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Original Article

Rapid effect of a single-dose buprenorphine on reduction of opioid craving and suicidal ideation: A randomized, double blind, placebo-controlled study

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Abstract

Objective: Opioid use disorder is a prevalent addiction problem that can be treated with buprenorphine, but dependence, diversion, and abuse of buprenorphine occur. Although including naloxone reduces these problems, the combination formulation is not available worldwide. The administration of the medication under supervision may also be useful in decreasing unintended uses of the medication. The objective is to assess the influence of a single, physician-administered dose of buprenorphine on withdrawal craving and suicidal ideation in opioid-dependent patients over a period of 4 days of abstinence from opioids. **Materials and Methods:** Sixty-one men who used heroin, opium, or prescription opioids and met Diagnostic and Statistical Manual of Mental Disorders Five Edition criteria for opioid use disorder were randomized to receive a single, sublingual dose of buprenorphine (16 mg, 32 mg, or placebo; n's = 20, 20, and 21 per group). The study was carried out in an inpatient psychiatric ward, with appropriate precautions and monitoring of cardiovascular and respiratory measures. Buprenorphine was administered when the patients were in moderate opioid withdrawal, exhibiting four to five symptoms. Self-reports of craving (The Opioid Craving Scale) and suicidal ideation (Beck Scale for Suicidal Ideation) were taken at baseline and on each of the 4 days after treatment. **Results:** The group did not differ significantly on demographic features, and all of the patients completed the 4-day study. Craving was reduced from baseline during the observation period in each of the three groups, demonstrating a significant effect of treatment ($P < 0.0005$), and the dose-by-time interaction ($P < 0.0005$). Both 32 mg and 16 mg groups differed significantly from the placebo group. No significant differences were observed between the 32 and 16 mg groups, suggesting that the maximal effect on craving reduction was achieved with the 16-mg dose. Suicidal ideation was decreased from baseline during the observation period in each of the three groups, demonstrating a significant effect of treatment ($P < 0.0005$), and the dose-by-time interaction ($P < 0.017$).The 32 mg group differed significantly from the placebo group. No significant differences were observed between the 16 and placebo groups, suggesting that the maximal effect on suicidal ideation reduction was achieved with the 32 mg dose. **Conclusions:** A single high dose of 16 mg or 32 mg buprenorphine reduces opioid craving, but a single high dose of only 32 mg buprenorphine reduces suicidal ideation.

Keywords: *Buprenorphine, Opioid withdrawal craving, Suicidal ideation*

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Introduction

Buprenorphine is safer with respect to other opioids, particularly methadone. First, Buprenorphine has potential benefits compared to short-acting opioids with regard to withdrawal symptomatology. The severity of buprenorphine withdrawal symptoms is less than short-acting opioids due to its longer half-life and slower elimination. Second, accidental overdosing is self-limiting, due to an early ceiling effect, such that tolerant subjects do not have that risk [1]. Buprenorphine a partial agonist at mu opioid receptors and antagonist at delta- and kappa-opioid receptors, has been investigated mainly for the treatment of Opioid Use Disorder [2-13]. It is considered safer than methadone [5-7], with 8 mg of buprenorphine

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being as efficient as 60 mg of methadone [8]. Buprenorphine is well absorbed following sublingual administration [4,9,10]. In animals, buprenorphine illustrates a flattened or inverted U-shaped curve, with dose-correlated rises in antinociceptive influence at lower doses and either no greater antinociception or a decrease in effect at higher doses [14,15]. Buprenorphine has not only typical mu opioid agonist effects, such as sedation, euphoria, and analgesia, but also its partial agonist action at mu opioid receptors has favored the use of buprenorphine over methadone and especially, the minimal respiratory depressant influences of buprenorphine create greater safety [14-26].

The primary goal of this research study was to detect the effects of single, doses of buprenorphine (16 and 32 mg) and placebo in the management of craving during opioid withdrawal. Craving is associated with symptoms of withdrawal and is a core 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 Five Edition (DSM-5; American Psychiatric Association) [3,17,20,21]. Craving persists after detoxification is completed and can raise relapse rate [3,17,21,22].

The other purpose of this study was to explore the effects of single, doses of buprenorphine in the management of suicidal ideation in opioid-dependent patients because a significant number of patients with opioid use disorders-severe type have suicidal ideation [18].

