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Provision of Ancillary Medications during Buprenorphine Detoxification Does Not improve Treatment Outcomes

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Abstract

For opioid-dependent individuals, recovery efforts begin with a period of withdrawal that typically include discomfort from symptoms, possibly precipitating a return to drug use. The study described here investigated whether the provision of ancillary medications for opioid withdrawal symptoms affects treatment outcomes in 139 participants receiving buprenorphine in a 13-day detoxification trial. Outcome measures include the number of opioid-free urine samples collected and retention in treatment. Ancillary medications were provided to 70% of participants: 59% received medication for insomnia, 45% for anxiety, 40% for bone pain, 35% for nausea, and 28% for diarrhea. Findings indicate no difference in the number of opioid-free urine samples between the group receiving ancillary medication and the group who did not, although tests of specific ancillary medications indicate that those who received diarrhea medication had fewer opioid-free urines than those who did not ($p = 0.004$). Results also indicate that participants attended fewer days of treatment if they received anxiety, nausea, or diarrhea medication compared to no medication (all p values < .05).

Introduction

The 2007 National Survey on Drug Use and Health (NSDUH) reports that approximately 3.8 million Americans age 12 and older reported using heroin at least once in their lifetimes1. Additionally, in 2007, 2.5 million Americans age 12 and older reported using prescription drugs non-medically for the first time2. Although heroin use is stable, prescription drug use has seen steep increases across the United States. The rate of past-year abuse for prescription narcotics for Americans age 12 and older increased from 4.7% in 2002 to 5.0% in 2007, and a higher number of first-time drug misusers (2,147,000) abused opioid pain relievers than any other drug in 20073.

Practical and effective means of treating opioid dependence remain elusive, but research has shown the use of substitution therapy or medication maintenance is an effective way of managing opioid dependence. Of the available compounds proven effective in the agonist class, buprenorphine appears especially suitable for community-based treatment because of its safety profile and legislative relief allowing its office-based prescribing. Buprenorphine is a mu-opioid partial agonist approved by the FDA in October of 2002 as a pharmacotherapy for the treatment of opioid dependence following Congressional authorization of its use in 2000 in the Drug Abuse Treatment Act. Controlled clinical trials in several thousand patients over the past 15 years have provided overwhelming support for its therapeutic efficacy in opioid-dependent individuals4–11. Suboxone, a sublingual combination tablet containing both buprenorphine and naloxone (an opioid antagonist) has been developed to mitigate abuse and diversion.

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Although buprenorphine appears to be an effective treatment for opioid dependence and may reduce the discomfort typically occurring when transitioning from illicit opioid use, it does not eliminate withdrawal symptoms, which may be severe at the induction stage[12]. One barrier to successful treatment and continued abstinence may be the discomfort of withdrawal symptoms. Some individuals initially committed to a goal of abstinence may be unsuccessful due to withdrawal symptoms that can precipitate continued drug use. Whereas, drug use may begin as a desire to experience euphoria, chronic drug use may persist as a compulsion to avoid unpleasant withdrawal effects.

In a treatment setting, the provision of medications to lessen withdrawal effects may increase the possibility of successfully getting past the initial withdrawal period. Ancillary medications may be prescribed to alleviate physical opioid withdrawal symptoms such as insomnia, diarrhea, bone pain, headache, nausea and lethargy, and psychological symptoms such as depression and anxiety. Providing these medications may increase the likelihood of a successful transition from active drug use to non-use.

For treatment providers and medical personnel, efforts to alleviate pain and discomfort are more than a humane gesture[12]. Providing optimal care includes managing withdrawal discomfort so that the patient can focus on the other details of treatment and recovery. An individual who is preoccupied with physical ailments cannot fully comprehend and adhere to the requirements of treatment plans and compliance issues. Although a review of the existing literature found no empirical studies on the provision of ancillary medications for withdrawal symptoms, an American Academy of Addiction Psychiatry consensus conference addressing clinical care of opioid-dependent patients included a recommendation that physicians be prepared to use ancillary medications during detoxification and pharmacotherapy[13]. Additionally, a recent review indicated that provision of ancillary medications in conjunction with pharmacotherapy can reduce withdrawal severity in opioid users[14].

