Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: A retrospective study

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Abstract

The present study compared retrospectively in a clinical non-experimental setting the efficacy of buprenorphine (BUP) in different subgroups of dually diagnosed and non-dually diagnosed opioid-dependent patients: all the subjects included in the study showed severe long-lasting heroin addiction and 68.4% were affected by psychiatric comorbidity. Participants (206) (mean age 32.2 ± 8.9, 177 males–29 females) were applicants to a long-term buprenorphine treatment program (mean doses 7.9 ± 0.42 mg). Aim of the study was to evaluate dual diagnosis variables possibly influencing retention rate and abstinence from illicit drugs. The patients were divided into 5 subgroups on the basis of dual diagnosis: group 1: major depression (MD) 29.61%; group 2: generalized anxiety (GAD) (11.2%); group 3: personality disorders (PD), antisocial-borderline (21.84%); group 4: schizophrenia (SC)(6.3%); group 5: substance use disorder without overt psychiatric comorbidity (SUD) (31.1%). Group 1 patients affected by MD showed the highest retention rate at 12 months (72.1%) in comparison with the other groups of patients: group 2 GAD (39.1%), group 3 PD (17.8%), group 4 SC (7.7%) and group 5 SUD, without comorbidity (45.3%) (p = 0.006, p < 0.001, p < 0.001, p = 0.002). Similarly, at 12 months, the patients affected by MD showed less risk of illicit opioid use (16.4%) than those affected by GAD (34.8%), PD (42.2%), SC (53.8%) and SUD without comorbidity (34.4%) (p = 0.06, p = 0.003, p = 0.008, p = 0.017). When evaluated on the whole sample, retention rate was not influenced by dose. In contrast, the higher BUP doses were associated with less risk of illicit opioid use, than lower doses (p < 0.001). Multivariate analysis and factor analysis showed a greater association of outcome measures (retention rate and negative urines rate) with comorbid diagnosis (depression) (respectively 0.64) than with buprenorphine doses (respectively 0.54). Our data need to be interpreted with caution because of the retrospective methodology applied to a clinical non-experimental setting. BUP seems to be more effective in opioid-dependent patients affected by depression, probably due to the kappa opioid-receptors antagonist action, countering dysphoria, negativism and anxiety. High doses of BUP appear to predict a better outcome, in terms of negative urines, but not in terms of retention.

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1. Introduction

A variety of studies has indicated the need of further research to determine if buprenorphine (BUP) treatment is more effective in particular settings or in particular subgroups of patients (Barnett et al., 2001). The hypothesis that a specific subtype of addicted individuals may be benefiting from BUP was also formulated by Fischer and co-workers (1999a,b) but the pronostic factors able to characterize patients-subtypes and to predict BUP outcome are still unclear and confused.
Patients who dropped out from BUP treatment were reported to differ significantly from those who stayed, in terms of lower level of social integration and a higher level of psychopathological symptoms (Pani et al., 2000), without any apparent relationship between specific dual diagnoses and outcome measures.

The evidence of buprenorphine effectiveness in the pharmacological treatment of affective disorders was reported many years ago. A double blind investigation showed BUP to induce strong antidepressant effects in patients with endogenous depression (Emrich et al., 1983). Accordingly, depressive symptoms were found to decrease significantly in the heroin addicted patients who were depressed at intake to BUP treatment (Kosten et al., 1990).

Buprenorphine was re-tested as antidepressant in non-addicted individuals. In an open-label study, subjects with treatment-refractory, unipolar major depression showed clinical improvement in both subjective and objective measures of depression after BUP treatment (Bodkin et al., 1995).

The reports of Schottenfeld et al. (1998) indicate that a significantly better retention during BUP treatment for heroin addiction was associated with female gender with lifetime sedative dependence: the reason of a more positive outcome in these patients could be due to unrecognised depression that was repeatedly reported to be associated with benzodiazepines inappropriate treatment and dependence (Kupfer, 1999; Voyer et al., 2005; Valenstein et al., 2004), particularly among female patients (Sonnenberg et al., 2003).

In agreement with these evidence, our previous findings (Gerra et al., 2004), obtained in a 12-week observational study, indicated that BUP might obtain more successful results in the subgroup of patients affected by depression, both in terms of retention and opioid negative urines, in comparison with non-depressed individuals.

