Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: Preliminary results of an open randomized study

Felice Nava a,⁎, Ezio Manzato a,b, Claudio Leonardi a,c, Alfio Lucchini a,d

a Italian Society of Addiction Medicine (FeDerSerD), Milan, Italy
b Department of Addiction Medicine, Verona-Zevio, Italy
c Department of Addiction Medicine, Rome, Italy
d Department of Addiction Medicine, Milan, Italy

Abstract

An open randomized study lasting 12 months was performed to evaluate the efficacy of methadone or buprenorphine to suppress alcohol use in two hundred and eighteen heroin addicts with alcohol dependence. Daily maintenance doses of methadone were 80, 120, 160, and 200 mg/day, while doses of buprenorphine were 8, 16, 24, and 32 mg/day.

As expected, both treatments were able to reduce both heroin use and addiction severity (measured with ASI interview). However, although both medications were able to suppress alcohol use, the highest dose of buprenorphine was better than the highest dose of methadone, in reducing alcohol craving, ethanol intake (measured as daily number of drinks), and the ASI subscale of alcohol use.

The mechanism underlying the effects of the opioid maintenance therapy on the reduction of alcohol intake is still unclear. The results of the present study may represent the first clinical evidence of the potential effective use of the highest doses of buprenorphine for the suppression of ethanol intake in heroin addicts with alcohol dependence.

© 2008 Elsevier Inc. All rights reserved.

1. Introduction

Heroin users often drink alcohol excessively (Almog et al., 1993; Backmund et al., 2003) and while this often has serious health consequences (Gossop et al., 2002) there is limited epidemiological data on prevalence.

Excessive alcohol use is also frequent in methadone-treated patients. Depending on how alcoholism is defined, it occurs in 5% to 50% in methadone-treated patients (Backmund et al., 2003; Rittmannsberger et al., 2000).

Alcohol dependence can worsen the outcome of methadone treatment (Gossop et al., 2006; Ottomanelli, 1999) and is associated with increased psychiatric symptoms (Westreich, 2005) and reduced quality of life (Sنبانjo et al., 2006). Moreover, alcohol use appears to be associated with more illicit drug use, higher rates of drop-out and higher mortality (Joseph and Appel, 1985; Zador and Sunjic, 2000).

Since the effect of the opioid maintenance therapy on alcohol consumption in heroin addicts is not yet defined, we decided to evaluate it to those treated with methadone and buprenorphine.

2. Methods

2.1. Subjects

We screened heroin addicts with co-existing alcohol dependence who provided informed consent to participate in the study. Individuals who met the criteria for the inclusion in the study were randomized to study conditions (see Fig. 1). The characteristics of the subjects selected for the study are reported in Table 1.

The patients received a weekly, free individual standardized counseling session for drug use, family and vocational issues. All subjects were admitted directly to treatment without a waiting list. The rationale of the study was blinded to the participants.

Study inclusion required: (1) DSM-IV TR diagnosis for heroin and alcohol dependence; (2) age 18 years or older; (3) no pregnancy; (4) no axis I or other drug-dependence disorders; (5) no HIV antibodies; (6) no serious physical illness (e.g. active tuberculosis, acute hepatitis or cirrhosis, renal and cardiovascular illness, unstable diabetes); (6) willingness to accept a substitute pharmacological treatment for heroin dependence; (7) to refuse a specific pharmacological treatment for...
alcohol dependence; and (8) no previous pharmacological treatment for drug abuse (including any psychopharmacological treatment or an opioid substitutive therapy). HCV positive patients were not excluded from the study. Subjects who had recent histories of violence or who were on parole/probation were excluded from the research.

Individuals who met the above criteria were evaluated by medical history and physical examination, chest X-ray, EKG and chemistry, hematology and urinalysis testing.

The study was approved by the local ethics committees and it was conducted according to the Principles of Helsinki Declaration, the Good Clinical Practice Consolidated Guidelines and the Italian Law on Privacy of Personal Data.