Ancillary medications are often an essential part of regular treatment for other health disorders. Their role is to increase the likelihood of the patient continuing with his/her prescribed treatment, despite possible iatrogenic side effects caused by the prescribed treatment. One example is the use of anti-emetics in patients being treated with chemotherapy. The objective of incorporating anti-emetics such as type three 5-hydroxytryptamine (5-HT3) receptor antagonists, and the neurokinin-1 (NK1) receptor antagonists aprepitant and fosaprepitant, is the prevention of anticipated chemotherapy-induced nausea and vomiting[15]. The expected nausea due to chemotherapy is not unlike the expected nausea of the opioid addict withdrawing from opioids. In this case, nausea may be exacerbated by pharmacotherapy with Suboxone due to its relatively higher affinity to mu receptors, effectively forcing out lesser-affinity opioids such as heroin, and subsequently causing withdrawal symptoms. Without adequate control of treatment side effects such as nausea, compliance with treatment and treatment success may not be possible for many patients, especially those lacking strong motivation and extensive social support.

The current study addresses the use of ancillary medications in an opioid-dependent sample participating in research comparing the effectiveness of buprenorphine (Suboxone) with that of clonidine[11] provided for a 13-day detoxification trial. Because the buprenorphine group had better outcomes, and buprenorphine is being increasingly used to treat opioid dependence, these analyses include only the group randomly assigned to receive buprenorphine. Analyses compare study participants in the buprenorphine condition who received ancillary medication (s) for withdrawal discomfort with study participants who received no such medication. Outcome measures include the number of opioid-free urine samples collected and treatment retention. Our study objective was to address whether participants undergoing detoxification with buprenorphine for opioid dependence had better outcomes based on the provision of

ancillary medications. Specifically, we examined whether participants given ancillary medications stayed in treatment longer, and gave more opioid-free urine samples as compared to the group not receiving ancillary medications. This information contributes to the very scarce literature on the use of ancillary medications in the treatment of opioid dependence, and it provides guidance to clinicians treating opioid-dependent patients with buprenorphine.

Methods

Study Design

This study is a secondary analysis of individuals enrolled in a parallel-group comparison study of outpatients randomized to an open-label trial of buprenorphine (Suboxone) or clonidine for a 13-day opioid detoxification at six community treatment programs participating in the National Institute on Drug Abuse's Clinical Trials Network (CTN)[11]. The analysis reported here included only those participants assigned to the buprenorphine condition, comparing the outcomes of those who received ancillary medications for typical opioid withdrawal symptoms including anxiety, bone pain, diarrhea, nausea, and/or insomnia. Outcomes include the number of opioid-free urine samples collected over the course of the 13-day detoxification and treatment retention.

All study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000[16]. All study procedures were reviewed and approved by the UCLA Medical Institutional Review Board. Additionally, this trial was registered on clinicaltrials.gov, identified as trial NCT00078117.

Participants

Participants were enrolled from January 2001 through February 2002 and included treatment-seeking adults at least 18-years-old and in good general health, who met Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV)[17] criteria for opioid dependence, and who were in need of medical management for opioid withdrawal. Potential participants were excluded if they had a serious psychiatric or medical condition that would make participation medically hazardous (e.g., suicidal behavior, uncontrolled diabetes); had a known allergy or sensitivity to buprenorphine, naloxone, or clonidine; were receiving medications contraindicated with clonidine or had a systolic blood pressure < 100 mm Hg or pulse < 56 bpm. They were also excluded if they had been enrolled in a methadone or LAAM treatment program or had participated in another investigational drug study within 30 days of study enrollment, or if they could not remain in the area for the duration of active treatment. Co-dependence on other drugs did not exclude individuals from participation unless immediate medical attention was required to manage these disorders. Females who were pregnant or lactating were excluded, and enrolled females were required to have a negative pregnancy test prior to randomization.

