Multi-centre observational study of buprenorphine use in 32 Italian drug addiction centres

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Abstract

Aim: To examine how buprenorphine is currently being used across Italy, and to identify simultaneously best practice protocols to guide physicians in optimising the safety and efficacy of this treatment option.

Design: Retrospective, observational, multi-centre study.

Participants: A total of 979 opioid-dependent patients were included from 32 centres involving the initiation of 1122 treatments.

Findings: During the study period 33.4% of patients relapsed during the induction phase. Lower induction doses resulted in markedly higher relapse rates (51.2% of those who received 2 mg versus 20.6% of those who received 10 mg of buprenorphine relapsed). Over 89% of patients who received 16 mg of buprenorphine during the induction phase successfully went on to maintenance treatment. The percentage of drug-positive urines also decreased over time on buprenorphine treatment (cocaine-positive urines decreased from 25.8% at study entrance to 0% at 24 months). Psychosocial support in addition to buprenorphine pharmacotherapy further decreased the risk of relapse and was associated with lower levels of heroin craving. Retention in treatment was increased by less-than-daily dosing of buprenorphine.

Conclusions: Higher induction doses of buprenorphine significantly decreased relapse rates and increased the percentage of patients achieving maintenance treatment. Psychosocial support and/or less-than-daily dosing also appeared to promote positive treatment outcomes.

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Keywords: Buprenorphine; Opioid; Addiction; Treatment

1. Introduction

Buprenorphine has been available in Europe since 1995. In 2000 it was introduced to Italy's network of 557 public sector addiction treatment centres (Ser.T.). In this particular study all patients were opioid dependent with some being polydrug-abusers. By 2003, approximately 16,000 patients were receiving buprenorphine (Lucchini and Leonardi, 2003). It is thought that buprenorphine treatment now accounts for roughly 25% of prescribed maintenance treatments in the Italian system, with regional figures varying between 15 and 55%. As buprenorphine prescribing becomes increasingly commonplace across Italy, the need for buprenorphine treatment guidelines is growing. These guidelines would ensure that Italian patients consistently receive the optimal benefit from their treatment, in terms of both safety and efficacy.

Data supporting buprenorphine’s comparative efficacy to other medication-assisted options such as methadone or naltrexone (with or without psychosocial support) have been the subject of greater debate, with reports of equivalence, superiority and inferiority (Mattick et al., 2004). It has been suggested that the wide variety of induction protocols and dosing strategies used in the studies may account for the discrepancies in findings, with lower induction doses (Petitjean et al., 2001), less frequent dose increments (Petry et al., 2001) and lower maintenance doses (Eder et al., 1998) being associated with poorer outcomes.

Since its introduction into Europe, numerous international studies have demonstrated interesting clinical advantages for buprenorphine, such as identification of a ceiling to buprenorphine’s effects on respiratory depression (Walsh et al., 1994; Ciraulo et al., 2006), few CYP enzyme interactions (Kilicarslan
and Sellers, 2000; Iribane et al., 1998; McCance-Katz, 2005) and no reports of cardiac arrhythmias (reviewed by Krantz and Mehler, 2004), further supporting suggestions of clinical safety benefits such as reduced risk of fatal overdose when used alone (Auriacombe et al., 2001, 2004; Reynaud et al., 1998) and reduced risk of metabolic drug–drug interactions (Chang and Moody, 2005; McCance-Katz et al., 2001; Kilicaslan and Sellers, 2000). Buprenorphine’s pharmacology also allows flexible treatment strategies including ease of transfer to other treatment options such as methadone or naltrexone (Lintzeris et al., 2001), less-than-daily dosing (Johnson et al., 1995; Marsch et al., 2005), ease of withdrawal from maintenance through dose taper (Breen et al., 2003) as well as safe and cost-effective initiation in primary care settings by trained GPs (Gibson et al., 2003).

