.5)	6 (54.5)	.7608	21 (56.8)	16 (43.2)	.7084
No	79 (52.0)	73 (48.0)		65 (51.6)	61 (48.4)	
Still enrolled in clinic, No. (%)						
Yes	11 (29.7)	26 (70.3)	.0028	7 (63.6)	4 (36.4)	.5418
No	73 (57.9)	53 (42.1)		79 (52.0)	73 (48.0)	
Time to treatment failure, mo	5.1	8.4	.0251	6.8	5.3	.2209

Discussion

This study found that doses of buprenorphine/naloxone >8 mg resulted in fewer treatment failures in patients with an opioid use disorder. It is hypothesized that patients prescribed higher doses of buprenorphine/naloxone experienced adequate symptom control, which may not have been achieved with lower doses. Another hypothesis is that patients receiving higher doses of buprenorphine/naloxone found better control of comorbid pain, if present, as buprenorphine has partial opioid agonist activity.

A previous study[11] suggested that use of adjunctive medications may confer better treatment outcomes. Findings from this study did not find that buprenorphine/naloxone and concomitant use of cyproheptadine, hydroxyzine, quetiapine, or trazodone had a significant effect on treatment outcomes.

This study has several limitations. First, this was a retrospective chart review. Second, dosages of medications were simply assessed as ≤8 mg or >8 mg, which only provides a rough estimate for the most efficacious dose in the majority of patients. A third limitation was the determination of treatment failure. This was not always well documented in the chart, so it is possible that the incidence of treatment failure was overestimated since patients who were lost to follow-up were considered to have failed treatment. A fourth limitation is that individual sedating medications, combinations of certain medications, or dose-based effects were not assessed. It is possible that a certain individual agent or certain combinations may have had a more profound effect on treatment failure. Also, this study only assessed 4 sedating medications; therefore, it may not be possible to extrapolate conclusions of this study to all sedating medications. Lastly, the patient population included in this study was majority male, as this is typical for the Veteran's Affairs population. Therefore, it may not be possible to extrapolate these results outside the Veteran's Affairs system where a larger percent of women may be seen.

Conclusion

This study found that doses of buprenorphine/naloxone >8 mg demonstrated better treatment response and prolonged time to treatment failure. The use of concomitant cyproheptadine, hydroxyzine, quetiapine, or trazodone did not have a statistically significant effect on treatment response or time to treatment failure.

References

1. United Nations Office on Drugs and Crime [Internet]. World Drug Report 2016 (United Nations publication, Sales No. E.16.XI.7). Available from: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf
2. Teater D. The Psychological and Physical Side Effects of Pain Medication; National Safety Council. Available from: http://www.nsc.org/RxDrugOverdoseDocuments/900006497-ADV-Rx-Side-Effects-WhitePaper.pdf
3. Lobmaier P, Gossop M, Waal H, Bramness J. The pharmacological treatment of opioid addiction–a clinical perspective. Eur J Clin Pharmacol. 2010;66(6):537-45. DOI: 10.1007/s00228-010-0793-6. PubMed PMID: 20169438.
4. Australian Government Department of Health and Ageing. Review of methadone treatment in Australia. Canberra: Commonwealth of Australia; 1995.
5. The College of Physicians & Surgeons of Ontario. Methadone Maintenance Treatment Program Standards and Clinical Guidelines. 4th ed. Ontario, Canada: The College of Physicians & Surgeons of Ontario; 2011.

6. Comer SD, Collins ED, Fischman MW. Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. Psychopharmacology (Berl). 2001;154(1):28-37. PubMed PMID: 11292003.

7. Zubieta J, Greenwald MK, Lombardi U, Woods JH, Kilbourn MR, Jewett DM, et al. Buprenorphine-induced changes in mu-opioid receptor availability in male heroin-dependent volunteers: a preliminary study. Neuropsychopharmacology. 2000;23(3):326-34. DOI: 10.1016/S0893-133X(00)00110-X. PubMed PMID: 10942856.

8. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949-58. DOI: 10.1056/NEJMoa022164. PubMed PMID: 12954743.

9. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med. 2000;343(18):1290-7. DOI: 10.1056/NEJM200011023431802. PubMed PMID: 11058673.

10. Kristensen Ø, Espegren O, Asland R, Jakobsen E, Lie Ø, Seiler S. [Buprenorphine and methadone to opiate addicts—a randomized trial]. Tidsskr Nor Laegeforen. 2005;125(2):148-51. PubMed PMID: 15665884.

11. Amass L, Ling W, Freese TE, Reiber C, Annon JJ, Cohen AJ, et al. Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA Clinical Trials Network field experience. Am J Addict. 2004;13 Suppl 1:S42-66. DOI: 10.1080/10550490490440807. PubMed PMID: 15204675.