Although research has repeatedly suggested that buprenorphine may possess a specific antidepressant activity, contrasting data have been also reported in this field. Substitution treatment, with both buprenorphine and methadone, was found to improve depressive symptoms, with no differential benefit on depression for buprenorphine patients (Dean et al., 2004). Moreover, buprenorphine in association with desipramine was found to obtain a poor outcome in depressed opioid-dependent patients, casting doubts about its effectiveness in this subgroup of addicted individuals (Kosten et al., 2000).

For these reasons, in the present multi-centre retrospective study we decided to investigate the effectiveness of BUP maintenance treatment, in relationship with dual diagnosis, in a sample of heroin dependent outpatients.

Aim of the study was to evaluate whether or not comorbid psychopathologies were able to influence the endpoints of retention rate and reduction of illicit drug use during BUP treatment. The hypothesis was that BUP treatment outcome may be different in patients subgroups, not only in relationship with addiction severity or dose levels, but also with individual personality traits and comorbid psychiatric disorders. The mu-receptors agonist/kappa antagonist profile of buprenorphine could exert a specific action on the neurobiological changes underlying the psychiatric disorders that are commonly found in association with addictive behavior.

The study was conducted to determine retrospectively the responses of heroin dependent patients to BUP, in the first 12 months of a long-term treatment, measuring psychiatric diagnoses capacity to affect retention rates and positive urine rates.

2. Methods

2.1. Study population

Heroin-dependent subjects were selected from among patients participating in Milan, Caserta (Naples), Parma and Rome Addiction Services Programs (Servizi Tossicodipendenze—Ser.T) of the public health system during the period 2002–2003. Addiction Services in Italy provide outpatients treatment programs, with different therapeutic and rehabilitative strategies: methadone, BUP and naltrexone are administered in association with possible psychosocial intervention, such as psychotherapy, family therapy, group therapy, social support and medication for dually diagnosed patients. Most of the patients in Italian Addiction Services are seeking treatment for heroin dependence, although the same Services offer rehabilitative programs also for cannabis, cocaine and alcohol addiction. No exclusion criteria are applied to select patients in the public health system. All the patients have been routinely evaluated using a self-report and observer-rated questionnaire concerning addiction history and a psychiatric diagnostic screening. Data describing a detailed history of the patients were also obtained from previous drug addiction centres records.

Subjects eligible for the study were all the patients entering BUP long-term treatment during the 12 months between January and December 2002. After we obtained informed consent, the recorded data of participants (206) (mean age 32.2 ± 8.9) (177 males–29 females) (BUP mean doses 7.9 ± 5.5 mg) were included in the study and analysed during the first months of 2004. The 12-months outcome evaluation was conducted as a retrospective, non-randomized, study that has not influenced treatment choice decision, dosage, psychosocial intervention and diagnostic assessment. Participants were heroin-dependent from at least 5 years (mean 7.4 ± 2.0). Daily intake of heroin ranged from 1.5 to 3.0 g of street heroin. The diagnosis of heroin dependence is routinely established in the Italian Addiction Centres following the DSM IV criteria (American Psychiatric Association, 1994), and confirmed with positive urinalyses for morphine metabolites, before BUP treatment. The decision to treat with BUP was made by the clinicians of the Addiction Centres, in relationship to their evaluation of medical issues and patients needs: new patients who did not succeed in drug-free treatment (29.6%), non-responders to methadone treatment (27.1%), patients with the need of emancipation from a long-term methadone treatment for social or professional reasons (14.5%), patients who made the explicit request for BUP treatment, with the aim of
experimenting a “new treatment” (28.6%) were included into BUP treatment.

2.2. Buprenorphine doses

The patients included in the study were treated with BUP average dose of 7.9±0.4 mg (mean±S.E.) during the maintenance period. The highest dose of BUP administered during the study was 32 mg.

No significant difference in BUP average doses was evidenced in the centres participating in the retrospective study. No relevant missed doses and missed clinic visits were reported in the patients who remained in treatment.