In comparison to methadone, there have been conflicting results. A study in Italy found that retention rates were comparable in both treatment groups (buprenorphine and methadone), but buprenorphine treated subjects had significantly lower rates of illicit opiate consumption (Vigezzi et al., 2006). On the other hand, a study in the USA showed that in co-occurring cocaine and opioid dependence, patients on daily methadone remained in treatment significantly longer and achieved significantly longer periods of sustained abstinence, compared to patients who received daily buprenorphine (Schottenfeld et al., 2005). Also in long-term opioid dependent patients, high-dose methadone maintenance appears to be superior to buprenorphine (Kristensen et al., 2005).

In order to understand how buprenorphine is currently being used across Italy and to simultaneously identify best practice protocols to guide physicians in optimising the safety and efficacy of this treatment option, a wide scale, multi-centre, observational study was undertaken, which is reported here. The study aimed to record induction doses, rate of progress to maintenance through dose tapering was determined by the prescribing physician, and doses were based on each patient’s individual needs. The induction dose is defined as the dosage of buprenorphine that remained unchanged. Patients who relapsed during the maintenance phase. Some centres started with a first dose of 2 mg followed by a 2 mg increase in dose each time withdrawal symptoms were evident. No upper limit for dosage during first, second and third day of the induction phase was imposed. Other centres adopted the same induction protocol but stopped any increase at the maximum of 8 mg on the first day, 16 mg on the second day and 24/32 mg on the third day. Alternatively, at other centres, a first dose of 4 mg was given on day 1 and increased by 4 mg for each subsequent dose.

All patients completed a 3-day induction period and day 4 was considered the beginning of the maintenance period in each centre. During this phase the dosage of buprenorphine remained unchanged. Patients who relapsed during the study period were offered the option of restarting buprenorphine treatment following a short wash-out period. As a consequence, the number of treatments recorded in the study is higher than the number of patients enrolled. A patient was considered to have relapsed when he/she voluntarily stopped treatment and/or when his/her urine toxicology was positive during the induction or maintenance phase. Quantitative urine toxicology was carried out in order to distinguish between a real relapse and heroin use before the induction phase.

In all centres buprenorphine was administered as a sublingual tablet. Dose tapering was determined by the prescribing physician, and doses were based on each patient’s individual needs. The induction dose is defined as the dosage reached at the end of the induction phase. Patients on maintenance therapy either came into the clinic daily or if being treated with alternate day regimen, went to the clinic on a consistently scheduled basis. No treatment was self-administered at home.

2.2. Study assessments

Before treatment with buprenorphine was initiated, all participants were required to undergo urine toxicology as well as completing and Readiness to Change Questionnaire/Heroin (RTCQ/H) questionnaires (Deodato et al., 1995). Patients were also required to undergo a full medical examination, a psychosocial interview, and to take the Minnesota Multiphasic Personality Inventory 2 (MMPI2) test. These tests (bar the urine toxicology) were carried out by psychologists who also reported on patient compliance for each assessment.

All patients deemed eligible to participate were regularly assessed during the study: urine toxicology at least once a day in the first 3 days of treatment and then once a week; the RTCQ/H every 3 months in the first year, and the MMPI2 1 year from treatment initiation.

2.3. Treatment protocol

Treatment protocols differed between the participating centres for initial dose values as well as the protocol for increasing this dose over the induction phase. Some centres started with a first dose of 2 mg followed by a 2 mg increase in dose each time withdrawal symptoms were evident. No upper limit for dosage during first, second and third day of the induction phase was imposed. Other centres adopted the same induction protocol but stopped any increase at the maximum of 8 mg on the first day, 16 mg on the second day and 24/32 mg on the third day. Alternatively, at other centres, a first dose of 4 mg was given on day 1 and increased by 4 mg for each subsequent dose.

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2.4. Study instruments

2.4.1. Data card. A data card was generated for each patient, on which extensive treatment information was recorded for 24 months following treatment initiation. Information gathered included personal/social information, urine toxicology, buprenorphine doses used throughout the induction and maintenance treatment phases, reasons for leaving treatment, as well as the results of any

psychometric tests. Reasons for leaving treatment were recorded as either (a) relapse or (b) lost to the follow-up.

