mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Relapse rates among veterans on maintenance doses of combination buprenorphine and naloxone for opioid use disorder

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How to cite: Binger KJ, Ansara ED, Miles TM, Schulte SL. Relapse rates among veterans on maintenance doses of combination buprenorphine and naloxone for opioid use disorder. Ment Health Clin [Internet]. 2020;10(3):80-4. DOI: 10.9740/mhc.2020.05.080.

Abstract

Introduction: Opioid use disorder (OUD) can cause significant morbidity and mortality with more than 115 people dying from an opioid overdose daily in the United States. Treatment with buprenorphine/naloxone (BUP/NAL) can be effective; however, there is conflicting evidence on the utility of higher doses in preventing relapse. This study was designed to assess BUP/NAL maintenance doses and the rate of relapse in veterans with OUD.

Methods: Patients diagnosed with OUD who received a prescription for BUP/NAL through the substance use disorder recovery program were retrospectively evaluated. Patients were categorized into 2 treatment groups: those prescribed ≤16 mg of BUP/NAL daily and those prescribed >16 mg of BUP/NAL daily. The primary outcome was to determine rates of relapse between maintenance doses of BUP/NAL. Secondary outcomes included evaluating the difference in rates of relapse between daily versus take-home dosing, tablets versus films, time to relapse, and use of illicit substances during treatment.

Results: Patients prescribed >16 mg of BUP/NAL daily had statistically significantly lower rates of relapse compared to patients prescribed ≤16 mg of BUP/NAL daily ($P=.0018$). Regarding secondary outcomes, there was a statistically significant difference in time to relapse ($P=.036$) and dosage form ($P=.0124$). Difference in administration of dose and illicit substance use during treatment were not statistically significant.

Discussion: This study identified that rate of relapse can be lowered and time to relapse can be lengthened when doses >16 mg of BUP/NAL are prescribed in the veteran population for OUD.

Keywords: opioid use disorder, buprenorphine/naloxone, veterans, relapse rates

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Disclosures: The authors of this study have no real or potential conflicts of interest to disclose.

Introduction

Opioid use disorder (OUD) is a problematic pattern of opioid use that involves prolonged self-administration of opioid substances that are used for no legitimate medical purpose or in doses that exceed the amount needed for a medical condition.[1] The misuse and addiction to opioids, including prescription pain medications, heroin, and synthetic opioids such as fentanyl, has more than tripled over the past 2 decades. According to the Centers for Disease Control and Prevention[2] more than 115 people die from an opioid overdose every day in the United States,

confirming the devastating effects of the current increasing trend. Opioid use disorder may also lead to a multitude of other health problems, including infectious diseases, hypogonadism, hyperalgesia, cognitive impairment, respiratory depression, and death due to overdose.[3] In addition to the morbidity and mortality that OUD causes, economic effects can also be seen. The Centers for Disease Control and Prevention estimates that the total financial burden of prescription opioid misuse is more than 78 billion dollars annually in the United States. This encompasses costs of health care, substance use disorder treatment, lost productivity, and criminal justice involvement.[4]

Due to the morbidity, mortality, and social issues associated with OUD, it is important that patients receive effective treatment. Treatment options include psychotherapy and pharmacotherapy, such as methadone, buprenorphine/naloxone (BUP/NAL), and naltrexone. Since BUP/NAL received Food and Drug Administration approval in 2002, it has been increasingly used in the treatment of OUD for both detoxification and maintenance. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor, and it is often used in combination with naloxone, an antagonist at the mu-opioid receptor, to prevent abuse.[5]

The range of dosing for BUP/NAL can be anywhere from 4 mg to 24 mg daily of the buprenorphine component with the package insert recommending a target dose of 16 mg/d.[5] Although a target dose is recommended, studies are conflicting on what dosing is best to prevent relapse. One study[6] found that patients who relapsed were more likely to be on higher doses of buprenorphine maintenance therapy, and a recent meta-analysis[7] has suggested that higher buprenorphine doses (16-32 mg/d) predicted better retention in treatment compared with a dose less than 16 mg/d. Literature does not provide concrete evidence regarding adequate dosing levels needed to control cravings, prevent withdrawal syndrome, and maintain patients in treatment.[8]

Currently, there are few studies that analyze characteristics of veteran patients, and no studies have examined the effect of BUP/NAL dosing on the rate of relapse. The intent of this study is to provide information on BUP/NAL maintenance dosing in veteran patients with OUD who are being treated in the substance use disorder recovery program (SUDRP). Additionally, this study looked at rates of relapse comparing daily window dosing versus take-home dosing, films versus tablets, time to relapse, and use of illicit substances during treatment.

