The Effect of Single High-dose Buprenorphine on Opioid Craving and Relapse

Jamshid Ahmadi (✉ jamshid_ahmadi@yahoo.com)

Substance Abuse Research Center Shiraz University of Medical Sciences <https://orcid.org/0000-0002-7060-469X>

Mina SefidfardJahromi

Shiraz University of Medical Sciences

Dara Ghahremani

University of California Los Angeles

Edythe D. London

University of California Los Angeles

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Abstract

Background: Buprenorphine, a treatment for Opioid Use Disorder, has liability for diversion and abuse. Use of single high doses of buprenorphine that are supervised avoid issues with diversion that occur with unsupervised or take home doses. Such doses have the potential to act as an initial opioid detox, facilitate transition to opioid antagonists or drug free treatments, as well as to maintenance treatment.

Objective: To assess effects of a single, physician-administered high dose of buprenorphine on craving and on early relapse.

Method: Sixty men who used heroin, opium or prescription opioids and met DSM-5 criteria for Opioid Use Disorder received a single, sublingual dose of buprenorphine (32 mg, 64 mg or 96 mg; n's = 20, 21, and 19) as inpatients on a psychiatric unit. Buprenorphine was administered when patients were in moderate opioid withdrawal (4-5 symptoms). Self-reports of craving were taken at baseline and daily for the next 13 days, and relapse was assessed 1 and 2 months.

Findings: Craving was reduced from baseline in each of the three groups ($p < 0.0005$), but the doseXtime interaction did not reach statistical significance ($p = 0.069$). Follow-up assessments at 1- and 2-months indicated significantly lower relapse rates for the higher-dose groups than for the low-dose group ($p < 0.05$). **Conclusions:** A single high dose of buprenorphine provides rapid relief of opioid craving and positively impacts relapse rate in the initial 1- and 2-months of outpatient treatment. Further investigation of single high-dose buprenorphine for early treatment of patients with Opioid Use Disorder is warranted as an alternative when buprenorphine/naloxone or long-acting buprenorphine dosage forms are not available.

Keywords: Buprenorphine; opioid dependence; opioid withdrawal; craving

Background

Buprenorphine is safer with respect to other opiates. First, withdrawal from buprenorphine, is quite easy, due to its longer half-life and slower elimination. Second, incidental overdosing is self-limiting, due to an early ceiling-effect, such that tolerant subjects do not have that risk (1). Buprenorphine a semisynthetic partial agonist at mu-opioid receptors and antagonist at delta- and kappa-opioid receptors, has been assessed largely for the management of Opioid Use Disorder (2-13). It is regarded safer than methadone (5, 6, and 7), with 8 mg of buprenorphine being as effective as 60 mg of methadone (8). Buprenorphine is very well absorbed after sublingual administration (4, 9, and 10). In animals, buprenorphine demonstrates a flattened or inverted U-shaped curve, with dose-correlated rises in antinociceptive influence at lower doses and either no greater anti nociception or a reduction in effect at higher doses (14, 15).

Buprenorphine has not only typical mu-opioid agonist effects, such as analgesia, sedation, and euphoria, but also its partial agonist action at mu-opioid receptors has favored the administration of buprenorphine over methadone and especially, the minimal respiratory depressant effects of buprenorphine produce greater safety (14-26).

The main purpose of this research was to determine the influences of single, high doses of buprenorphine (32 mg, 64 mg and 96 mg buprenorphine) in the treatment of craving during and after opioid withdrawal because decreased craving is a function of buprenorphine decreasing withdrawal. Craving persists after detoxification is ended and can increase relapse rate (3, 17, and 20). Doses of buprenorphine higher than those that are commonly administered clinically (i.e., 16-24 mg) were used to raise the effective half-life of the medication (plasma elimination half-life of buprenorphine is 36-72 h after sublingual administration). A single, high dose was tried because repeated buprenorphine administration raises the possibility of dependence, diversion and abuse (3, 18, and 22). It should be mentioned In Iran, buprenorphine is not available in a formulation that contains naloxone to decrease this possibility.

Although not ideal, it is often the case in this center that opioid-dependent individuals leave the hospital after detoxification - without medication-assisted treatment, which is the gold standard. It should be emphasized that the idea of having a patient with Substance Use Disorder withdraw in the hospital under supervision and then appointment for psychosocial follow up and returning him to the supportive family often happens in this center. In follow-ups, if a patient needs medication we would begin appropriate treatment such as buprenorphine maintenance treatment.

Furthermore, buprenorphine was used rather than methadone because of the risk of overdose with a single, high dose of methadone.

In short, use of single high buprenorphine doses would be useful clinically. Such doses have the potential to act as an initial opioid detox, facilitate transition to opioid antagonists or drug free treatments, as well as to maintenance treatment.

