European Review for Medical and Pharmacological Sciences 2011; 15: 871-874

Buprenorphine/naloxone versus methadone in opioid dependence: a longitudinal survey

F. CURCIO, T. FRANCO[§], M. TOPA[#], C. BALDASSARRE[#]; and Gruppo Responsabili U.O. Sert.T.

U.O. Ser.T. 31 and S.C. Tutela della Salute Dipartimento Farmacodipendenze, ASL Napoli 1 Centro, Napoli (Italy)
[§]S.S. Valutazione Ricerca e Monitoraggio Dipartimento Farmacodipendenze, ASL Napoli 1 Centro, Napoli (Italy)
[#]S.C. Tutela della Salute Dipartimento Farmacodipendenze, ASL Napoli 1 Centro, Napoli (Italy)
*U.O. Sert.T., ASL Napoli 1 Centro, Napoli (Italy): M. Scala, F. Auriemma, S. De Rienzi, R. Stimolo, V. Ferrara, A.M. Santonicola, M. Siconolfi, G. De Rosa, F. Del Vecchio, S. Del Tufo

Abstract. – *Background and Objectives:* **Buprenorphine and methadone are widely used for the treatment of opioid dependence, but their diversion and/or misuse are frequent. In principle, buprenorphine/naloxone combination therapy should be associated with a lower frequency of drug abuse/misuse than methadone. This study assessed the efficacy of the substitution of buprenorphine treatment with the buprenorphine/naloxone combination in opioid-dependent patients.**

Material and Methods: **3812 drug-addicted outpatients selected from 10 Italian Public Services for Addiction (Ser.T.) centres in Naples (Italy) were enrolled: 3105 (81.5%) were treated with methadone and 707 (18.5%) with buprenorphine. The buprenorphine treatment was switched to buprenorphine/naloxone (4:1), and the patients were followed for about 1 year. The number of subjects still on treatment after 1 year, their status according to social, educational and toxicologic (assessed by a urine toxicology test) parameters were assessed.**

Results: **1 year after the therapy switch, the number of patients still on treatment was similarly reduced with methadone (2883; –7.5%) and buprenorphine/naloxone (632; –10.6%; p=0.369). However, in patients treated with buprenorphine/naloxone, a significant improvement was reported in social life status (63% versus 39% of the buprenorphine/naloxone and methadone treated subjects, respectively, were married/cohabiting p<0.001), in the educational level (43% of buprenorphine/naloxone treated versus 32% of the methadone treated subjects obtained at least a high school certificate, p<0.001) and in the toxicological conditions (53% of buprenorphine/naloxone treated subject versus 30% of methadone treated individuals had opioid- and cocaine- negative urine tests, p<0.001) .**

Discussion: **These preliminary data suggest that buprenorphine/naloxone treatment of opioid dependence reduces the percentage of treated subjects similarly to methadone, and is associated with an improvement in social life, educational and toxicological conditions, compared with methadone treatment. However, we cannot exclude a selection bias, i.e. patients who were more likely to stabilize their opiate dependence switched to buprenorphine/naloxone.**

Key Words:

Dependence, Opioid, Buprenorphine, Naloxone, Methadone.

Introduction

The partial μ-opioid receptor agonist buprenorphine (Subutex®) and the full agonist methadone have been shown to be clinically active and more cost effective than lack of pharmacological therapy in dependent opiate users[1,2]. Therefore, their use as abuse-deterrent drugs in the treatment of opioid dependence is currently extensive[3,4]. However, among opioid-dependent patients, the risk of abuse and misuse (i.e. non-medical use) of these drugs remains high, and their diversion in the illicit street markets is frequent[5], especially for the inhaled and intravenous formulations[6].