2.2. Study design

An open randomized prospective study evaluating the effects of methadone and buprenorphine in heroin addicts with alcohol dependence was performed. The study was conducted in Lombardia and Lazio regions (Italy) and it was publicized by notices, word-of-mouth and written information. The evaluation period started in October 2005 and ended in October 2007. If the eligibility criteria were met, participants were invited to come to the outpatient clinic on the morning before the admission day to provide a urine specimen and they were invited to immediately stop their heroin use. Sixteen of the subjects who met the eligibility criteria refused to participate in the study and they received

Table 1
Demographic characteristics and drug use of participants on admission to treatment

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
<th>Methadone (n = 108)</th>
<th>Buprenorphine (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (S.D.), years</strong></td>
<td></td>
<td>31.61±7.94</td>
<td>33.36±5.65</td>
</tr>
<tr>
<td><strong>Men (%)</strong></td>
<td></td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>**High School education (%)</td>
<td></td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td><strong>Degree or PhD (%)</strong></td>
<td></td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Stable employment (%)</strong></td>
<td></td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td><strong>Unstable employment (%)</strong></td>
<td></td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td><strong>Married (%)</strong></td>
<td></td>
<td>54</td>
<td>45</td>
</tr>
</tbody>
</table>

**Living situation**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With family or friends (%)</strong></td>
<td></td>
<td>68</td>
</tr>
<tr>
<td><strong>Alone (%)</strong></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td><strong>No stable living arrangements (%)</strong></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Controlled environment (%)</strong></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Heroin use**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years, mean (S.D.)</strong></td>
<td></td>
<td>4.13±0.66</td>
</tr>
<tr>
<td><strong>Grams/week (S.D.)</strong></td>
<td></td>
<td>4.56±0.89</td>
</tr>
</tbody>
</table>

**Alcohol abuse**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years, mean (S.D.)</strong></td>
<td></td>
<td>2.43±0.86</td>
</tr>
<tr>
<td><strong>Alcohol intake/day, mean (S.D.)</strong></td>
<td></td>
<td>10.27±1.63</td>
</tr>
<tr>
<td><strong>Total ASI composite score, mean (S.D.)</strong></td>
<td></td>
<td>1.92±0.36</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or mean±S.D. No statistical difference was noted between groups (Chi square or Student’s t-test as appropriate).

Table 2
Number of drop-outs in group during the course of the study

<table>
<thead>
<tr>
<th></th>
<th>1st month</th>
<th>3rd month</th>
<th>6th month</th>
<th>12th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>
other therapeutic programs in our clinics. The individuals who returned the following day in opioid withdrawal and had positive urine toxicology for heroin in urine screening were randomly assigned to either methadone or buprenorphine treatment. All patients assigned to a treatment accepted the medication assigned.

All patients were followed for 12 months. The Addiction Severity Index (ASI) interviews were administered upon entry and the end of the study, respectively. Alcohol and heroin craving and ethanol intake were evaluated at admission and every week. The heroin and alcohol use cessations were self-reported and confirmed every week by urine analysis or a breath alcohol test. Urine samples were collected under staff observation. Subjects were discharged from the study if they missed 3 consecutive medication doses. Patients who discontinued medication or dropped out from treatment were offered other therapeutic programs in our clinics.

Participants attended the outpatient clinic facility 6 days per week to receive their methadone or buprenorphine dose. On Saturdays, patients were given the medication to be taken on Sunday. The initial methadone and buprenorphine dosage was 40 mg/day and 8 mg/day, respectively. The methadone was administered orally, while buprenorphine was given sublingually. The dosage was increased until patients’ urine was opioid-free and it was not decreased until the end of the study. Daily maintenance doses of methadone were 80, 120, 160, and 200 mg/day, while for buprenorphine they were 8, 16, 24, and 32 mg/day. After any three consecutive opioid-positive urine tests, we offered the patient a dosage increase. If the patient refused to increase the dosage or she/he requested a decrease in the dosage she/he was excluded from the study. However, in our study there were no dose increases after the first month of treatment. The maximum methadone and buprenorphine dosage was 200 mg/day and 32 mg/day, respectively.