Methods

Subjects: The current research study was approved and monitored by the Ethic Committee of Shiraz University of Medical Sciences which adhered to the Declaration of Helsinki Ethical Principles for Medical Research involving human subjects. The subjects were 60 inpatients at this referral psychiatric ward, where only men were hospitalized. Patients recruited from outpatient addiction clinic. Although the subjects did not receive any compensation, however, they were hoping to detox from use of the single dose.

Prior to referring to this hospital, they had been abusing heroin, opium, illegal or prescribed opioids. Those patients who had initial eligibility requirements on screening, were administered the Structured Clinical Interview for DSM-5, Clinical Version (SCID-I), by a board-certified psychiatrist, to be sure that they had the criteria for Opioid Use Disorder (Diagnostic and Statistical Manual of Mental Disorders, Five Edition).

Daily opioid use for at least one year was a requirement. Participants were excluded if they had substance use disorders other than opioids (excluding tobacco), major medical diseases (pulmonary, cardiovascular, renal, gastrointestinal or hepatic), organic mental disorders, or any type of psychosis.

Sixty patients were randomly assigned to three groups. All 60 patients received only a single high dose of buprenorphine and were observed for 13 days. Sublingual buprenorphine (one dose only) was administered while the patients were in moderate withdrawal from opioids (having four or five symptoms). The presence of fewer than four symptoms of opioid withdrawal symptoms was considered as constituting mild withdrawal, and the presence of 6 symptoms or more was regarded as severe withdrawal (3). Buprenorphine was administered at a dose of 32 mg, which is the maximum dosage presently administered clinically, as well as 64 and 96 mg.

We described the goals of the study, and guaranteed confidentiality. All the patients gave written informed consent prior to entering into the study. The questioning, interview and examination were conducted on at the treatment hospital.

Randomization: In a double blind manner the participants were randomly allocated in one of the three treatment groups. We used a standard randomization procedure produced by computer to have random sample set.

Procedure: The pills had the same color and shape. It was given sequentially in 8 mg increments. Placebo pills were given, so that patients on each dose did not know whether they were receiving 4, 8 or 12 dose units of 8 mg.

A visual analogue scale (The Opioid Craving Scale) was used to measure the opioid craving, ranging from 0 to 10 (0 means no craving at all and 10 means severe craving), (19). The Opioid Craving Scale, a modification of the Cocaine Craving Scale, is a short, 3-item scale used to measure opioid craving. The measure consists of 3 items rated on a visual analogue scale from 0-10. 1- How much do you currently crave opiates? (rated from not at all to extremely). 2- In the past day, please rate how strong your desire to use opiates has been when something in the environment has reminded you of opiates (rated from no desire to extremely strong). 3- Please imagine yourself in the environment in which you previously used opiates. If you were in this environment today and if it were the time of day that you typically used opiates, what is the likelihood that you would use opiates today? (rated from not at all to I'm sure I would use opiates), (19).

A placebo group was not included because of the high possibility of severe withdrawal without active pharmacological treatment. Outcome was monitored and measured by daily scoring of craving.

Although our ward was a controlled environment, however, for more observation, urine (TLC) was carried out before administration of the single dose, twice a week and at the end of the trial. To ensure safety, adverse effects, vital signs, gastrointestinal, respiratory and cardiovascular effects were monitored every hour for the first day, and then every 6-hour. For this research study withdrawal and detoxification were done in hospital because we administered "high doses" instead of standard dose. We advocate administering a single large dose on an inpatient basis and then have the patients released drug-free without medication assistance and with appointment for psychosocial follow up. In the follow-ups, if a

patient requires medication we would begin appropriate treatment such as buprenorphine maintenance treatment.

Statistical analysis:

Data analyses had both inferential and descriptive statistical methods. Data analysis was carried out by using SPSS version-21. We performed a repeated-measures two-way ANOVA with day and group as the two factors and Greenhouse-Geisser correction for violation of sphericity. Post-hoc t-tests of differences in means were achieved, and Chi-square was used to test for differences in frequencies among the groups. All tests were two-sided with significance set at $P \leq 0.05$.

Results

Data were obtained from 60 men whose mean age was 32.98 ± 7.42 years. All the patients whom were screened, entered the trial and all of them who entered, completed the study (Appendixes 1 and 2). During the period of the research, no illicit opioid consumption was found (regarding interview and urine drug screening tests). Three groups did not differ on education, job and marital status; $p > 0.05$). Based on table 1 they did not differ on age and duration of opioid abuse.

Figure 1 illustrates craving scores of the three groups during the 14-day treatment course. A significant main effect of day ($F(2, 2.08) = 147.90, p < 0.0005$) and group ($F(2, 57) = 4.09, p = 0.022$) and a non-significant group-by-day interaction ($F(2, 4.17) = 2.21, p = 0.069$) were detected.