Individual patient data cards were kept anonymous in accordance with Italian privacy laws. All cards were analysed at the District Unit for the Prevention and Treatment of Drug Dependence and Alcoholism, Drug Addiction Centre D/XI-ASL Rome C.

2.4.2. Psychometric tests. The RTCQ/H (Italian Version) is a quick and objective test that allows the measurement of the willingness of the patient to change in relation to psychoactive substances dependency. It is based on a transtheoric model of Prochaska and DiClemente (1982) and the motivational approach of Miller and Rollnick (1991). The latter is a counselling and therapeutic model aimed at evaluating the patient motivation and his/her willingness to agree to and be adequately treated. The levels of willingness to change are: pre-contemplation (failing to recognise the substance(s) dependency as a problem), contemplation (frankly ambiguous patient’s attitude towards his/her dependency), determination (looking for a solution to the dependency problem), action (acting on the adopted solutions), maintenance (consolidating new habits as long as the dependency problem is not considered to be present anymore) and relapse (possible regressions to previous states) (Spiller and Guelfi, 1998).

The MMPI-2 is a broad spectrum personality questionnaire used to evaluate main characteristics of the patient’s personality and any emotional disorders they may have. It consists of a set of statements that the patient describes as ‘true’, ‘mainly true’, ‘mainly false’ and ‘false’ as far as his/her condition is concerned. Developed by psychologist Hathaway and neuropsychiatrist McKinley around 1940, this pragmatic diagnostic tool provides effective diagnosis for psychiatric disorders and measures the level of severity of psychopathological conditions, which has been re-standardised by Butcher et al. (1992).

2.5. Statistical analysis

Statistical analyses were carried out using two-tailed Student t-tests or Mann–Whitney U-tests where appropriate. P-values < 0.05 were deemed significant.

The initial group of drug-addicted patients has progressively expanded during the study. During the period October 2001–February 2002, the number of drug-addicted treatments was 354. This progressively grew to 641, 793 and finally to 1122. Thus, the sample was not strictly statistically defined but based on the data provided by those treatment centres that agreed to collaborate. Importantly, each round of data processing revealed the same results as those reported here. Thus, despite no statistical criteria being imposed when collecting the sample population, each successive data processing, on the addition of subjects, reconfirmed the results and conclusions drawn. For this reason, we believe that there is no possibility that the relationships have been due to confounding variables.

3. Results

3.1. Study population

Thirty-two Ser.T. centres participated in this observational study, involving 979 patients and a total of 1122 treatments. The majority of patients were male (n = 848, 86.6%), and out of the total study group 81.5% of patients came voluntarily to the Ser.T. centres. As the CRF only recorded two options; ‘voluntary access to treatment’ or ‘non-voluntary access to treatment’, the study was not able to define precisely the reasons for the remaining 18.5% of the study starting treatment. Slight differences were observed in the male and female patient profiles; however, these were not statistically significant (Table 1). In brief, male patients were younger, more likely to be single and more likely to be in employment than their female counterparts. Employment status was recorded at the beginning of the study only.

3.2. Treatment history

In total, 65.2% of patients entering the observational study were receiving methadone maintenance treatment. These cases were transferred to buprenorphine because they were continuing to use illegal drugs (heroin, cocaine and tetrahydrocannabinoid (THC)) despite being treated with medium to high doses of methadone. As the study was purely observational, full details of the transition procedures were not requested in the CRF. However, for all the patients, the induction protocol was based on the Australian clinical guidelines for the use of buprenorphine (2000). At the time of the trials these were the only scientifically based guidelines available. This meant all switches from methadone to buprenorphine were carried out starting from a 20 mg dose of methadone with the time from the last methadone to buprenorphine were carried out starting from a 20 mg dose of methadone with the time from the last methadone dose to the first buprenorphine dose being no longer than 24 h.

The remaining 34.8% of patients had not received any prior medication-assisted treatment before the initiation of buprenorphine. No ‘precipitated withdrawal’ was recorded in either treatment-naïve patients (heroin-dependent) or patients coming from methadone treatment.