After the study period all patients were allowed to continue their respective maintenance programs.

![Fig. 2. Percentage of drop-outs from treatment at 1, 3, 6, and 12 months. No statistical difference was found (Kaplan–Meier survival analysis).](image)

![Fig. 3. Time course of the reduction of heroin craving (panel A) and positive-opioid urine (panel B) after buprenorphine and methadone treatment. Panel A: Methadone ANOVA $F_{3,42} = 16.66, p < 0.01$; after the 6th month the effects of the doses of 120, 160, and 200 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 80 mg/day (Neuman–Keuls test); Buprenorphine ANOVA $F_{4,42} = 3.97, p < 0.01$; after the 3rd month the effects of the doses of 24 and 32 mg/day, and after the 6th month the effects of the dose of 16 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 8 mg/day (Neuman–Keuls test); Panel B: Methadone $F_{3,42} = 407.3, p < 0.01$; after the 6th month the effects of the doses of 120, 160 and 200 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 80 mg/day (Neuman–Keuls test); Buprenorphine $F_{3,42} = 296.3, p < 0.01$; after the 6th month the effects of the doses of 16, 24, and 32 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 8 mg/day (Neuman–Keuls test); All data are expressed as mean ± S.D. S.D. values are not more than ±10.18.](image)
2.3. Instruments

The data regarding this study were collected through the use of following instruments:

- Sheet of personal data and drug addiction history: this contained the socio-demographic and drug addiction history information of the subjects involved in the study.

- A visual analogical scale (length 10 cm) labeled zero at one end (no craving for heroin or alcohol) and 10 at the other end (the most intense craving ever experienced for heroin or alcohol) to measure craving for heroin or alcohol (Nicholson, 1978). Patients were asked to indicate their peak craving for heroin and/or alcohol at any time during the past day.

- The Addiction Severity Index (ASI) interviews to assess patient problem severity in seven dimensions: somatic morbidity, work, alcohol use, illegal drug use, crime, family situation, and psychiatric morbidity (McLellan et al., 1992). Composite scores were used instead of severity scores because they are derived from objective data and have a higher reported degree of psychometric stability than severity scores (McLellan et al., 1992).

- A daily-self report of drinking with the amount of alcohol intake (one standard drink was defined as 0.35 L of beer, 0.15 L of wine, or 0.04 L of 80 proof liquor). Self-reported drinking or abstinence was confirmed every week by determinations of breath alcohol concentration (Envitec Alcoquant 3020, Germany).

![Fig. 4. Reduction of total ASI composite scores induced by methadone (open bar) and buprenorphine (solid bar) at the end of the study. Asterisk p < 0.01 (Student's t-test) vs the 1st day of treatment. No statistical differences were found between treatments (Student's t-test, p = 0.18, methadone vs buprenorphine). All data are expressed as mean ± S.D.](image-url)

![Fig. 5. Time course of the reduction of alcohol craving (panel A) and alcohol intake (panel B) after methadone and buprenorphine treatment. Panel A: Methadone ANOVA $F_{3,45} = 9.89$, $p < 0.01$; after the 1st month the effects of the dose of 200 mg/day, and after the 3rd month the effects of the dose of 160 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 80 mg/day (Neuman–Keuls test); Buprenorphine ANOVA $F_{3,45} = 7.75$, $p < 0.01$; after the 1st month the effects of the dose of 24, and 32 mg/day, and after the 3rd month the effects of the dose of 16 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 8 mg/day (Neuman–Keuls test). Panel B: Methadone $F_{3,45} = 3.30$, $p = 0.01$; after the 1st month the effects of the doses of 160 and 200 mg/day, and after the 3rd month the dose of 120 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 80 mg/day (Neuman–Keuls test); Buprenorphine $F_{3,48} = 2.68$, $p = 0.05$; after the 1st month the effects of the dose of 24 and 32 mg/day, and the 3rd month the dose of 16 mg/day were statistically significant ($p < 0.01$) in comparison with the effect of the dose of 8 mg/day (Neuman–Keuls test). All data are expressed as mean ± S.D. S.D. values are not more than ±2.11.](image-url)
Urine samples collected every week to detect heroin and alcohol using an immunoassay technique with a cut-off of 200 ng/ml and 100 ng/ml, respectively (urine was also tested for cocaine, amphetamine, and benzodiazepines). The data were expressed as percentage of positive-opioid and alcohol urine (with eventual missing specimens considered as positive).

