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Ultrarapid Influence of Buprenorphine on Major Depression in Opioid-Dependent Patients: A Double Blind, Randomized Clinical Trial

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ABSTRACT

Objective: To examine the impact of different doses of buprenorphine on depression symptoms in opioid dependent inpatient over a three-day interval, using a randomized clinical trial design (RCT).

Design: Patients were randomized and assigned to three groups.

Participants: Forty males who were admitted to an inpatient psychiatric unit and who fulfilled the DSM-5 criteria for both opioid dependence and major depressive disorder.

Intervention: Patients randomly received 32 mg, 64 mg, or 96 mg of buprenorphine as a single high dose. Out of 40 patients, 11 (27.5%) received 32 mg, 14 (35%) received 64 mg and 15 (37.5%) received 96 mg of buprenorphine. We conducted medical precautional measures, including cardiovascular and respiratory monitoring.

Measurements: Depression was measured by the Beck Depression Inventory (BDI). All patients completed the three-day treatment duration. The results showed a significant reduction in depression symptoms within each of the three groups ($p = 0.00$), although there was no significant difference in depression outcome across the groups ($p = 0.90$).

Conclusions: The results suggest that a single high dose of buprenorphine could provide a safe, simple and speedy means of depression improvement. A single high dose of buprenorphine can be used as medication that supplies a fast and maintained treatment for major depressive disorder in patients who are opioid dependent. Placebo-controlled trials of longer periods and larger sample sizes are needed to test ability and safety, as well as the physiological and psychological impact of extended exposure to this drug.

Introduction

Findings from several studies have shown that patients with substance-use disorders suffer from high grades of depression (Dorus & Senay, 1980; Ross et al., 1988; Rounsaville et al., 1982), personality disorders (Dejong et al., 1993; Nace et al., 1991), and minor psychopathology (Darke et al., 1992; Swift et al., 1990). Clinical assessments have demonstrated that major psychiatric symptomatology is associated with the failure or success of detoxification from opioid dependency (Kosten et al., 1982) and that coexisting mental illness, primarily depression, can negatively affect recovery. Moreover, studies have found that opioid-dependent patients who experience depression at the beginning of treatment are less likely to be substance-free at follow-up than opioid dependents with normal mood (Rounsaville et al., 1985). Buprenorphine, ketamine, and ayahuasca have been found to lower the rate of depression (Ahmadi, 2016a; 2016b; Falcon et al., 2015; Gerra et al., 2006; Gracer, 2007; Ipser et al., 2013; Maremmani et al., 2011; Osório Fde et al., 2015; Sadock et al., 2015; Sanches et al., 2016). Likewise, buprenorphine can moderate the level of depression and suicidal tendencies (Ahmadi, 2016a; 2016b).

As a partial agonist, buprenorphine has an eminent attraction to $\mu$-opioid receptors. Additionally, buprenorphine binds more firmly than methadone to these receptors. Furthermore, buprenorphine shows pharmacological influences that are more characteristic of an antagonist. Accordingly, these factors can have important indications for clinical practice. Buprenorphine is characterized by the dual effects of inducing opioid reactions while obstructing the influence of extra opioid use.

Although previous studies have found that buprenorphine can reduce depression, the (US) Food and Drug Administration has not approved buprenorphine as a treatment for depression. Because of buprenorphine's addiction potential, it is not usually prescribed to treat depression. Still, we are optimistic that research will examine single-dose buprenorphine as a treatment for depression in patients who are opioid-dependent.
Buprenorphine is used to reduce cravings and withdrawal associated with opioid dependency, and has also been used as a treatment for major pain (Sadock et al., 2015). Presently, we are using a single dose of sublingual buprenorphine as a novel approach for the treatment of depression, because we consider and theorize that the biochemistry involved in depression is more or less the same as opioid dependence (Falcon et al., 2015; Gerra et al., 2006; Ipser et al., 2013; Maremmani et al., 2011; Sadock et al., 2015). In addition, major depressive disorder has been associated with dysregulation of the endogenous opioid system (Fava et al., 2016).

Buprenorphine is a partial agonist at \( \mu \)-opioid receptors so it reduces the level of depression, dysphoria, anxiety, pain, and opioid withdrawal symptoms. In addition, buprenorphine is a strong kappa receptor antagonist, therefore it decreases the amount of depression, anxiety, and hostility (Falcon et al., 2015; Gerra et al., 2006; Ipser et al., 2013; Maremmani et al., 2011; Sadock et al., 2015).