3.3. Dose induction and maintenance protocols

On day one 55.3% of treatments were initiated with a ‘tester’ dose of between 4 and 8 mg of buprenorphine, and 21.7% were started on a total daily dose of buprenorphine between 12 and 32 mg. The remaining patients were initiated with a dosage of less than 4 mg. The average buprenorphine dose administered at the end of the induction phase was 8.83 ± 4.8 mg. It was noted that the dose reached in the first three days of treatment remained unchanged thereafter in 56.3% of treatments that were initiated with 4 mg of buprenorphine and in 24% of treatments that were initiated with 8 mg.

Table 1

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single (n = 471)</td>
<td></td>
<td>Single (n = 45)</td>
</tr>
<tr>
<td>Married (n = 271)</td>
<td></td>
<td>Married (n = 25)</td>
</tr>
<tr>
<td>Cohabitant (n = 106)</td>
<td></td>
<td>Cohabitant (n = 61)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.1 ± 7.8</td>
<td>32.3 ± 8.9</td>
</tr>
<tr>
<td>Employment</td>
<td>Yes: regular job (n = 314, 37.0%)</td>
<td>Yes: regular job (n = 24, 18.3%)</td>
</tr>
<tr>
<td>Length of dependence (years)</td>
<td>12.2 ± 2.1</td>
<td>14.2 ± 3.4</td>
</tr>
</tbody>
</table>
3.4. Treatment relapse

During the study, 33.4% of patients lapsed or relapsed during induction and were later restarted. Lower induction doses resulted in significantly higher relapse rates: over half of all treatments induced with 2 mg of buprenorphine relapsed (51.2%), whereas 39.2% of those on 4 mg, 31.5% of those on 8 mg and 20.6% of those on 10 mg did so (Fig. 1).

Almost all inductions in which a patient received an induction dose of buprenorphine of 16 mg or over were successfully completed (89.7%), and patients went on to maintenance treatment.

In the patient group that had received methadone prior to the study it was also observed that in over half of the relapse cases that occurred within the induction phase (57.7%) the patients had used heroin in the seven days preceding the start of treatment.

3.5. Treatment retention

At the time of study completion, 501 of the 979 patients enrolled in the study remained in treatment (51.2% of total study population), 327 had relapsed (33.4%) and 151 (15.4%) had reached a drug-free condition (defined as not using heroin any more).

During the study, 12.7% of patients restarted treatment following relapse and 1.9% restarted for a third time. The majority of patients who stopped and later restarted treatment (78.7%) were given the same dose of buprenorphine as that administered initially.

3.6. Daily and alternate-day dosing

In patients treated with buprenorphine doses ≥16 mg, less-than-daily dosing resulted in better compliance and retention in treatment compared with daily dosing (Fig. 2). The reason for starting alternated daily dosing was not collected but repeated negative urine toxicologies could be hypothesised as the most likely reason for adopting this dosing protocol. In the alternated daily dosing protocol patients went to the centres three times a week where they took consistent multiple buprenorphine dosages.

3.7. Secondary substances of abuse

Toxicology results showed that cannabinoids and cocaine were the most common secondary substances of abuse at treatment induction (34.0 and 25.8%, respectively). Overall, a decrease in urines positive for cannabinoids or cocaine was observed as the duration of treatment with buprenorphine increased (Fig. 3). The most notable percentage reductions in secondary substance abuse were seen in patients treated with buprenorphine doses greater than 16 mg (Table 2).

3.8. Psychosocial involvement

Psychosocial support was not compulsory in this observational study design but was freely provided by the clinics involved. Only one quarter (24.3%) of patients were given psychosocial support (frequency of support is unknown) with the remainder given pharmacological treatment alone. The latter patients, who received no psychosocial support, met solely with physicians and did not receive any other kind of intervention.