2.3. Study design

The retrospective evaluation of the patients, included in 5 subgroups on the basis of different dual diagnoses, has taken into account both retention and negative urinalyses, 6 months and 12 months after the beginning of buprenorphine therapy, as major endpoints. Stable dosage of BUP has been reached on the first 2 weeks of treatment in most of the patients: the patients received a first dose of 2 mg, 8 h after the last injection of heroin, or 24 h after the last METH administration; then they received another 2 mg or 4 mg of BUP, when they did not present withdrawal symptoms, during the first day. Adjunctive BUP doses have been administered to rapidly reach high doses: in some cases, first day BUP was limited to 2 mg because withdrawal symptoms were clearly BUP-induced. Flexible dosing schedule was applied in all the centres during maintenance treatment.

BUP has been administered daily in the outpatient centres for 79.13% (163) of the patients and three times a week for 20.87% (43) of the patients. Weekly take home BUP was not permitted in the first 3 months of treatment and used in 29.13% (60) of the patients during the following months. No significant difference in the rate of take home BUP was found in the five subgroups of patients.

BUP treatment was routinely integrated with psychosocial support, including weekly individual counseling for most of the patients. Patients with psychiatric comorbidity were also referred to a weekly meeting with the psychiatrist.

In agreement with the criteria of the Addiction Services, no patient was discharged because of consecutive positive urine test results.

2.4. Data collection strategy

The data collection strategy routinely utilized in the centres involved in the study consisted of a form for maintenance program counselors to complete for each patient in the outpatient program who entered substitution treatment during 2002. The patients form requested the following information: patient identification; previous treatment; employment status; highest school grade completed; quality of interpersonal relationships; marital status; legal problems; commitments; time in prison; number of arrests; number of violent crimes; perception of alcohol as a current problem. New selective psychopharmacological treatment associated with substitution treatment (BUP) has been also recorded.

Employment status was defined as unemployed, stable job (the same company during the year, regularly paying taxes), or unstable job (different short-term jobs during the last 12 months).

The counselors and the psychiatrists of the outpatient centres had been previously trained to collect data on BUP dose, administration frequency (daily in the outpatients centre, or three times a week), measures of previous illicit drug use and problematic alcohol use, social status, health status, and possible DSM Axis I and Axis II comorbid diagnoses (American Association of Psychiatry, 1994). Relevant data have been also recorded concerning substance abuse other than heroin and possible stressful events.

2.5. DSM diagnosis and subgroup characteristics

DSM-IV clinical evaluation (American Association of Psychiatry, 1994) was routinely performed by trained psychiatrists in the centres involved in the study, at the beginning of the program. Axes I and II disorders were evaluated using the Structured Clinical Interview (SCID) for Axis I disorders (Spitzer et al., 1990) (Italian version: Intervista Clinica Strutturata per il DSM-III-R, Fava et al., 1993) and the Structured Interview for DSM-IV Personality Disorders (SIDP) for Axis II disorders (Pfohl et al., 1989) (Italian version: Maffei et al., 1997). Current DSM diagnoses were accurately recorded and the data utilized for the study.

On the basis of DSM current psychiatric diagnosis the patients were divided into 5 subgroups: group 1: major depression (MD) 29.61% (61); group 2: generalized anxiety (GAD) 11.2% (23); group 3: personality disorders (PD); antisocial-borderline 21.8% (45); group 4: schizophrenia (SC) 6.3% (13); group 5: substance use disorder without overt psychiatric comorbidity (SUD) 31.1% (64) (Table 1).

Among the depressed patients 10 subjects showed bipolar disorder symptoms, but they did not completely fit the criteria for DSM diagnosis: mania symptoms could have masked by addictive behavior in these patients.

Some cases were affected by more than one psychiatric comorbidities, in particular Axis II disorders (personality disorders) in association with depression, anxiety or schizophrenia: these patients have been assigned to the groups taking into account the main diagnosis in terms of severity, behavioral consequences and current symptoms.