Now, we are administrating only a single high dose of sublingual buprenorphine as an original inlet for the rapid management of suicide, because we theorize that the biochemistry involved in suicidal thought is approximately similar to opioid dependence and has been accompanied with dysregulation of the endogenous opioid system [18]. Moreover, buprenorphine is a strong kappa and delta receptor antagonist; therefore, it lowers the level of suicidal ideation [18]. To the best of our knowledge, we could rarely find published controlled trials on this important affair (use of a single high dose of buprenorphine for the treatment of suicidal ideation) [18].

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 use) and to enhance mu opioid receptor occupancy.

A single high dose was tested because repeated buprenorphine administration (and also based on our clinical experiences in Iran) in outpatients raises the possibility of buprenorphine dependence, diversion, or abuse [1,3,18,22,27,28]; thus, single high dose would have advantageous effect and make the initial withdrawal duration easier. It is often the case in this university center that opioid-dependent patients 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 occurs in this center. In follow-ups, if a patient needs pharmacotherapy, we would begin appropriate treatment such as buprenorphine maintenance treatment. Moreover, buprenorphine was used rather than methadone because of the risk of overdose with a single, high dose of methadone [22-24].

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee of the institute. Informed written consent was obtained from all patients prior to their enrollment in this study. At screening, patients were interviewed and examined by a board certified psychiatrist to have eligibility. Prior to each questioning and interview, we explained the aims of the study, and guaranteed confidentiality. All the patients gave written informed consent before enrolling into the research.

The study was approved and monitored by the Ethics Committee of Shiraz University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research.

The interview, examination, and questioning were conducted on the premises of the treatment hospital because it seemed a comfortable and nonthreatening environment. To consider confidentiality and increase the validity of information, data were collected from the patient in the absence of those who accompanied the patient.

Only male patients were considered for the study because only male are hospitalized in this referral psychiatric ward. Those patients who had initial eligibility requirements on screening, were administered the Structured Clinical Interview for DSM-5, Clinical Version, by a board-certified psychiatrist, to confirm that they had the criteria for opioid use disorder [3]. Sixty-one patients were randomly entered into three treatment groups. All 61 participants took only a single dose of buprenorphine or placebo and completed the 4-day trial period.

Daily opioid abuse for at least 1 year (to establish tolerance) was a requirement. Patients were excluded if they had substance use disorders other than opioids (excluding tobacco), organic mental disorders, major medical diseases (pulmonary, cardiovascular, hepatic, renal, or gastrointestinal), or any type of psychosis. Those who were not interested in recruitment at the start of the trial were kept out.

Sublingual buprenorphine or placebo (one dose only) was administered while the participants were moderately in opioid withdrawal (having four or five symptoms). The presence of two or three symptoms of opioid withdrawal symptoms was regarded as constituting mild withdrawal, and the presence of six symptoms or more was considered as severe withdrawal [3]. The buprenorphine doses examined were 16 mg or 32 mg, which is the maximum dosage currently administered clinically.

Randomization

In a double-blind manner, the participants were randomly enrolled in one of the three treatment groups. We administered a computer standard randomization procedure (random number tables) to have random sample set.

Procedure

The research team was fully trained and includes: general psychiatrist, addiction psychiatrist, nurse, psychologist, and statistician. The pills had the same shape and color. 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 0, 2, or 4 dose units of 8 mg.

The patients and the research team were blind to the administered medications for the course of the study. The ratings and interviews were achieved by a fully trained physician who was unaware of medications and adverse effects.

A visual analog 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 three items rated on a visual analog scale from 0 to 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].

The psychometric assessment of beck scale for suicidal ideation was administered to the inpatients to monitor the level of suicidal ideation [20] before developing of opioids withdrawal symptoms.

Scoring of craving and suicidal ideation was measured in the morning on each day. Patients did not receive any form of compensation. The sublingual tablet covered by the hospital system. During the inpatient stay, there were not employed any other methods of coping with craving (e.g., group sessions focused on relaxation/mindfulness/distraction/etc.).

Patients randomly received 16 mg or 32 mg buprenorphine or placebo as a single dose only while they developed moderate opioid withdrawal symptoms. Patients were followed up for 4 days. Outcome was monitored and scored by once daily measuring of craving and suicidal ideation.

Although our inpatient facility was a controlled environment, however, for more observation and accuracy, urine toxicology was carried out before administration of the single dose and during the trial. To ensure safety, adverse effects, vital signs, respiration, and gastrointestinal effects were monitored every day.

Statistical analysis

Data analyses included both descriptive and inferential statistical methods. Data analysis was achieved using PASW Statistics version 21 software (SPSS, Chicago, IL, USA). We conducted a repeated-measures two-way ANOVA with group and day as the two factors and Greenhouse-Geisser correction for violation of sphericity. *Post hoc t*-tests of differences in means were performed, and Chi-square was used to examine for differences in frequencies among the groups. All tests were two-sided with statistical significance set at $P \leq 0.05$.

