Clinical profile of responders to buprenorphine as a substitution treatment in heroin addicts: results of a multicenter study of 73 patients

Marie-France Poirier*, Xavier Laqueille, Valérie Jafre, Dominique Willard, Marie Chantal Bourdel, Jacques Fermanian, Jean Pierre Olié

Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique, Hôpital Sainte-Anne, Faculté Cochin Port-Royal, Université Paris V, Paris, France

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Abstract

In France, high-dosage buprenorphine (HDB) is the main substitution treatment for narcotic addiction. Few data have been published concerning clinical factors predicting a good response to this treatment in a daily practice. A hospital-based multicenter clinical research program (PHRC) was undertaken in heroin-addicted patients, diagnosed according to DSM-III-R, to detect clinical criteria susceptible of predicting a good response to HDB administered during a 3-month treatment period. At the inclusion time in the study, a diagnostic structured interview (DIGS) was performed, and the Addiction Severity Index (ASI), Zuckerman scale, depression scale from Jouvent, and CGI were scored. MMPI was also administered. Good response was defined as an ongoing participation in the study, with absence of opiate detected in 75% of urine collected during the last month of treatment. Only subjects treated for at least 1 month were eligible for analyses. One hundred fifteen patients were recruited and 73 were analyzed. Patients received 8.5 ± 2.6 mg (M ± S.D.) of buprenorphine for 1 to 3 months. A forward stepwise logistic regression showed that six clinical parameters may predict a good response to treatment: probability to respond to buprenorphine was higher in subjects having a high psychopathology (ASI) subscore, low disinhibition and boredom susceptibility factor scores (Zuckerman scale), no alcohol dependence, no family history of addiction or mood disorder, and duration of opiate dependence less than 10 years. Only the MMPI D subscale was a psychological pattern correlated to a good response to substitution treatment. These findings are important to consider when making the decision to prescribe HDB substitution treatment in opiate addiction.

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1. Introduction

Buprenorphine is a partial agonist of μ-opioid receptor that has been intended as an alternative to traditional full agonist maintenance therapy for the treatment of opioid addiction. As a partial agonist, the effects of buprenorphine on nontolerant individuals are dose-dependent within a limited therapeutic interval, above which increasing dosages do not produce dose effect. Therefore, for certain pharmacological consequences (e.g. respiratory depression and sedation), buprenorphine may present an enhanced safety profile compared with full opioid agonists.

The potential utility of buprenorphine for the treatment of opioid addiction was demonstrated in the definitive work of Jasinski et al. (1978): daily sublingually dosages of 8 mg blocked the effects of subsequently administrated morphine and did not appear to induce a physical dependence. Different dose-ranging studies and short-term clinical trials have shown that buprenorphine suppresses heroin use in addicted drug-dependent individuals in a research ward. This substitution heroin replacement treatment also blocks the effects of experimentally administered opiates (Bickel et al. 1988).

The study carried out by Johnson et al. (1992) suggested that 8 mg of buprenorphine showed an efficacy superior to
20 mg of methadone and equivalent to 60 mg of methadone. This suggestion was drawn up according to three criteria: retention in treatment throughout the 17-week study, illicit opioids use as determined by urinalysis and the Addiction Severity Index (ASI) score.

Kosten et al. (1993) compared buprenorphine (2 and 6 mg) versus methadone (35 and 65 mg) based on efficacy criteria: treatment continuation during the 6 months of study, absence of opioids in urinalysis in at least in 70% of urine samples, number of sequences of three consecutive weeks of drug abstinence, substance use reported by patients, signs of withdrawal symptoms, and scores in the ASI. This study seemed to suggest that administering buprenorphine in 2 and 6 mg daily doses was less effective than 35 or 65 mg of methadone given daily.

Ling et al. (1996), in a double-blind control study covering 225 patients with a mean age of 41 years, compared 80 and 30 mg of methadone versus 8 mg of buprenorphine. The mean duration of substance abuse was 18 years. It seemed that 80 mg of methadone was superior to 30 mg of methadone and to 8 mg of buprenorphine after 6 and 12 months, but with marked improvement in all three groups from the first week.