Figure 2 demonstrates abstinence from opioids. Determination of relapse status at the end of 1- and 2-month outpatient follow-up done through patient interview and collateral information indicated a significant difference across the groups ($p < 0.05$).

Chi-square tests for 1-month out-patient follow up indicated that the 32-mg group differed significantly from both the 64 mg and 96 mg groups ($DF=2, \text{Chi square}=9.414, p=0.009$), with less relapse rate seen for the higher dose groups. No significant differences were seen between the 64-mg and 96-mg groups ($DF= 1, \text{Chi square} = 0.005, p\text{-value}= 0.942$), suggesting that the maximal effect on relapse rate was achieved with the 64-mg dose.

Chi-square tests for 2-month out-patient follow up showed that the 32-mg group differed significantly from 96 mg group ($DF= 1, \text{Chi square}= 5.757, p\text{-value} = 0.016$), with less relapse rate observed for the higher dose group. No significant differences were seen between other groups ($p\text{-value} > 0.05$), suggesting that the maximal effect on relapse rate was achieved with the 96-mg dose.

Adverse effects:

Some nausea did occur, which did not lead to vomiting. Five patients reported significant vomiting or hypotension; and they were treated administering antiemetic medications or hydration. No severe cardiovascular, respiratory, or gastrointestinal adverse effects were observed.

Discussion

For the craving decrease, the data indicated significant craving reduction for all 3 groups.

The outcomes demonstrate that a single large dose of buprenorphine can provide an effective and rapid means of treatment of opioid craving over 13 days during opioid withdrawal. Craving is associated to symptoms of withdrawal and is a core and essential feature of substance use disorders, as evidenced by its recent addition to the diagnostic criteria for these disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association), (3). Notably, doses higher than 16-24 mg are thought to raise the effective half-life of buprenorphine. Use of buprenorphine as a single large dose decreases concerns about compliance as well as the possibility of diversion of the drug for abuse. Further, cost considerations are favorable, particularly when considering administration to outpatients without hospital admission.

It should be mention that the idea of having an addict withdraw in the hospital under supervision and then returning him to the supportive family often occur in this center.

The advantage of a single high-dose treatment that we have employed is particularly suited to either referral to antagonist treatment, which could likely be started at an earlier point than it might be with traditional detoxification protocols lasting many days or even weeks. This would be a distinct advantage. However, it could also result in a more appropriate titration of agonist treatment, potentially with lower maintenance doses being required, or even use of depot forms of buprenorphine. In patients who are inappropriate for or disagree with either agonist or antagonist treatment, it would allow more rapid referral to either a residential or intensive outpatient treatment program.

Strengths of this research included the randomized clinical trial design and a reasonable number of patients, carefully diagnosed using DSM-5 criteria and urine drug screening test.

However, the research had some limitations. They included lack of a placebo group, and restriction of recruitment to men only. It would be important to know if the findings are generalizable to both sexes and the course of the effect of single-dose buprenorphine on opioid craving. The use of a single high dose of buprenorphine may be far more likely to result in respiratory or cardiovascular complications in older patients with underlying occult disorders, particularly sleep apnea.

Conclusions

The single high dose buprenorphine treatment provided safe and rapid treatment of opioid craving and positively impacted relapse in the initial 1- and 2-month outpatient treatment duration for opioid dependence. The results support further investigation of the administration of a single high dose of buprenorphine as an efficient and safe approach to early treatment of these patients. In addition, the findings support further studies to reduce opioid craving and relapse over more extended time frames.

Abbreviations

RCT: Randomized Clinical Trial; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; VAS: Visual Analogue Scale

Declarations

- Ethics approval and consent to participate: Yes, Ethics committee of Shiraz University of Medical Sciences and also Dr. Hashemi, Vice Chancellor for Research of the university, approval the research project.
- Informed consent has been received from all patients.
- Consent for publication: The patients in the study have agreed to the publication of their data.
- Availability of data and materials: Yes
- Competing interests: The authors declare that they have no competing interests.
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- Authors' contributions: JA proposed the idea, wrote the proposal and drafted the manuscript, MS collected the data and assisted writing the manuscript, DG and EL contributed to data analysis and interpretation and finalizing the manuscript. All authors read and approved the final manuscript.
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Tables

Table 1. Characteristics of Research Participants

Buprenorphine dose	32 mg (n = 20)	64 mg (n = 21)	96 mg (n = 19)	p value ^a
Age (years) ^b	35.0 ± 7.38	32.5 ± 9.14	31.4 ± 4.70	0.284
Opioid misuse ^b duration (years)	10.8 ± 5.70	10.4 ± 7.37	9.94 ± 5.91	0.908

^aThe three groups were compared by ANOVA.

^bNumbers shown are means ± SD.

Figures

Figure 1

Craving scores of the three groups during the 13-days following buprenorphine administration.

Figure 2

Abstinence from opioids at 1 and 2 months following discharge from hospital.

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