A total of 157 male and female participants who met DSM-IV criteria for opioid dependence and were seeking treatment were randomized to the buprenorphine condition. Participants received compensation for screening and each of three follow-up assessments (1-, 3-, 6-month post-intake), but did not receive any compensation during the 13-day detoxification.

Procedures

After providing informed consent, participants completed a two- to three-hour screening assessment to collect comprehensive information across a range of measurement domains. Demographic and drug use information was collected with the Addiction Severity Interview (ASI)18. To assess withdrawal and craving, both observer (Clinical Opiate Withdrawal Scale

(COWS)19; and self-report (Adjective Rating Scale for Withdrawal (ARSW) 4,20–21; withdrawal ratings were completed. Participants also completed the Visual Analogue Scale (VAS), a measure of severity of craving. Urine samples were collected at baseline and at four time-points during the detoxification phase using FDA-approved devices for monitoring specimen integrity. Urine drug screens collected during treatment were analyzed centrally (Northwest Toxicology, Inc., Salt Lake City, Utah). After beginning the detoxification phase, participants completed daily self-report measures, provided urine samples at four time-points, and received study medications and counseling sessions over the 13-day duration.

Ancillary Medications

Ancillary medications were provided in bulk supply to each study site in accordance with physician request. Physicians were not required to dispense each ancillary medication but rather to provide them according to their personal preference, practice, and patients' clinical need but within protocol dosing guidelines.

Protocol dosing guidelines dictated that only one type of ancillary medication for any given symptom was to be dispensed on any given day. That is, physicians could not dispense multiple ancillary medications for a given symptom on a given day, although across days they could elect to try different medications. Table 1 lists the medications provided to study physicians to dispense for each withdrawal symptom and dosing parameters. Participants received these ancillary medications in a child-proof bottle for self-administration at home in accordance with instructions listed on the bottle. At the start of the detoxification, participants were instructed on the use of each medication. Refills were available during each scheduled clinic visit.

Data Analyses

Analyses included a comparison of outcome (number of opioid-free urine samples, retention) by ancillary medication status (received any ancillary medication, received no ancillary medications). Additionally, analyses addressed outcome by the provision of medication for each specific withdrawal symptom (anxiety, bone pain, nausea, diarrhea, insomnia). Participants were scheduled to provide four urine samples after starting the detoxification phase, and analyses summed the number of opioid-free samples collected from each participant. This method avoids analyses of missing samples as both opioid-positive samples and missing samples are omitted in the analyses. Retention is defined as the number of days retained in the study as indicated on clinic attendance records.

Results

Characteristics of the Sample

Of the 157 participants randomly assigned to receive buprenorphine, 18 did not have urine data following the first dose of medication, likely due to drop out. Therefore, the final sample for these analyses included 139 participants. Seventy percent of the sample received one or more ancillary medications to treat five withdrawal symptoms. Fifty-nine percent of participants received medication for insomnia, 45% received medication for anxiety, 40% received medication for bone pain, 35% received medication for nausea, and 28% received medication for diarrhea.

The two groups, those who received ancillary medications and those who received none, did not statistically differ in age, education, baseline heroin use, or gender. The mean age was 38 (SD = 10), mean years of education was 12 (SD = 2), mean heroin use was 26 days out of the prior 30 (SD = 9), and 27% were female. A Chi-square test indicated an association between receipt of ancillary medication and ethnicity ($\chi^2 = 9.94$, $p < .01$, phi = .28). Within each ethnicity category, substantially more participants received ancillary medication than did not receive

medication (White: 84% vs. 16%, Black: 58% vs 42%, and Hispanic: 61% vs 39%). Within the White ethnic category however, a substantially higher proportion of participants received ancillary medication compared to other ethnic groups.