The study by Strain et al. (1996) covered 164 patients, ranging from 18 to 50 years of age, with a history of at least one year of opioid dependence. It was the first substitute treatment trial for these patients in which methadone or buprenorphine were used during 16 weeks in a double-blind and double-placebo trial. The evaluation criteria were identical to those used in previous studies. The average daily dose was 54 mg of methadone and 9 mg of buprenorphine. The rates of treatment maintenance for 16 weeks were equivalent in both groups (50%), urine control analysis showed positive results in 40% of individuals in the buprenorphine group and 44% in the methadone group. Subjects staying in the study were slightly older.

Uelhinger et al. (1998) compared the efficacy of methadone and buprenorphine with adequate doses in a double-blind, double-placebo study during 6 weeks. This study showed superior efficiency of methadone with a treatment continuation rate of 90% versus 55%. Twelve milligrams of buprenorphine and 30–80 mg of methadone were the most common doses for the patients with a mean age of 28 years and 4.7 years history of heroin addiction.

The most recent study on the efficacy of buprenorphine, published in 1998 by Ling et al., aimed to define an effective dose for buprenorphine in a comparative protocol with 1, 4, 8, and 16 mg of buprenorphine (alcoholic solution type) carried out in 736 subjects. The patients, with a mean age of 36 years, were followed-up in 12 centers during 6 months and were treated in the usual clinical context. Results suggested that 1 mg of buprenorphine was significantly less effective than other doses in all efficacy domains, while 16 mg of this treatment was a more effective treatment for one variable, namely, the percentage of negative urinalysis during 13 consecutive weeks.

Furthermore, buprenorphine did not appear to be more effective than methadone on the consumption of cocaine in heroin abusers (Schottenfeld et al. 1997), or when associated with desipramine (Olivetto et al. 1999).

The definition of opioid substitution treatment response is unclear. In many studies, no effective criteria have been selected. Recently, Ling et al. (1998) used four outcome measures to evaluate efficacy: retention in treatment, illicit opioid use as determined by urinalysis, opioid craving and global ASI scores rated by patients and staff.

Little is known about whether specific subgroups of opioid-dependent patients might respond differentially to methadone or buprenorphine. Early studies suggested that buprenorphine might be superior to methadone for maintenance treatment of patients with concurrent opioid and cocaine dependence (Kosten et al., 1989; Mello et al., 1989), but this hypothesis has not been supported in controlled clinical trials (Johnson et al., 1992; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994). Various measures of psychopathology (especially depression and sociopathy) have been evaluated as important predictors of substance abuse treatment outcome in general (McLellan et al., 1983; Rounsaville et al., 1986), but their prognostic significance has not been systematically evaluated in studies on buprenorphine maintenance. Depression is also of interest because it is a risk factor for escalating cocaine use and continued illicit opioid use after entry into substitution maintenance treatment (Kosten et al., 1987). Moreover, buprenorphine has been used experimentally to treat depression (Bodkin et al. 1995; Nutt et al. 1995), and decreased symptoms of depression have been reported in buprenorphine-maintained patients (Kosten et al. 1990).

In France, high-dosage buprenorphine (HDB) is the main replacement therapy for narcotic addiction. Few data have been published concerning clinical factors predicting a good response to this treatment in a daily practice. Gasquet et al. (1999) have tried to define the response factors to buprenorphine from a retrospective follow-up study of 956 patients done by 200 general practitioners.

Subjects were treated with buprenorphine openly with an adjustable dosage and results were evaluated with quantitative socio-behavioral and medical indicators. Some criteria were found to be correlated with a good response: a fixed address and regular income from work, treatment of any associated psychiatric disorder, previous moderated and nonregular use of heroin, and at least one previous attempt at withdrawal. Nevertheless, this study had some limits from a methodological standpoint: absence of validated definition for response criteria, variable duration of treatment, and no standardized psychiatric evaluation.

The present multicenter open hospital clinical research program (PHRC) was carried out to determine clinical
criteria predicting a good response to HDB substitution treatment in a prospective study during a 3-month period.

2. Methods

Nine centers participated in this open clinical study (two centers included only two patients).