Results

Data were collected from 61 men whose mean age was 36.50 ± 9.06 years. All the patients, whom were screened, entered the research study and all of them who entered, completed the trial [Diagrams 1 and 2]. During the trial, no illicit opioid abuse was detected (regarding everyday interview and urine toxicology). Three groups did not differ on age, duration of opioid abuse and job [Table 1]. Table 2 illustrates craving-mean ratings at baseline and on each of the 4 days. Figure 1 shows craving scores of the three groups during the 4-day treatment time. A significant main effect of day (F [2, 2.776] = 139.292, $P < 0.0005$) and group (F [2, 58] = 45.823, $P < 0.0005$) and group by day interaction (F [2, 5.552] =29.306, $P < 0.0005$) were detected.

Both the 32 mg and 16 mg groups differed significantly from the placebo group. No significant differences were observed between the 32 and 16 mg groups, suggesting that the maximal effect on craving reduction was achieved with the 16-mg dose.

Table 3 illustrates suicidal ideation-mean ratings at baseline and 4 days. Figure 2 shows suicidal ideation scores of the three groups during the 4-day treatment time. A significant main effect of day (F [2, 1.692] =139.292, $P < 0.0005$) and group (F [2, 58] =4.724, $P < 0.013$) and group by day interaction (F [2, 3.384] =3.375, $P < 0.017$) were detected.

The 32 mg group differed significantly from the placebo group. No significant differences were observed between the 16 mg and placebo groups, suggesting that the maximal effect on suicidal ideation reduction was achieved with the 32 mg dose.

Table 1: Characteristics of research participants in three treatment groups

Group	Placebo (*n*=21)	16 mg (*n*=20)	32 mg (*n*=20)	Total (*n*=61)	χ^2	*F*	df	*P*[a]
Age[b]	33.38±8.89	37.70±8.44	38.60±9.37	36.50±9.06		2.022	2	0.142
Duration of opioid abuse (years)[b]	7.42±5.75	11.50±7.16	9.32±5.65	9.38±6.34		2.194	2	0.121
Job[c], *n* (%)								
Un employed	6 (28.6)	7 (35)	7 (35)	20 (32.8)	13.899		4	0.084
Self employed	14 (66.7)	13 (65)	8 (40)	35 (57.4)				
Employee	0	0	4 (20)	4 (6.6)				

[a]The three groups were compared by ANOVA (continuous measurement variables) and Chi-square analysis (categorical data), [b]Numbers tabulated indicate means±SD, [c]Numbers tabulated indicate how many participants were in each category. SD: Standard deviation