As expected, the groups statistically differed in withdrawal severity, averaged across the 13 days of detoxification. Participants who received ancillary medications had higher mean COWS scores than those who did not receive medication (X = 4.4 vs. 1.6; $F_{1,137} = 38.3$, $p < .001$) and higher average ARSW scores (X = 33.7 vs. 18.2; $F_{1,137} = 12.9$, $p < .001$).

Opioid-free Urine Samples

Forty-four percent of the sample (n = 61) continued opioid use throughout the detoxification phase while 11% (n= 15) remained abstinent. Participants provided an average of 1.3 (SD = 1.4) opioid-free urines out of four possible. A test of the hypothesis that receipt of ancillary medication was related to opioid-free urine tests was not supported ($t_{1, 137}=.87$, $p > .05$). There was no difference in opioid use, measured by urine toxicology tests, by ancillary medication condition. Tests of specific withdrawal symptoms however, indicated that those who received diarrhea medication had poorer outcomes, measured as fewer opioid-free urines (X = .85) than those who did not receive diarrhea medication (X = 1.52; $t_{1, 137} = 2.92$, $p = .004$). Analysis addressing whether poorer outcomes were more likely as a function of increasing number of medications, indicates no statistically significant correlation between the number of symptoms for which medications were prescribed and the number of negative urines provided.

Retention

Participants remained in the 13-day program for an average of 11 days (SD = 2). Only 15 participants dropped out by the end of the first week. A test of the hypothesis that receipt of ancillary medication was related to retention was supported ($t_{1, 134} = 4.99$, $p < .001$); those who received mediation had significantly fewer days of treatment (X = 10.4, SD = 3.3) than those who did not receive medication (X = 12.3, SD = 1.2). A test of the hypothesis that provision of ancillary medications for specific withdrawal symptoms negatively influenced retention was supported for 3 of the 5 withdrawal symptoms. T-tests indicated that participants attended fewer days of treatment if they received any medication for anxiety (X = 10.3 vs. 11.5), nausea (X = 9.7 vs. 11.6), or diarrhea (X = 9.9 vs. 11.3) compared to no medication (all p values < .05). There was a trend for receipt of insomnia medication (X = 10.6 vs. 11.5, $p = .057$).

Discussion

These findings indicate that providing ancillary medications for the treatment of opioid withdrawal symptoms during detoxification with buprenorphine is not associated with improved treatment outcomes. Individual analyses of each withdrawal symptom and the provision of ancillary medication, however, demonstrates that providing ancillary medications for diarrhea was associated with poorer treatment outcome measured as opioid-free urine samples. Providing ancillary medications for anxiety or nausea or diarrhea was associated with poorer retention measured as fewer days in treatment.

Participants who received ancillary medication had higher craving scores both by clinical assessment and self-report. Although no attempt was made in the initial study to collect information describing the prescribing practices of site study physicians, it is logical that participants reporting greater withdrawal distress would be more likely to be given medications to alleviate their discomfort. Prescribing medications for withdrawal symptoms may seem beneficial in terms of expectation of improved outcomes, but individuals in this trial who received medications did not have better outcomes than individuals not getting ancillary

medications. In fact, those getting diarrhea medication were more likely to have worse outcomes in terms of lower rates of treatment retention and lower rates of opioid-free urine tests. Those given anxiety or nausea medication also had lower rates of retention.

Individuals who required ancillary medications for withdrawal symptoms may have higher levels of craving and withdrawal than those not getting ancillary medications, and ancillary medications do not relieve craving. When looking at the specific symptoms related to worse outcome, it may be that the nature of these symptoms—anxiety, nausea, and diarrhea — are so debilitating that individuals suffering from them are unable to leave their homes, thus failing to come to the clinic, whereas those getting medication for insomnia or bone pain may be more able and willing to leave home to attend the clinic.