- At the inclusion date eligible patients met the DSM-III-R (American Psychiatric Association, 1987) criteria for current opioid dependence and had an opioid-positive urine toxicology test.
- Exclusion criteria included psychosis, bipolar disorder, recent suicide attempt, significant medical illness, pregnancy, and the inability to read or to understand rating forms and symptom checklists.
- All subjects signed informed consent statements.

2.1. Assessments

- At baseline, a semi-structured diagnostic interview (DIGS) (Nurnberger et al. 1994) evaluating lifetime and current substance use and psychopathological disorder was carried out by the same investigator (V.J.). ASI (McLellan et al. 1992), Zuckerman Sensation Seeking Scale (Z.S.) (Zuckerman et al. 1972), depression scale from Jouvent (Jouvent et al. 1988), and Clinical Global Impression (CGI) (Guy et al. 1976) were also completed. Socio-demographic, medical, and addiction backgrounds were recorded. MMPI was also administered to assess the personality profile. Supervised urine samples for toxicological testing were obtained at baseline and twice weekly during the study.

2.2. Treatment

According to a standardized procedure, all the subjects received daily tablets of buprenorphine during the first week: Days 1 and 2, 2 mg; Days 3 and 4, 4 mg; Days 5 and 6, 6 mg; and from Day 7, 8 mg. Then, the dosage was adjusted between Week 1 and Week 4 within a 4- to 16-mg dose range, according to clinical symptomatology. By Month 1, the dosage had to remain stable until the end of the study.

The treatment was delivered twice weekly.

Good treatment response was defined as absence of opiates detected in 75% of urine collected during the last month of treatment and ongoing participation in the study for 3 months.

2.3. Statistical analyses

Only subjects with at least 1 month of treatment were eligible for analyses.

First, univariate analysis tests for all the variables were performed to compare male and female, and patients with or without comorbidity. Mann–Whitney nonparametric test or $\chi^2$ test (for categorical variables) were used.

Then, two stepwise logistic regressions were performed in order to fit the treatment’s response.

This method allowed us to define a relevant clinical profile for “responder” subjects:

- One with socio-demographic, clinical data and scales as independent variables (11 variables were retained).
- Another with MMPI and IQ as independent variables (six variables were retained).

For these analyses, 73 and 63 subjects, respectively, were obtained; $P$ level to enter or remove terms in the regression was fixed at 10%.

3. Results

3.1. Sample characteristics

One hundred fifteen patients were screened and 73 were eligible for the analyses (subjects treated for at least 1 month). From the total, 10 subjects did not return to the outpatient clinic department after the preliminary screening contact, 3 had an IQ under 80, and 29 patients withdrew from the study before Day 28, mainly because of withdrawal symptoms (10 patients did not show up after the first intake of treatment, 7 patients dropped out before Day 7, 8 patients between Day 10 and Day 20, and 4 patients between Day 21 and Day 28).

There were 60 men (82%) and 13 women (18%), with mean age of 30 years (18 to 44 years).

Patients received $8.5 \pm 2.6$ mg ($m \pm S.D.$) of buprenorphine (4 to 16 mg dose range), for 1 to 3 months.

Twenty-seven subjects (16 responders and 11 nonresponders) received concomitant psychotropic medication.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comorbidity of patients</th>
<th>Present time</th>
<th>Life time</th>
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<tbody>
<tr>
<td></td>
<td>$n$ (%)</td>
<td>$n$ (%)</td>
<td></td>
</tr>
<tr>
<td>Dependence:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>21 (28.8)</td>
<td>29 (41.1)</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>16 (21.9)</td>
<td>24 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>23 (33.8)</td>
<td>35 (51.5)</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>8 (11.9)</td>
<td></td>
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<tr>
<td>Sedatives</td>
<td>23 (33.8)</td>
<td></td>
<td></td>
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<tr>
<td>Opiates</td>
<td>73 (100)</td>
<td>73 (100)</td>
<td></td>
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<tr>
<td>MDE</td>
<td>4 (5.5)</td>
<td>18 (26.15)</td>
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<tr>
<td>Dysthymia</td>
<td>6 (8.8)</td>
<td>6 (8.8)</td>
<td></td>
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<tr>
<td>Antisocial personality disorder</td>
<td>13 (19.1)</td>
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</tbody>
</table>
Forty-eight patients were good responders to substitutive treatment and 25 were not (13 dropouts before Month 3, 12 patients with opiates detected in urine collected during the last month).