2.6. Urinalyses

The week immediately before and during BUP treatment, urine samples have been routinely screened once a week on random days for amphetamines, methamphetamines, morphine, METH, cannabis, cocaine, barbiturates, benzodiazepines and alcohol, in all the centres involved in the study. Urinalyses were performed with immunoenzymatic methodology (polyclonal antibodies with glucose-6-phosphate dehydrogenase:
Table 1
Psychiatric diagnoses rates (%) among the patients treated with buprenorphine, and respective demographic, social and clinical characteristics of the patients, included into the 5 subgroups

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>GAD</th>
<th>PD</th>
<th>SC</th>
<th>SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=206</td>
<td>29.61% (61)</td>
<td>11.2% (23)</td>
<td>21.8% (45)</td>
<td>6.3% (13)</td>
<td>31.1% (64)</td>
</tr>
<tr>
<td>Gender rates (males, 177)</td>
<td>86.89% (53)</td>
<td>78.26% (18)</td>
<td>86.67% (39)</td>
<td>84.6% (11)</td>
<td>87.5% (56)</td>
</tr>
<tr>
<td>Age</td>
<td>35.70±0.56</td>
<td>30.8±0.92</td>
<td>34.3±0.7</td>
<td>33.3±1.06</td>
<td>31.6±0.56</td>
</tr>
<tr>
<td>Daily heroin dose</td>
<td>7.3±2.0</td>
<td>6.9±1.9</td>
<td>7.6±2.1</td>
<td>6.5±1.2</td>
<td>6.4±1.3</td>
</tr>
<tr>
<td>Years of heroin addiction history</td>
<td>8.21±0.4</td>
<td>8.57±0.78</td>
<td>8.16±0.47</td>
<td>7.69±0.94</td>
<td>8.52±0.4</td>
</tr>
<tr>
<td>Other psychotropic drugs use</td>
<td>24.59% (15)</td>
<td>30.43% (7)</td>
<td>24.44% (11)</td>
<td>38.46% (5)</td>
<td>20.31 (13)</td>
</tr>
<tr>
<td>Good interpersonal relationships quality</td>
<td>19.67% (12)</td>
<td>26.09% (6)</td>
<td>13.33 (6)</td>
<td>15.38 (2)</td>
<td>21.87(14)</td>
</tr>
<tr>
<td>Stable job</td>
<td>49.18% (30)</td>
<td>52.17% (12)</td>
<td>33.33% (15)</td>
<td>38.46% (5)</td>
<td>54.69% (35)</td>
</tr>
<tr>
<td>Alcohol problems</td>
<td>32.79% (20)</td>
<td>30.43% (7)</td>
<td>31.11% (14)</td>
<td>38.46% (5)</td>
<td>31.25 (20)</td>
</tr>
<tr>
<td>Previous methadone treatment</td>
<td>54.10% (33)</td>
<td>43.47% (10)</td>
<td>57.78% (26)</td>
<td>53.85% (7)</td>
<td>40.62% (26)</td>
</tr>
<tr>
<td>Previous residential treatment rates</td>
<td>24.59% (15)</td>
<td>21.74% (5)</td>
<td>22.22% (10)</td>
<td>38.46% (5)</td>
<td>25% (16)</td>
</tr>
</tbody>
</table>

Major depression (MD), generalized anxiety disorder (GAD), personality disorder (PD), schizophrenia (SC), substance use disorder (SUD).

EMIT, Syva, Italy) and positive results were confirmed by thin layer chromatography, using commercial kits (Toxi-lab; ANSYS Technologies, Lake Forest, CA). Missing urinalyses have been counted positive.

2.7. Statistical analysis

The variables were compared between subgroups arms utilizing standard Chi-square-tests. A survival analysis, on an intention-to-treat basis (Kaplan–Meier), was used retrospectively to measure the efficacy of BUP in terms of retention, in the five subgroups of patients with different comorbid diagnoses. Positive urine samples for heroin were analyzed with a Chi-square-test and ANOVA for repeated measures to evaluate the changes over time, comparing the five subgroups.

The Intention-to-treat sample (ITT-Analysis) was 61 in group 1, 23 in group 2, 45 in group 3, 13 in group 4 and 64 in group 5, totally 206 patients.

High BUP doses (≥ or >8 mg) vs. low doses (<8 mg) have also been evaluated in terms of retention and negative urines utilizing survival analysis.

Multivariate analysis was used to control for potential confounding factors. In particular, we used multivariate model-fitting analysis and factor analysis to exclude the possible interferences of BUP doses, age, gender, substance abuse history (years of addiction), psychotropic medication associated to substitution treatment, previous methadone treatment and residential treatment on the outcome measures obtained during BUP treatment in the 5 subgroups.