2.4. Data analyses

Data were analyzed using the Statistical Package for the Social Science (SPSS) version 11.0. A two-way analysis of variance (ANOVA) (treating drop-outs as missing values), followed by a post-hoc test (Neuman–Keuls test), was used to test for differences in continuous variables. Comparison between groups was performed using a Student’s t-test or a chi-square analysis as appropriate. Retention in treatment was analyzed using a Kaplan–Meir survival analysis. All statistical tests were two-tailed and all significant levels were set at p<0.05. Data are number (%) or mean±S.D.

3. Results

The two groups were similar in baseline characteristics, including the severity of addiction (measured with ASI interview) (Table 1).

Of the four hundred and seventy-three (n=473) patients, two hundred and thirty-four (n=234) fulfilled the inclusion criteria for entry into the study and two hundred and eighteen (n=218) of them were randomly assigned to either methadone or buprenorphine treatment (Fig. 1). The drop-outs in each group during the course of the study is shown in Table 2.

The retention in treatment was similar in both groups (Fig. 2), although at the 3rd and 6th month of treatment methadone showed a less percentage of drop-outs (Table 2). In the methadone arm, patients were discharged for the following reasons: 7 patients discontinued medication, 3 refused a dosage increase and 1 requested a dosage decrease. In the same group of patients, 7 dropped out for drug-related events (4 for severe constipation, 2 for excessive sweating, and 1 for vomiting) and 3 for undefined causes. In the buprenorphine arm, patients were discharged for the following reasons: 5 patients discontinued medication, 7 refused the dosage increase, and 3 requested a dosage decrease. In the same group of patients 7 dropped out for drug-related events (4 for headache, 2 for vomiting, and 1 elevated transaminase levels) and 5 for undefined causes.

Both treatments were well tolerated. Severe side effects were not reported at any dose, although the patients treated with the highest doses of methadone showed in a high percentage constipation and excessive sweating.

As expected, both methadone and buprenorphine reduced heroin craving and positive-opioid urine (Fig. 3). At the lower doses, methadone was more effective in reducing both heroin craving and positive-opioid urine (p<0.01, Student’s t-test, methadone 80, 120, and 160 mg/day vs buprenorphine 8, 16, and 24 mg/day, respectively), while at the highest dose both treatments were equally effective. At the end of the study the highest doses of both treatments reduced the severity of dependence equally (Fig. 4). The treatments also reduced both ethanol craving and alcohol intake (Fig. 5). At the lower doses, methadone and buprenorphine were equally effective in reducing alcohol craving and consumption, while the highest dose of buprenorphine (32 mg/day) proved to be more effective than the highest dose of methadone (200 mg/day) (Fig. 6). At the end of the study the highest dose of buprenorphine also showed a better reduction of the ASI subscale of alcohol use (Fig. 7).

4. Discussion

The study shows that methadone and buprenorphine maintenance treatment are each able to reduce, in a dose-dependent manner, both
heroin craving and heroin use in opioid addicts with alcohol dependence. Our findings also indicate that the methadone and buprenorphine treatment was able to suppress alcohol use in heroin addicts. This effect was more evident at the 6th and 12th month of treatment in the patients that received the highest doses of buprenorphine (32 mg/day).

The mechanism underlying the effects of the opioid maintenance therapy on the reduction of alcohol intake is still unclear although there are some promising theories.