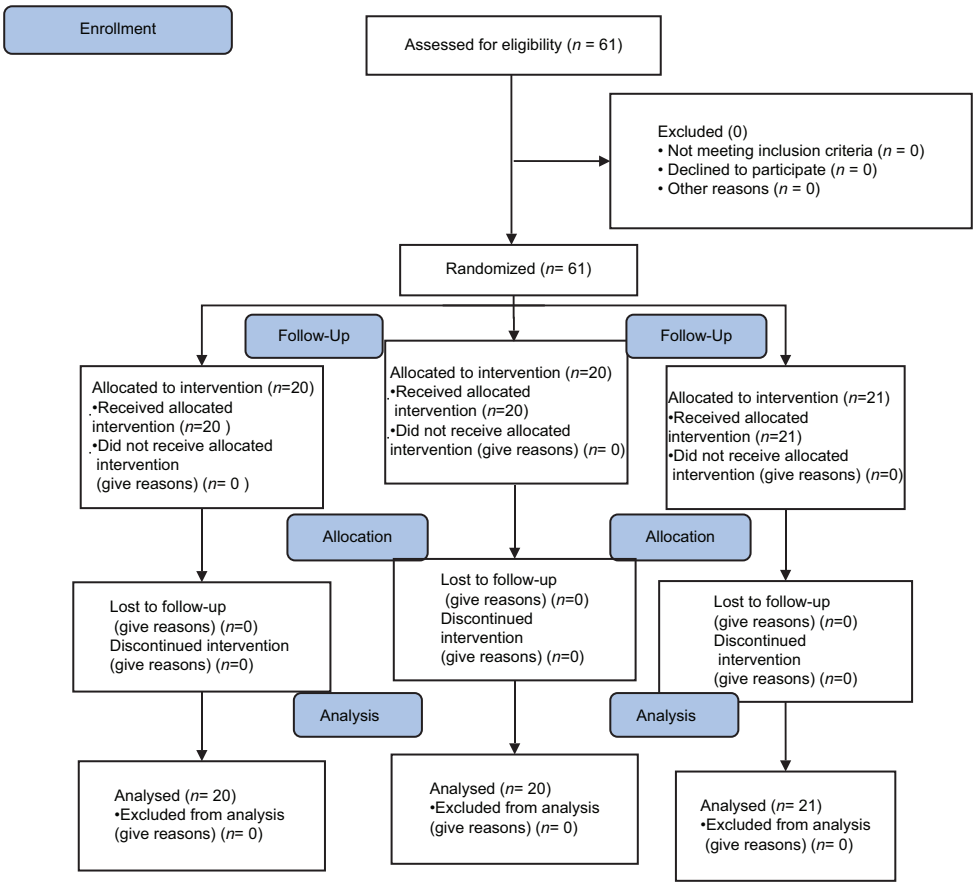

Diagram 1: Consolidated Standards of Reporting Trials flowchart of the patients in this trial

Table 2: Craving - mean ratings at baseline and 4 days

Day/ group	Placebo (*n*=21)	16 mg (*n*=20)	32 mg (*n*=20)	*F*	df	*P*[a]
Baseline[b]	9.71±0.64	9.85±0.48	9.10±2.40	1.517	2	0.228
Day 1[b]	9.28±1.007	5.95±1.79	5.50±3.88	13.909	2	<0.0005
Day 2[b]	7.90±1.17	1.20±1.10	3.70±3.54	47.352	2	<0.0005
Day 3[b]	7.23±1.22	0.00±0.00	2.50±3.03	78.765	2	<0.0005
Day 4[b]	5.95±1.46	0.00±0.00	1.70±2.57	78.765	2	<0.0005
F	82.730	463.960	46.284	66.418		
P	<0.0005	<0.0005	<0.0005			
df	4	4	4			

[a]The three groups were compared by ANOVA, [b]Numbers shown are means±SD. SD: Standard deviation

Mean craving[b]	Mean±SD	*P*[a]
Placebo versus 16 mg	4.61±0.505	<0.0005
Placebo versus 32 mg	3.51±0.505	<0.0005
16 mg versus 32 mg	1.100±0.511	0.089

[a]The three groups were compared by *post hoc t*-tests, [b]Numbers shown are means±SD. SD: Standard deviation

Table 3: Beck scale for suicidal ideation - mean ratings at baseline and 4 days

Day/group	Placebo (*n*=21)	16 mg (*n*=20)	32 mg (*n*=20)	*F*	df	*P*[a]
Baseline[b]	6.38±1.93	7.10±3.82	5.65±3.75	0.981	2	0.381
Day1[b]	3.90±2.64	1.95±3.39	1.30±2.17	4.896	2	0.011
Day2[b]	2.42±2.23	0.200±0.894	0.050±0.223	16.965	2	0.00
Day3[b]	0.809±2.04	0.00±0.00	0.00±0.00	3.144	2	0.051
Day4[b]	0.333±1.15	0.00±0.00	0.00±0.00	1.664	2	0.198
F	69.073	48.004	36.713			
P	0.00	0.00	0.00			
df	4	4	4			

[a]The three groups were compared by ANOVA, [b]Numbers shown are means±SD. SD: Standard deviation

Mean BSSIb	Mean±SD	*P*[a]
Placebo versus 16 mg	0.921±0.455	0.116
Placebo versus 32 mg	1.37±0.455	0.011
16 mg versus 32 mg	0.450±0.461	0.595

[a]The three groups were compared by *post hoc t*-tests, bNumbers shown are means±SD. SD: Standard deviation, BSSI: Beck scale for suicidal ideation

Adverse effects

None of the patients reported significant nausea, vomiting, or hypotension. No severe cardiovascular, respiratory, or gastrointestinal adverse effects were observed.

Discussion

The outcomes indicate that a single dose of buprenorphine (16 mg or 32 mg) can provide a rapid, effective, and safe means of treatment of opioid craving over 4 days during opioid withdrawal. All treatment groups decreased suicidal ideation at 4 days posttreatment. Remarkably, dose higher than 16–24 mg, i.e., 32 mg is thought to increase the effective half-life of buprenorphine, therefore, was more effective in reduction of suicidal ideation. The administration of buprenorphine as a single large dose reduces concerns about compliance

Diagram 2: **CONSORT 2010 checklist of information to include when reporting a randomized trial***

Section/topic	Item number	Checklist item	Reported on page number
Title and abstract	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	3
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	3
	8b	Type of randomization; details of any restriction (such as blocking and block size)	3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how	3
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	3
	13b	For each group, losses and exclusions after randomization, together with reasons	3
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3
	14b	Why the trial ended or was stopped	3
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	4

Contd...