3. Results

3.1. Demographic and clinical history data

As reported in Table 1, no significant differences in mean age, gender, daily heroin dose, years of heroin addiction history, other non-prescribed psychotropic drugs use (lifetime), interpersonal relationships quality, job performance, alcohol problems and previous METH and residential treatment rates were evidenced in the 5 subgroups. Antisocial patients (Group 3) had a significantly higher rate of legal problems, in comparison with all other groups (t=2.9 p<0.005; t=2.6 p<0.01; t=3.1 p<0.005; t=4.1 p<0.001).

Both depressed and antisocial subjects (group 1 and group 3) showed higher benzodiazepines abuse (non-prescribed BZD) and cocaine use in the history, but not significantly. Accordingly, anxious subjects and schizophrenic subjects (groups 2 and 4) showed higher cannabis use in the history, but not significantly.

The rates of benzodiazepines and antidepressant prescribed to heroin addicted patients during BUP treatment did not significantly differentiate the 5 subgroups, being higher, but not significantly among depressed and anxious subjects (Group 1 and 2) in comparison with group 3, 4 and 5; neuroleptic agents were more frequently prescribed to group 4 patients, affected by schizophrenia, in comparison with group 1, 2 and 5 (p<0.05; p<0.05; p<0.001). The rates of neuroleptic agents prescribed to group 4 and 3 (cluster B personality disorders) were not significantly different. Most of the dually diagnosed patients were not treated with specific psychotropic medication in combination with BUP treatment. The Addiction Services Programs of the Italian public health system do not systematically provide, in combination with substitution treatment, the appropriate psychopharmacological therapy for comorbid psychiatric disorders, because of a long lasting separation between Addiction Outpatients Programs and Mental Health Department. For the same reason, psychosocial intervention, such as psychological support, family therapy and group therapy were provided in similar rates of patients among the 5 subgroups, independently from dual diagnosis.

No significant difference in BUP average doses was found in the five subgroups related to dual diagnosis (7.77±0.8 mg in group 1, 8.17±1.39 mg in group 2, 7.73±0.86 mg in group 3, 7.85±1.16 mg in group 4 and 8.19±0.76 mg in group 5).

3.2. Retention rate

Retention rates evaluated retrospectively on the whole sample were 54.1% (110 patients) and 43.8% (89 patients), respectively at 6 months and 12 months.

Group 1 patients affected by MD showed the highest retention rate at 12 months 72.1% (44), in comparison with
other groups: group 2 GAD 39.1% (9); group 3 PD 17.8% (8); group 4 SC 7.7% (1) and group 5 SUD, without comorbidity 45.3% (29) ($\chi^2 = 7.81, p = 0.006$; $\chi^2 = 30.61, p < 0.001$; $\chi^2 = 18.67 p < 0.001; \chi^2 = 9.25, p = 0.002$) (Fig. 1).

Survival analysis showed that the rate of BUP maintained patients affected by depression who dropped out during the 12 months program was significantly lower, with respect to the intention to treat sample ($p < 0.001$), in comparison with maintained patients affected by GAD ($p < 0.001$), PD ($p < 0.001$), SC ($p < 0.001$) and SUD without psychiatric comorbidity ($p < 0.005$) (Fig. 2).

Survival analysis showed that the rate of BUP maintained patients affected by SUD without comorbidity who dropped out during the 12 months retrospective evaluation were significantly lower, respect to the intention to treat sample ($p < 0.01$, in comparison with maintained patients affected by GAD ($p < 0.005$), PD ($p < 0.005$) and SC ($p < 0.001$).

The risk for retention failure was similar between BUP high dose and BUP low dose at month 6 and month 12. Retention rates at month 6 were respectively 53.3% (32) and 56.2% (82), with no significant difference, in low-dose BUP and high-dose BUP patients. Retention rates at month 12 were respectively 43.3% (26) and 45.2% (66), with no significant difference, in low-dose BUP and high-dose BUP patients.