Methods

Study Design

This study was a retrospective electronic chart review of patients with a diagnosis of OUD who were treated with BUP/NAL at the Richard L. Roudebush Veterans Affairs Medical Center in Indianapolis, Indiana. Medication fill records from January 1, 2014, through December 31, 2017, were used to generate a list of patients who filled BUP/NAL and were being treated in SUDRP. To be included in the study, patients had to be $\geq$18 years of age, have a diagnosis of OUD, and be treated with BUP/NAL through SUDRP. Patients were excluded if they were prescribed opioids besides BUP/NAL, were not receiving treatment through SUDRP, or were pregnant. Patients were categorized into 2 treatment groups: those taking $\leq$16 mg of BUP/NAL daily and those taking $>$16 mg of BUP/NAL daily. They were reviewed from the start of their treatment and followed for 12 months after their maintenance dose was established or until first relapse, whichever came first. Relapse was determined through self-report or urine drug screens (UDS) that were presumptive positive for opioid use during the study period. The UDS utilized checked for opiates, which included morphine and its metabolites and oxycodone. Liquid chromatography mass spectrometry panels are encouraged, but not required. This study was approved under exempt status by the Indiana University Institutional Review Board and the Veteran Affairs Research and Development Board because of lack of personal identifiers collected from the data.

Study Outcomes

The primary outcome was to determine rates of relapse between maintenance doses of BUP/NAL. Secondary outcomes of the study included evaluation of the difference in rates of relapse between daily window dosing versus take-home dosing; tablets versus films; time to relapse; and use of other illicit substances during treatment, which included amphetamines, benzodiazepines, cocaine, and marijuana.

Statistical Analysis

Study data and analysis were completed using the REDCap (research electronic data capture) tool[9,10] hosted at the Richard L. Roudebush Veterans Affairs Medical Center. REDCap is a secure, Web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for data integration and interoperability with

TABLE 1: Baseline characteristics of the current study

	BUP/NAL >16 mg Daily (n = 54)	BUP/NAL ≤16 mg Daily (n = 74)	*P* Value
Age, y, mean ± SD	42 ± 13.5	41 ± 14.1	.316
Sex, n (%)			
Male	51 (94.4)	67 (90.5)	.517
Race, n (%)			
White	48 (88.9)	67 (90.5)	.759
Black	5 (9.2)	6 (8.1)	.818
Other	1 (1.9)	1 (1.4)	1
Mental health disorders, n (%)			
Anxiety disorder	12 (22.2)	15 (20.3)	.789
Depressive disorder	22 (40.7)	27 (36.5)	.625
Posttraumatic stress disorder	18 (33.3)	26 (35.1)	.832
Bipolar disorder	3 (5.6)	3 (4.1)	.696
Schizophrenia	0 (0)	0 (0)	1
Other	5 (9.3)	9 (12.2)	.603
BUP dose, mg, mean ± SD	27 ± 5	13 ± 4	<.0001

BUP = buprenorphine; NAL = naloxone.

external sources. A program based off Statistical Package for the Social Sciences[11] was used in addition to REDCap. Descriptive statistics were used to characterize patient demographics. Fisher exact and χ^2 tests were used for nominal data. Student *t* and Mann-Whitney *U* tests were used for categorical data as appropriate. A power calculation was not used given the relatively small sample size. Alpha level was set at 0.05.

Results

A total of 426 patients were identified for potential inclusion in the analysis. One hundred twenty-eight patients met inclusion criteria with 54 in the >16 mg BUP/NAL group and 74 in the ≤16 mg BUP/NAL group. Primary reasons for exclusion included BUP/NAL treatment outside of the SUDRP (n = 106) and less than 12 months at maintenance dose at time of data collection or lost to follow-up (n = 114). Table 1 shows baseline demographic characteristics and mental health diagnoses, which were similar in both groups. The average dose of buprenorphine in the >16 mg of BUP/NAL daily group was 27 mg compared to 13 mg in the ≤16 mg of BUP/NAL daily group.

A total of 55 patients in the study relapsed within the specified study period. Thirty-three percent (n = 18) of patients taking >16 mg of BUP/NAL daily relapsed compared to 64% (n = 47) of patients taking ≤16 mg of BUP/NAL daily. The difference in relapse rates between the 2 study groups were found to be statistically significant (*P* = .0018). Of those patients who relapsed, 78% (n = 14) in the >16 mg of BUP/NAL were identified through positive UDS versus 55% (n = 26) in the ≤16 mg of BUP/NAL.