In general, the combination of no psychosocial support and low dosing of buprenorphine (<16 mg/day) was associated with consistent high levels of craving. High average scores on the RTCQ/H were obtained from patients receiving psychosocial support (n = 238, 24.3% total...
Cannabinoids

Substance of secondary abuse and the percentage of positive urines in relation to the buprenorphine dose administered

<table>
<thead>
<tr>
<th>Substance of secondary abuse</th>
<th>Buprenorphine dose in mg (daily)</th>
<th>Reduction in positive urines (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>≥16</td>
<td>44.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>≤8</td>
<td>36.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cocaine</td>
<td>≥16</td>
<td>19.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≤8</td>
<td>12.4</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

* P-value detects the statistical significance between buprenorphine maintenance clusters (≤8 and ≥16 mg) and reduction of positive urine analyses to cocaine and cannabinoids.

study cohort) for the following variables: readiness-to-change (R = 60), self-efficacy (S = 18) and internal conflict (F = 20). In 124 relapsed patients, the scores obtained for the readiness-to-change and self-efficacy variables diminished substantially (R = 18, S = 6) from those obtained prior to relapse.

4. Discussion

In 2000, when buprenorphine was first introduced in Italy, it became apparent that there was a lack of methodological rigour among all centres involved in substitution treatment. In order to address the variability, this study was designed to gather experiences from the Ser.T. Centres throughout Italy. By looking at the data collected from the first four years of buprenorphine treatment, the aim was to identify the best practices that led to optimal outcomes.

The aim of the induction phase is to achieve a stable maintenance dose as rapidly as possible, ideally within 1–3 days (Johnson et al., 2003). The data from this study suggest that a critical factor in a successful treatment is the correct induction onto buprenorphine at an adequate dose. According to the data collected in this study, initial induction doses of 16 mg were associated with better treatment compliance and retention rates, while lower induction doses were associated with a higher percentage of relapse and secondary substance abuse. Previous studies have also reported and emphasised the benefits of induction doses of 16 mg of buprenorphine, and induction doses as high as 32 mg/day have been recommended (Ling et al., 1998). However, as has previously been reported, it is not only the initial dose that is important, but also the speed at which this dose is reached. Rapid dose titration has been strongly associated with substantially increased patient compliance and lower risk of treatment drop-out (Johnson et al., 1995; Di Petta and Leonardi, 2005). The latter study also found that patients who abstain from heroin use for a period of at least seven days have a greater period of retention in treatment and appear more motivated.

Once the maintenance phase has been reached, higher doses are also associated with better treatment outcomes. During the induction phase, if high dosages of buprenorphine were reached, only small dose changes are needed in the maintenance phase to meet fully the needs of the patient. In this study, buprenorphine doses tended to increase during maintenance from around 8 mg/day to around 12 mg/day. Higher maintenance doses of buprenorphine (12–32 mg/day) also reported, were shown to be well accepted, and were associated with good compliance rates and improved chance of a successful outcome. Conversely, lower doses of buprenorphine in the maintenance phase were associated with increased heroin cravings that may go some way to explain higher rates of relapse. Additionally, although not a defined cluster at the beginning of the study, the patients who injected heroin in the week before commencement of the buprenorphine treatment were found to have a greater risk of relapse in comparison with those who did not use heroin in the same week. This risk further increased if the induction dosage of buprenorphine was ≤8 mg.

Two studies have suggested that less-than-daily dosing is an alternative treatment method over a daily dosing regimen (Amass et al., 2001), may reduce treatment costs, and in agreement with this study, facilitates retention in treatment (Amass et al., 1998). Overall, less-than-daily dosing improves clinical flexibility, and as less time is spent by a physician on the treatment of one individual patient, it may assist in increasing the number of patients treated. It is worth noting that in Italy there are only two different treatment protocols: on a daily basis or on alternate days, where out-patients can only take buprenorphine at the public Drug Addiction Centres. Thus, the study does not document any self-treatment at home.