No significant differences in age (34.3 ± 3.8 vs. 35.2 ± 2.8), gender (males 72.3% vs. 73.0%), substance abuse history (years of addiction) (9.5 ± 2.8 vs. 8.6 ± 3.6), psychotropic medication associated to substitution treatment 23.15% (58) vs. 27.47% (25), previous methadone treatment 49.51% (102) vs. 49.45% (45) and residential treatment 24.76% (51) vs. 31.87% (29) were evidenced between the Intention-to-treat sample and the completers.

3.3. Urinalysis

The rates of urines negative for opioids, evaluated retrospectively on the whole sample, were 74.4% and 68.0% (138 patients) respectively at 6 months and 12 months.

At 12 months, the patients affected by MD showed less risk of illicit opioid use 16.4% (10) than those affected by GAD 34.8% (8); PD 42.2% (19); SC 53.8% (7) and SUD without comorbidity 34.4% (22) ($\chi^2 = 3.5, p = 0.06$; $\chi^2 = 8.7, p = 0.003$; $\chi^2 = 8.5 p = 0.008; \chi^2 = 5.3, p = 0.017$) (Fig. 3).

At 12 months, the patients affected by SUD without comorbidity showed less risk of illicit opioid use (34.4%) than those affected by PD (42.2%) and SC (53.8%) ($\chi = 8.9, p = 0.002; \chi = 6.4, p = 0.009$). No significant difference between SUD and GAD patients was evidenced at 12 months.

When evaluated on the whole sample, patients treated with high dose BUP showed a significantly lower rate of positive urines for morphine metabolites 23.3% (14), as expression of heroin use, than those treated with low dose BUP (35.6%) (52)
at month 12, in the patients who remained in treatment. ANOVA for repeated measures showed a significant effect of time ($F=7.5$, $df=3$, $p<0.005$), group ($F=12.3$, $df=4$, $p<0.005$) and group per time ($F=23.21$, $df=3$, $p<0.001$) in opioid positive urine changes (Fig. 4).

No significant differences in age, gender, substance abuse history (years of addiction and heroin doses), psychotropic medication associated to substitution treatment and previous METH and residential treatment were evidenced between the negative urines patients and the opioid-positive urines patients.

The rates of urines positive for cocaine metabolites, evaluated retrospectively on the whole sample, were 8.5% and 13.6% respectively at 6 months and 12 months. No significant difference in cocaine positive urines was evidenced among the 5 groups, in relationship to psychiatric comorbidity.

3.4. Multivariate analysis

Multivariate fitting analysis showed a greater association of retention with comorbid diagnosis (depression) (respectively 0.64) than with buprenorphine doses (respectively 0.54). The association of retention with comorbid diagnosis was also greater than with age (0.12), gender (0.29), substance abuse history (years of addiction) (0.14), psychotropic medication associated to substitution treatment (0.09), previous methadone treatment and residential treatment (0.23).

Similarly, multivariate fitting analysis showed a greater association of negative urines with comorbid diagnosis (depression) (respectively 0.68) than with buprenorphine doses (respectively 0.46). The association of negative urinalyses with comorbid diagnosis was also greater than with age (0.07), gender (0.25), substance abuse history (years of addiction) (0.18), psychotropic medication associated to substitution treatment (0.1), previous methadone treatment and residential treatment (0.14).

4. Discussion

At this retrospective multi-centre evaluation, BUP maintenance treatment seems to obtain a better outcome, in terms of retention in treatment and negative urines, in depressed heroin dependent patients, in comparison with the other dually diagnosed patients and addicted individuals without psychiatric comorbidity. Alternatively, the subgroups of patients affected by cluster B personality disorders (antisocial and borderline) and schizophrenia appeared less responsive to BUP treatment.

A high responsiveness of depressed heroin addicts to BUP treatment was not unexpected. Previous findings, obtained in a 12-week observational study, have evidenced a more positive outcome in depressed opioid dependent subjects, in comparison with non-depressed individuals, both in terms of retention and less risk of heroin use (Gerra et al., 2004). In agreement with our results, higher scores on depression subscale (D) at MMPI (Minnesota Multiphasic Personality Inventory) were recently reported as a psychological pattern directly correlated to a good response to buprenorphine substitution treatment (Poirier et al., 2004).