In light of the above evidence, we hypothesize that use of the highest doses of buprenorphine could represent a potential effective treatment for heroin addicts with alcohol dependence and a possible therapeutic option in methadone-maintenance patients with an uncontrolled increase in alcohol intake. In this class of patients, the switching from methadone to buprenorphine is advised only for the subjects that are in methadone treatment with a maximum dose range of 30–40 mg/day (Breen et al., 2003). In the above cases the initial buprenorphine dose should not be greater than 8 mg/day. An evident disadvantage for the use of the highest doses of buprenorphine is the higher cost of treatment per year (about 3,120 euros), if compared with methadone (about 1,820 euros). Another important limitation is the long time (up to a half-hour) needed to administer the drug sublingually.

We are aware that our study presents some important limitations, the first one being the small size of the samples and the fact that it was not blinded. Indeed, only a double-blind study would allow us to draw firmer conclusions about the causes responsible for the reduction of alcohol intake induced by both treatments. Moreover, since methadone and buprenorphine may induce different pharmaco-physiological effects and subjective emotive reactions in patients, only a double-blind study could examine the true differences between the two drugs. However, the evidence that both groups of patients at the beginning of the study had the same degree of addiction severity (measured with ASI interviews), together with the fact that both groups showed the same rate of retention in treatment and were similarly able to reduce heroin use, leads to the conclusion that there were no significant differences in the pharmacological responses to the two medications between the two cohorts. The second limitation of the research is the highly selective nature of the sample, which does not include patients with severe addiction. In fact, clinical experience suggests that buprenorphine is as effective as methadone in reducing heroin use in opioid addicts who have moderate craving, while it is less effective in subjects with a higher degree of addiction severity (Ling, Wesson, 2003; Mattick et al., 2004). The third limitation is that the study does not allow us to evaluate the effects of both treatments on the possible subtypes of alcohol-dependent subjects that may be present in our patients’ sample. In fact, the patients that were classified in the study as alcohol-dependent might actually comprise different categories of alcoholics. In particular, different types of alcohol-dependent subjects, such as those that drink when they are unable to obtain sufficient supplies of opioids or those that drink regardless of the availability of heroin or of an opioid maintenance treatment, are all included in the same category of alcohol-dependent subjects. The fourth limitation is the lack of a non-medicated control group, which does not allow to draw any conclusions about the role of factors different from the drug (e.g. counseling) on the suppression of alcohol intake. The fifth limitation is that in the study there were no dose increases after the first month of treatment. This may due to several factors including the fact that all patients that required a dose increase (three and seven in methadone and buprenorphine arm, respectively) refused a dose progression and they preferred to drop-out from the study. The sixth limitation is that most clinicians only rarely use the highest dose of buprenorphine in routine clinical practice. The seventh limitation is that sometimes patients may refuse to take the highest dose of the drug or may prefer the methadone when it is available for treatment (Kakko et al., 2007). The eighth limitation is that, although the buprenorphine is used for the treatment of heroin addiction from several years, there are no observational or anecdotal reports on a reduction of alcohol consumption in heroin addicts with a dual dependence. This may be due to several reasons including the fact that only low doses of buprenorphine have been used in most clinical trials with the exception of the Kakko’s study. The last limit of our study is that several other explanations, such as the existence of selective drop-outs or coincidence may explain the buprenorphine effects on alcohol consumption. In the light of the above evidence, our study should be considered only a preliminary clinical report that need to be confirmed by further controlled studies.

Finally, despite the above limitations, to the best of our knowledge our study represents the first clinical report of the association between high-dose buprenorphine and the suppression of both alcohol craving and intake in heroin addicts with alcohol dependence. In view of our findings, we believe that patients with dual dependency might be considered candidates for higher doses of buprenorphine in the future.

Conflict of interest

C.L. has consulted for Schering Plough and served as speaker for Essex Italia S.p.A. and Reckitt Benckiser. All other authors declare that they have no conflicts of interest.

Acknowledgement

The study was supported by the Italian Society of Addiction Medicine (FeDeSerD).

References