To our knowledge, controlled trials have not investigated the effect of single high-dose buprenorphine on depression. Consequently, our clinical trial represents a novel approach. The main goal of this trial was to examine the single-dose effect of 32, 64, or 96 mg of buprenorphine on depression in male patients who are opioid-dependent.

Methods and materials

Subjects

Forty opioid-dependent men seeking treatment were selected randomly from the main and referral psychiatric hospital affiliated to Shiraz University of Medical Sciences in 2016. The subjects were diagnosed with both major depressive and severe opioid use disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Five Edition (DSM-5) criteria by a board certified psychiatrist through Structured Clinical Interview for DSM-5, Clinical Version (SCID-I). The study was restricted to males because the University’s main psychiatric ward is limited to men.

At screening, patients were questioned and examined by a board-certified psychiatrist so that eligibility could be ascertained. Before each interview, we explained the aims of the study, guaranteed confidentiality, and received written informed consent. The interviews and examinations were conducted on the premises of the treatment hospital because of its nontreating environment. Family members, relatives, and friends accompanied patients to the hospital; their involvement also helped to verify the data collected from the patients. The criterion for study participation was daily use of opioids for at least 1 year. Patients were excluded from the trial if they had substance-use disorder that did not include opioids, had been diagnosed with opioid-induced depressive disorder, or had been diagnosed with other serious medical illness (e.g., hepatic, renal, pulmonary, cardiovascular, or gastrointestinal diseases).

Sublingual buprenorphine (as a single dose only) was given slowly while the patients were moderately in withdrawal from opioids. All subjects provided written informed consent before participating in the study. The clinical trial was approved and monitored by the ethic committee of Shiraz University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research involving human subjects.

Procedure

This research was a randomized double blind clinical trial. The Beck Depression Inventory (BDI) was administered to patients in order to monitor the level of depression before developing opioid withdrawal symptoms. Patients were evaluated for 3 days. The main outcome was calculated by daily measurement of depression scores based on the BDI and also via structured interview. Safety and tolerability were assessed using spontaneously reported adverse event data and rates of premature termination for side effects. During the trial, no other intervention was allowed.

Patients were randomly assigned to single-dose buprenorphine of 32, 64, or 96 mg when the patients were experiencing moderate opioid withdrawal symptoms. Out of 40 patients, 11 (27.5%) received 32 mg, 14 (35%) received 64 mg, and 15 (37.5%) received 96 mg of buprenorphine. Patients were then monitored for 3 days.

Data analysis

SPSS version 18 was used to analyze the data. Chi-square and significance tests were utilized to examine differences in frequencies. Analysis of variance or t-test analyses were used to examine differences in means. All probability values were two-sided and statistical significance was set at the 5% level.

Results

Sample characteristics are presented in Table 1. The male patients had a mean age of 34 years and had been using drugs for 10.71 years on average. Most patients were self-employed (24/40; 60%) and reported their highest educational level to be primary (40%) or high school (35%). Nearly three-quarters (72.5%) of the patients were
Table 1. Demographic characteristics of the patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>32 mg N = 11</th>
<th>64 mg N = 14</th>
<th>96 mg N = 15</th>
<th>Total N = 40</th>
<th>Chi-square</th>
<th>df</th>
<th>p value</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>33.45 ± 8.44</td>
<td>34.21 ± 6.44</td>
<td>34.80 ± 5.38</td>
<td>34.22 ± 6.54</td>
<td>2</td>
<td>0.880</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>Duration of drug abuse (mean)</td>
<td>9.95 ± 7.43</td>
<td>11.57 ± 7.05</td>
<td>10.46 ± 5.44</td>
<td>10.71 ± 6.47</td>
<td>2</td>
<td>0.819</td>
<td>0.201</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2(18.2)</td>
<td>5(35.7)</td>
<td>3(20)</td>
<td>10(25)</td>
<td>2.761</td>
<td>4</td>
<td>0.599</td>
<td>—</td>
</tr>
<tr>
<td>Self-employed</td>
<td>8(72.7)</td>
<td>6(42.9)</td>
<td>10(66.7)</td>
<td>24(60)</td>
<td>6(42.9)</td>
<td>10(66.7)</td>
<td>24(60)</td>
<td>0.599</td>
</tr>
<tr>
<td>Employed</td>
<td>1(9.1)</td>
<td>3(21.4)</td>
<td>2(13.3)</td>
<td>6(15)</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>1(9.1)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>12.5</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>Primary school</td>
<td>3(27.3)</td>
<td>4(28.6)</td>
<td>9(60)</td>
<td>16(40)</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>High school</td>
<td>3(27.3)</td>
<td>7(50)</td>
<td>4(26.7)</td>
<td>14(35)</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>Higher education</td>
<td>4(36.4)</td>
<td>3(21.4)</td>
<td>2(13.3)</td>
<td>9(22.5)</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>4(36.4)</td>
<td>2(14.3)</td>
<td>4(26.7)</td>
<td>3.277</td>
<td>4</td>
<td>0.513</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>7(63.6)</td>
<td>11(78.6)</td>
<td>11(73.3)</td>
<td>29(72.5)</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
<tr>
<td>Divorce</td>
<td>0(0)</td>
<td>1(7.1)</td>
<td>0(0)</td>
<td>12.5</td>
<td>7.931</td>
<td>6</td>
<td>0.243</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2. Beck depression scores before and after buprenorphine administration.