Just as there are factors that improve opioid dependency treatment, this study has also identified factors that decrease the chance of a positive outcome. During the study, 33.4% of patients relapsed during induction and were later restarted. Even though it can be considered quite restrictive, this study defined a patient as having relapsed if they presented a single positive urine toxicology result (or had voluntarily stopped treatment). However, this may not reflect a full relapse to a previous state of heroin dependency. Instead it could be considered to be the result of inadequate dosing, especially during the induction phase, as at suboptimal doses buprenorphine may not provide sufficient cover to suppress cravings fully or provide receptor blockade that prevents the effects of additional heroin use from being felt. In spite of a decade of availability, it would appear that there is still no consensus regarding the identification and use of adequate ‘blocking’ doses of buprenorphine. This may to some extent result from the caution regarding dose escalations that characterised early prescribing tendencies when buprenorphine was still a ‘new’ treatment option. Until there is a common clinical agreement on the adequate blocking dose range for maintenance therapy, it remains difficult to quantify the true effectiveness of buprenorphine treatment or in fact make meaningful comparisons with methadone. Studies such as this Italian observation are needed to elucidate best treatment practices in order to answer some of these critical questions.
Underdosing and excessively slow induction may also be critical issues for patients who today are considered to be ‘non-responders’. It may be speculated that these ‘non-responders’ may only need an adequate dose of buprenorphine tailored to their individual needs to produce more positive treatment outcomes rather than disruption of treatment as they are transferred to alternative substitution therapy.

The main aim of opioid treatment is to prevent illicit drug use, and in order to be successful in doing this a number of factors must be taken into consideration. Interestingly, it has been observed that buprenorphine treatment reduces secondary drug use regardless of the dosing protocol employed (induction doses, maintenance doses, daily or alternate-day dosing, etc.), and that the level of secondary drug abuse decreased as the duration of buprenorphine treatment increased (Kosten et al., 1993; Schottenfeld et al., 1993). In agreement with this study, Oliveto and colleagues also found that maintenance treatment with buprenorphine decreases the consumption of cocaine (Oliveto et al., 1999). Buprenorphine treatment, therefore, clearly supports illicit drug abstinence. However, it should be noted that this effect may not be specific to buprenorphine alone, as a reduction in secondary substance use has also been reported during treatment with methadone (Di Petta and Leonardi, 2005; Schottenfeld et al., 1997). As such, the reduction in secondary substance abuse may partially reflect a treatment effect regardless of the maintenance opioid selected. Nevertheless, this study supports the finding that a buprenorphine maintenance dose of 16 mg or more is effective in reducing use of cannabinoids and cocaine whereas lower buprenorphine dosages do not seem to show a similar effect.

Overall this observational study suggests some conditions that can have a favourable influence on the progress of buprenorphine treatment. The results of this study seem to show that rapid induction to an adequate dose of buprenorphine is the key to successful treatment of opioid dependency, with better results seen in patients receiving 16 mg at induction. Adequate doses of buprenorphine, during both induction and maintenance, had a positive effect on treatment outcomes, including compliance and retention. This is the first reported observation study in Italy, based on clinical practice among a large number of patients, and may provide general indications towards better clinical management of their addiction using buprenorphine.

Due to the observational nature of this study, a number of limitations should be considered when evaluating the implications of the study findings. Absence of inclusion criteria did not guarantee homogenous population characteristics. The free treatment protocol regarding psychosocial support, lack of experience with buprenorphine in the clinical Italian setting and different methadone tapering strategies among the study centres, as well as the lack of any compliance monitoring system other than tracking the attended visits to the centres, could all have biased the final results, especially with regard to early relapses during the induction phase.

Since this study did not separately evaluate patients according to their previous use of opioids (methadone or heroin), and as this difference could affect the generalisability of the results, a specific study should be carried out. This study is among the largest multi-centre observational studies ever carried out using buprenorphine and aimed to provide an extensive data set for the development of Italian treatment recommendations. The study findings have helped to generate more evidence on the need for adequate doses of buprenorphine in order to provide more successful treatment outcomes.

Conflict of interest

Author Leonardi Claudio has consulted for Schering Plough. He has also served as a speaker for Essex Italia SpA and Reckitt Benckiser. All other authors declare that they have no conflicts of interest.

Acknowledgements


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