A second possible explanation for the results is that the dosage of buprenorphine may have been inadequate for those who received ancillary medications. Although guidelines for buprenorphine dosing typically suggest from 8mg to 24mg daily, there is no established objective method for establishing the proper dosage of Suboxone for an individual patient. In the parent study, the dosing schedule was identical across participants (day 1: 4mg (+ 4mg if necessary), 2: 8mg, 3: 16mg; 4: 14mg; 5: 12mg; 6: 10mg; 7: 8mg; 8/9: 6mg; 10/11: 4mg; 12/13: 2mg.), for a mean of 7.8mg daily over the 13 dosing days. This rigid schedule was due in part to the short duration of the detoxification schedule, but, theoretically, under-dosing could lead to incomplete resolution of withdrawal symptoms. In post-hoc analyses of dose amounts, the ancillary medication group received a mean of 6.4mg (sd = 1.8mg) buprenorphine daily, whereas the non-ancillary medication group received a mean of 7.3mg (sd = 0.64mg) daily. Clearly, the ancillary medication group received less medication, but whether this is a consequence of greater withdrawal symptoms associated with lower dose is unclear.

Another possibility is that participants given ancillary medications had higher rates of craving and withdrawal symptoms and required more ancillary medications because they were not taking their buprenorphine as prescribed. Some participants may have been diverting study drug for monetary gain, and others may not have taken their dose because they didn't experience the typical benefits and improvements in physical and psychological functioning, or they didn't like the effects. These individuals may have had better outcomes with a different treatment plan, such as pharmacotherapy with methadone.

Participants who received ancillary medications, at the very least, had higher rates of craving and withdrawal symptoms, indicating that these participants are systematically different from those not getting medications, although severity of opioid use assessed at baseline did not differ between the two groups. This suggests that although the level of dependence may not differ between the groups, the ensuing detoxification regime and/or study medication affected the groups differently.

Clinicians treating opioid-dependent individuals should consider high rates of craving and withdrawal symptoms and the need for ancillary medications as a red flag for further monitoring and assessment. Practice changes that may be required include adjusting buprenorphine dose, increasing provision of ancillary medications, switching to another pharmacotherapy or providing alternatives to medication for treating withdrawal symptoms, and monitoring patients to ensure that they are taking buprenorphine as instructed.

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Table 1

Ancillary medications used to treat withdrawal symptoms in the current study.

Indication	Medication	Dosage	Maximum Dosage (NTE)
Anxiety/restlessness	Oxazepam	15–30 mg orally every 6 hrs as needed;	60 mg or 120 mg/24 hrs
	Phenobarbital	15–30 mg orally every 6 hrs as needed;	60 mg or 120 mg/24 hrs
	Hydroxyzine Hydrochloride	50 mg orally every 6 hrs as needed;	200 mg/24 hrs
	Lorazepam	1–2 mg orally every 6 hrs as needed;	8 mg/24 hrs
Bone pain/arthralgias	Ibuprofen	800 mg orally every 8 hrs as needed;	3200 mg/24hrs
	Acetaminophen	650 mg orally every 4–6 hrs as needed:	3900 mg/24 hrs
	Methocarbamol	50–1000 mg orally every 6 hrs as needed;	2000 mg/24 hrs
Nausea	Trimethobenzamide	250 mg orally every 8 hrs as needed;	750 mg/24 hrs
	Trimethobenzamide	100–200 mg suppository;	750 mg/24 hrs
Diarrhea	Loperamide	2 mg orally as needed;	8 mg/24 hrs
	Donnatal	1–2 tablets orally q6–8 hrs as needed;	8 tablets/24 hrs
Insomnia	Zolpidem tartrate	10 mg 1–3 tablets orally before bedtime as needed	
	Trazadone Hydrochloride	50 mg 1–3 tablets orally before bedtime as needed	
	Doxepin Hydrochloride	50 mg 1–3 tablets orally before bedtime as needed	
	Diphenhydramine Hydrochloride	25–50 mg every 4–6 hrs orally as needed;	300 mg q 24 hrs