Cocaine was detected in four responders and three non-responders, amphetamine in two responders.

Sixty-one patients underwent 3 months of treatment (nonresponders, n = 13).

Table 1–3 show the demographic, clinical and psychopathological data of the study population.

Clinical variables were not different between men and women, neither were they in patients with or without comorbidity.

3.2. Multivariate analyses

Eleven potential variables predicting a positive response to buprenorphine treatment were selected due to their particular clinical interest: sensation seeking scale and its four dimensions, composite subscore of the ASI (psychopathology, alcohol), duration of the opiate addiction, current alcohol dependence, family history of alcohol or drug dependence, family history of mood disorder, any previous suicide attempts.

With six of the selected clinical predictors, the logistic model fits the data (Goodness of fit: $\chi^2 = 61.9$, df = 64, P = .55). Probability to respond to buprenorphine was higher in subjects having a high psychopathology ASI subscore, a low disinhibition score and boredom susceptibility (Zuckerman scale), no current alcohol dependence, and no family history of addiction or mood disorder. Duration of opiate dependence less than 10 years and boredom susceptibility factor tended to predict a positive response to buprenorphine substitutive treatment (Table 4).

This clinical model allowed correct classification for 87% of the “responders” and 67% of the “nonresponders.”

Six psychological variables were selected for the second multivariate analysis: IQ, anxiety index, four MMPI subscales (HS, hypochondry; D, depressive; PD, psychopathic deviation; PT, psychastheny). The only psychological profile that significantly predicted a good response to substitution treatment was a low score in the MMPI depressive subscale (Table 4) (Goodness of fit: $\chi^2 = 68.1$, df = 56, P = .13). This psychological model allowed correct classification for 80% of the “responders” and 48% of the “nonresponders.”

4. Discussion

Clinical variables were not different between men and women, neither were they in patients with or without comorbidity. There was no significant effect of gender on...
maintenance treatment and on retention and rates of opioid-positive urine tests, contrary to what was reported by Schottenfeld et al. (1997).

With six of the selected clinical predictors, the logistic regression allowed correct classification for 87% of the “responders” and 67% of the “nonresponders,” which was a good discrimination score.

The logistic model is more sophisticated than univariate tests; this method allowed us to define a relevant clinical profile for “responder” subjects, controlling for several confounders.

Probability to respond to buprenorphine was higher in subjects with a high psychopathology ASI subscore, low disinhibition scores (Zuckerman scale), no current alcohol dependence, and no family history of addiction or mood disorder. Duration of opiate dependence less than 10 years and boredom susceptibility factor tended to predict a positive response to buprenorphine substitutive treatment. However, since 10 patients did not show up after the first intake of treatment and 7 patients dropped out before Day 7, the initial dosage (2 mg/day) might have been too low. This could have introduced a selection of the less dependent patients included in the analysis.

According to Gasquet et al. (1999), a comorbid psychiatric psychopathology and a short duration of opiate addiction were associated with a good response to buprenorphine as found in our population. Nevertheless, a lifetime diagnosis of depression had no significant effect on buprenorphine treatment as reported by Schottenfeld et al. (1997). According to these authors and to Cacciola et al. (1995), antisocial personality disorder was not associated with outcomes in our study.

Contrary to Gasquet et al. (1999), we found no correlation between socio-demographic characteristics of patients and a good response to the substitutive treatment.

The only psychological profile that significantly predicted a good response to substitution treatment was a low score in the MMPI depressive subscale, which evaluates lack of self-assurance.

The psychological profile provided less information on the subtype of treatment responders with buprenorphine than did the clinical variables.

5. Conclusion

This multicenter open study showed some clinical characteristics predicting a good response to buprenorphine treatment in opiate addicts: no alcohol dependence, no family history of addiction or mood disorder, duration of opiate dependence less than 10 years, low disinhibition and boredom susceptibility factor scores, and a high psychopathological ASI subscore.

These findings need to be replicated in a controlled study. Indeed, these clinical data should be taken into consideration when making the decision to prescribe HDB substitution treatment in opiate addiction.

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References