When looking at secondary outcomes, there was a statistically significant difference in time to relapse between the treatment groups (*P* = .036). The average time to relapse was 197 days in those taking >16 mg of BUP/NAL versus 126 days in those who were taking ≤16 mg of BUP/NAL daily. Of those who relapsed, patients in the ≤16 mg of BUP/NAL daily used nonopiate illicit substances at a higher rate: 46.8% versus 27.7% than those in the >16 mg of BUP/NAL daily group (*P* = .164). The most common nonopiate illicit substances reported to be used during treatment by both treatment groups were marijuana (8.5%), amphetamines (2.3%), benzodiazepines (1.2%), and cocaine (0.9%). There was a statistically significant difference in rates of relapse found between dosage formulations of BUP/NAL with 72.3% of patients in the ≤16 mg of BUP/NAL group relapsing when on tablets versus 38.8% of the >16 mg of BUP/NAL group (*P* = .012). Administration of dosing between daily window dosing, take-home, or a combination of the 2 was comparable in both treatment groups (Table 2).

Discussion

This study evaluated the rates of relapse between maintenances doses of BUP/NAL in patients with OUD. The results showed that patients who were prescribed >16 mg of BUP/NAL had a lower rate of relapse

TABLE 2: Comparison of patients who relapsed

	BUP/NAL >16 mg Daily (n = 18)	BUP/NAL ≤16 mg Daily (n = 47)	*P* Value
Dosage form, n (%)			
Tablet	7 (38.8)	34 (72.3)	.012
Administration of dose, n (%)			
Daily window dosing	0 (0)	3 (6.4)	.555
Take home	15 (83.3)	37 (78.7)	1
Combination	3 (16.7)	7 (14.9)	1
Time to relapse, d, mean ± SD	197 ± 150	126 ± 107	.036
Use of nonopiate illicit substances during treatment, n (%)	5 (27.7)	22 (46.8)	.164

BUP = buprenorphine; NAL = naloxone.

compared to patients who were prescribed ≤16 mg of BUP/NAL daily. Additionally, patients who did relapse in the >16 mg of BUP/NAL group were able to abstain from opioid use for a longer period of time compared to those in the ≤16 mg of BUP/NAL daily group. Patients who were in the >16 mg of BUP/NAL group likely had better symptom control and reduced cravings on higher doses, reducing their risk of relapse and extending the time to relapse.

The association found in our study contradicts a larger study[12] that found patients who received 24 mg versus lower doses of buprenorphine had a higher rate of continued opioid use throughout treatment. Another study[6] had similar findings in which a higher buprenorphine maintenance dose increased the likelihood of relapse although these patients had higher rates of anxiety disorders and active benzodiazepine use than this study population. However, the relationship reported in this study was also noted in a previous meta-analysis[7] that showed patients who received higher doses of buprenorphine had significantly greater retention in treatment than those on lower doses.

There was no difference found between how doses of BUP/NAL were being administered: whether patients were getting daily window dosing, take-home, or a combination of both and rates of relapse. These results suggest that the type of administration does not have an effect on rates of relapse and that symptom control is more important than having a patient present for daily dosing. There was also no statistically significant difference in illicit substances used during treatment between the 2 treatment groups. This suggests that, even if patients are utilizing other illicit substances, if their cravings for opioids are well controlled, relapse may be prevented.

There was a statistically significant difference in rates of relapse found between dosage formulations of BUP/NAL. Those that were in the >16 mg of BUP/NAL group were more likely to be on films when they relapsed versus patients in the ≤16 mg of BUP/NAL daily group, who were more likely to be on tablets. For a period of time during the study time frame, films were unavailable for acquisition, and patients were switched to the tablet formulation. This change may have affected which patients were on tablets versus films when they relapsed, making this an incidental finding.

Limitations of this study include its retrospective nature, small sample size, single practice center, a primarily younger male patient population, and lack of documentation by providers. The small sample size could have impacted the rates of relapse in the treatment groups. Extending the study time frame or combining BUP/NAL patients that are seen at similar substance use disorder clinics at other Veterans Affairs facilities may have allowed more patients to be included in the study. The retrospective nature made complete data collection difficult. The lack of provider documentation at times made it hard to determine why dose changes were being made or if patients were experiencing cravings at the dose that they were taking. In order to determine relapse, we were relying on a UDS to return a presumptive positive result for any opioid or for a patient to report relapse. A UDS was ordered at every patient medication management appointment, but the frequency of these appointments could vary based on where a patient was in treatment. Additionally, a UDS provides only a presumptive positive result, and confirmatory tests were not often ordered to verify results.

Conclusion

This study identified that rate of relapse can be lowered and time to relapse can be lengthened when doses >16 mg of BUP/NAL are prescribed in the veteran population for OUD. Larger prospective studies are needed to confirm these findings.

Acknowledgments

The contents do not represent the views of the US Department of Veterans Affairs or the US Government. This material is the result of work supported with resources and the use of facilities at the Richard L. Roudebush Veteran Affairs Medical Center in Indianapolis, Indiana.

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