Diagram 2: Contd...

Section/topic	Item number	Checklist item	Reported on page number
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	6
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	6
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	6
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6

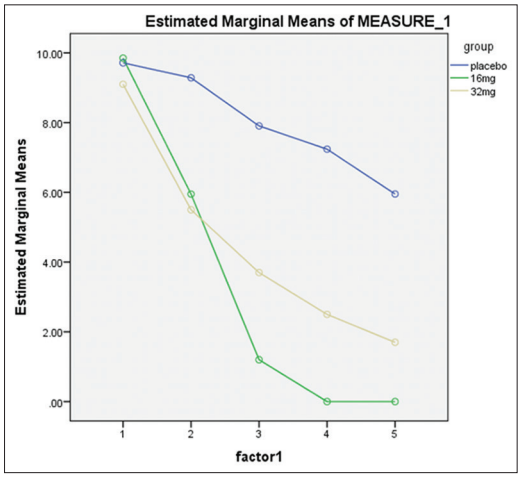

Figure 1: Craving scores of the three groups during the 4-day treatment time. A significant main effect of day (F [2, 2.776] = 139.292, $P < 0.0005$) and group (F [2, 58] = 45.823, $P < 0.0005$) and group by day interaction (F [2, 5.552] = 29.306, $P < 0.0005$) were detected

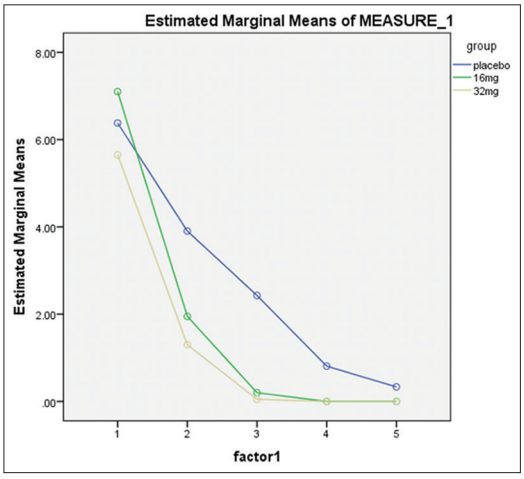

Figure 2: Suicidal ideation scores of the three groups during the 4-day treatment time. A significant main effect of day (F [2, 1.692] = 139.292, $P < 0.0005$) and group (F [2, 58] = 4.724, $P < 0.013$) and group by day interaction (F [2, 3.384] = 3.375, $P < 0.017$) were detected

as well as the probability of dependence, diversion, and abuse. In addition, cost considerations are favorable, especially when regarding administration to outpatients without hospitalization.

It should be regarded that the idea of having an addict withdraws in the hospital under observation and then returning him to the caring family usually happen in Iran.

The benefit of a single-dose treatment that we have administered is notably suited to either referral to antagonist treatment, which could probably be started at an earlier time than it might be with traditional detoxification schedule lasting many days or even weeks. This would be a distinct benefit. Moreover, it could also result in a more suitable titration of agonist treatment, potentially with lower maintenance doses being required or even administration of depot forms of buprenorphine. In patients who are unsuitable for or disagree either agonist or antagonist treatment, it would allow more rapid referral to either an intensive outpatient or residential treatment program.

We should mention that in Iran, we usually detoxify patients based on outpatient treatment programs by buprenorphine or methadone or clonidine.

Strengths of this study included the randomized clinical trial design and a sensible number of participants, carefully diagnosed using DSM-5 criteria and urine toxicology.

However, the study had some limitations. They included use of a single item to measure craving and restriction of recruitment to male only. It would be important to know if the results are generalizable to both sexes and the period of the effect of single-dose buprenorphine on opioid craving. The administration of a single high dose of buprenorphine may be far more likely to result in cardiovascular or respiratory complications in older patients with underlying occult disorders, especially sleep apnea.

Conclusions

The single-dose buprenorphine treatment provided safe and rapid treatment of opioid craving and suicidal ideation for opioid dependence. The outcomes support further exploration of the use of a single dose of buprenorphine as a safe and effective protocol to early treatment of these patients. Moreover, the findings support further investigations to decrease opioid craving and suicidal ideation over more extended time frames.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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