Buprenorphine could have improved outcome measures in the subgroup of depressed dually diagnosed patients, because of its specific effects on depressive symptoms. In fact, increased positive responses on scales of “liking,” “good effects” and euphoria have been reported during acute drug administration in an experimental setting (Pickworth et al., 1993). Accordingly, a recent study has indicated that BUP produces positive mood effects, although with substantial variability among participants (Umbricht et al., 2004), probably in relationship with personality traits and underlying biological correlates.

Better outcome in depressed patients, possibly related with the improvement of depressive symptoms, may tentatively be
attributable to the specific pharmacological profile of the drug, being BUP a partial mu agonist/kappa antagonist: in fact, kappa receptors agonist, such as butorphanol and endaline have been reported to increase dysphoria, confusion, sedation and to produce feelings of depersonalisation in humans (Greenwald and Stitzer, 1998; Walsh et al., 2001), supporting the hypothesis that BUP may counteract in depressed subjects the emotional and perceptual effects of kappa receptors system.

Accordingly, BUP capacity to control dysphoria, as a possible consequence of a dysfunction of the endogenous kappa opioid system, has been suggested also by combining BUP with naltrexone, theoretically leaving kappa antagonism as the major medication effect, and obtaining positive responses to treatment that exceeded those expected from naltrexone alone (Rothman et al., 2000).

Several lines of evidence indicate that endogenous kappa-opioid receptor system opposes the behavioral and neurochemical consequences of repeated drug use. The action of this opioid system in mediating alterations in mood and affect that occur during abstinence from prolonged exposure to drugs (Shippenberg et al., 2001) could be enhanced in depressed heroin addicts and counteracted by buprenorphine, as a kappa receptors antagonist. “K overdrive”, that has been hypothesized to contribute to the dysphoric mood observed in the protracted abstinence syndrome (Rothman, 1992; Rothman et al., 1991), could also underlie independent depression associated with substance use disorders. To this purpose, the kappa-opioid system has been demonstrated to have an important role in the learned helplessness depression in the experimental animals (Ukai et al., 2002).

In addition, kappa agonists have been found to stimulate hypothalamus–pituitary–adrenal (HPA) axis in man (Calogero et al., 1996), which was repeatedly reported hyperactive in depressed individuals (Rao et al., 1999). BUP may partly normalize the function of HPA axis in the subgroup of depressed individuals, antagonizing kappa receptors system overdrive, with possible consequences on mood and psychological traits.

In contrast with this hypothesis, prodynorphin or kappa opioid receptor mRNA levels were found unchanged in the dorsolateral prefrontal or cingulate cortices of bipolar disorder and major depressed subjects (Peckys and Hurd, 2001), suggesting the need of great caution in the interpretation of our findings.

The negative outcome evidenced in BUP patients affected by cluster B personality disorders (antisocial and borderline) may be attributable to the personality traits of these subjects, characterized by high disinhibition, impulsiveness and high boredom susceptibility (Zuckerman scale) (Conway et al., 2003; Levenson et al., 1995), which were found inversely correlated with BUP outcome measures in the French study (Poirier et al., 2004).

5. Conclusions

The present findings need to be interpreted with caution, because of the weakness of the design: the major limitation is the retrospective nature of the data and the lack of systematic and more periodic evaluation of the subjects. Although multivariate analysis excluded the interference of some variables, possible inter-individual and cultural variability, treatment variables, and other unmeasured confounds, may have reduced the strength and the validity of the study. The pronostic factors able to characterize patients-subtypes and to predict buprenorphine outcome are still unclear and confused, but depressive comorbid disorder seems to be a possible reliable candidate.

Also in the present study, high dose BUP was found to suppress heroin use better than low doses, without influencing retention rate, in agreement with previous findings (Mattick et al., 2003; Gerra et al., 2004). Nevertheless, BUP capacity to completely counteract heroin effects perception at high doses, evidenced in human laboratory studies (Comer et al., 2001), could have represented a factor reducing the compliance in less motivated individuals. In any case, depressive symptoms appear to be more significant than dose at multivariate analysis as prognostic factor for BUP treatment outcome, suggesting that dual diagnosis and personality traits have to be taken into account carefully when making the decision to prescribe BUP substitution treatment in opiate addiction.

Continued research is needed to better investigate the possible psychobiological traits, or overt comorbid psychopathology, characterizing addicted individuals with better responses to BUP treatment.

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