<table>
<thead>
<tr>
<th>Group</th>
<th>Day</th>
<th>32 mg N = 11</th>
<th>64 mg N = 14</th>
<th>96 mg N = 15</th>
<th>F</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>29.00 ± 10.02</td>
<td>27.00 ± 12.90</td>
<td>29.73 ± 10.85</td>
<td>0.213</td>
<td>2</td>
<td>0.809</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>13.54 ± 10.42</td>
<td>14.78 ± 14.29</td>
<td>13.73 ± 12.29</td>
<td>0.053</td>
<td>2</td>
<td>0.948</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>7.09 ± 7.81</td>
<td>12.00 ± 13.27</td>
<td>9.00 ± 12.87</td>
<td>0.712</td>
<td>2</td>
<td>0.497</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>4.09 ± 4.90</td>
<td>6.42 ± 12.62</td>
<td>4.33 ± 9.03</td>
<td>0.237</td>
<td>2</td>
<td>0.790</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>48.37</td>
<td>20.23</td>
<td>61.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total of days</td>
<td>13.25 ± 6.94</td>
<td>15.05 ± 11.72</td>
<td>14.20 ± 10.33</td>
<td>0.104</td>
<td>2</td>
<td>0.901</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Depression has been associated with dysregulation of the endogenous opioid system and buprenorphine/samidorphan combination is a promising candidate for treatment of patients who have an inadequate response to standard antidepressants (Fava et al., 2016). Karp et al. (2014) indicated that buprenorphine can be administered for treatment of resistant-depression in adults in mid-life and among elderly patients. However, those findings were limited by the low dose of buprenorphine that was administered and by the open label design of the trial (Karp et al., 2014). Yovell et al. (2016) showed that the short-term administration of very low dosages of sublingual buprenorphine resulted in reduced suicidal ideation in severely suicidal individuals without substance misuse. Although our trial is consistent with other studies, the findings in the present study are unique in that high-dose buprenorphine administered one time only significantly reduced depression regardless of dosage level that was administered. By the end of 3 days, none of the patients had major depressive disorder. We followed up with the patients 2 weeks later while they attended an outpatient clinic and their depression had not reduced to levels observed at baseline.

Our clinical trial illustrated that a single high-dose buprenorphine appears to be clinically safe, helpful, and effective. The findings indicate that a single high dose of buprenorphine can supply a simple, safe, speedy, and suitable means of treatment of depression. A single high-dose

Figure 1. Repeated measure.
dose of buprenorphine means that compliance is less of a problem and diversion is unlikely. In addition, the cost considerations appear to be favorable, particularly when outpatients do not need inpatient admission. Still, the present study is best described as a pilot and the findings of the present research need to be replicated with larger samples.

**Conclusion**

The findings showed a considerable reduction in depression symptoms within each of the three groups, but no significant differences in outcomes across groups. A single high dose of buprenorphine can be considered to be a new mechanism that offers quick treatment for major depressive disorder in opioid-dependent patients. Placebo-controlled trials of longer periods and with larger sample sizes are needed to evaluate safety, ability, and psychological and physiological impact of extended exposure to this medication.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

**Authors contributions**

JA proposed the idea, wrote the proposal and the manuscript. MS collected the data and assisted with writing the manuscript.

**References**