Therefore, in recent years new formulations of buprenorphine and methadone treatment have

Corresponding Author: Fabio Curcio, MD; e-mail: itinerari2008@alice.it

been developed, such as the sublingual tablet combination of buprenorphine and the μ-opioid receptor antagonist, naloxone. In principle, the combination therapy of buprenorphine and methadone with naloxone should be associated with a lower frequency of drug abuse/misuse. Recent large studies show a lower trend for the intravenous use of buprenorphine/naloxone and methadone/naloxone than for buprenorphine or methadone alone[7]. However, to our knowledge, studies investigating the substitution of buprenorphine therapy with buprenorphine/naloxone (Subuxone®), and its effects on the maintenance of opioid detoxification, the stability of social life, and on the level of educational progression in opioid-dependent individuals, are still lacking.

Therefore, the aim of this study was to assess the efficacy of the substitution of buprenorphine treatment with the buprenorphine/naloxone combination in opioid-dependent patients, in terms of social life stability, educational progression, and duration of detoxification from opioid and cocaine dependence, in comparison to methadone treatment alone.

Materials and Methods

Subjects

This longitudinal study evaluated, over a 1-year period, 3812 opioid-dependent outpatients (3422 [89.8%] males; mean age 39.3 ± 6.9 years), selected from 10 Italian Public Services for Addiction (Ser.T.) Centres in the city of Naples (Italy): 3105 (81.5%) of these opioid users were under treatment with methadone, whereas 707 (18.5%) were receiving buprenorphine. The mean duration of drug addiction before admission at Ser.T was 8.4 ± 6.2 years; mean age at Ser.T admission was 27.6 ± 6.4 years. With respect to occupational status, 36% of the subjects were unemployed, 4% held a part-time position, 7% were students, and the remaining 53% held a full-time position (although many of these did not have contracts).

Treatment Change and Tests

From June to September 2008, the buprenorphine treatment was switched to buprenorphine/naloxone (4:1) therapy (2 mg and 8 mg formulations), and the patients were followed for about 1 year. The buprenorphine and buprenorphine/naloxone doses administered during the short-term (<3 months), medium-term (3-6 months) and long-term (>6 months) treatments are shown in Table I.

The number of subjects still receiving treatment after 1 year was evaluated; and their status according to social, educational and toxicological (assessed by a urine toxicology test) parameters were also assessed.

Statistical Analysis

Data were analyzed by descriptive statistics. The χ^2 test was applied to test the null hypothesis of no differences between two percentages.

Statistical significance was set at $p<0.05$. The analyses were performed using the software Statistica (version 7.1, StatSoft, USA).

Results

One year after the therapy switch from buprenorphine to buprenorphine/naloxone treatment, the number of treated subjects was reduced with both methadone (2883, –7.5%) and buprenorphine/naloxone (632, –10.6%), and no differences between groups were reported (p=0.369).

Table I. Number of treated patients and mean dosages of buprenorphine and buprenorphine/naloxone, ordered by drugs and therapy duration (short-, medium and long-term).

Treatment	Short-term treatment (< 3 months)		Medium-term treatment (< 6 and > 3 months)		Long-term treatment (> 6 months)	
	Patients (n)	Dosage (mean) (mg/die)	Patients (n)	Dosage(mean) (mg/die)	Patients (n)	Dosage (mean) (mg/die)
Buprenorphine	54	7.7 ± 3.9	94	10.3 ± 3.2	599	13.5 ± 4.2
Buprenorphine/ Naloxone	54	10.2 ± 3.5	89	11.5 ± 3.6	488	14.8 ± 7.3

However, social life status, assessed by the percentage of subjects who were married or cohabiting, was improved in the buprenorphine/naloxone group, compared with the methadone-treated group: 398 out of 632 buprenorphine/naloxone patients versus 1124 out of 2883 methadone subjects, respectively, were married or cohabiting at the end of the follow-up period (p<0.001). The relative percentages of these data are reported in Figure 1 (Panel A).

With respect to the educational level, 43% of buprenorphine/naloxone-treated subjects versus 32% of the methadone-treated subjects had received at least a high school certificate (p<0.001) at the end of the follow-up period (Figure 1; Panel B).

Last, the toxicological conditions were improved to a significantly greater degree in patients treated with buprenorphine/naloxone, compared with those treated with methadone: 53% of buprenorphine/naloxone-treated subject versus 30% of methadone-treated individuals had opioid- and cocaine- negative urine tests (p<0.001).

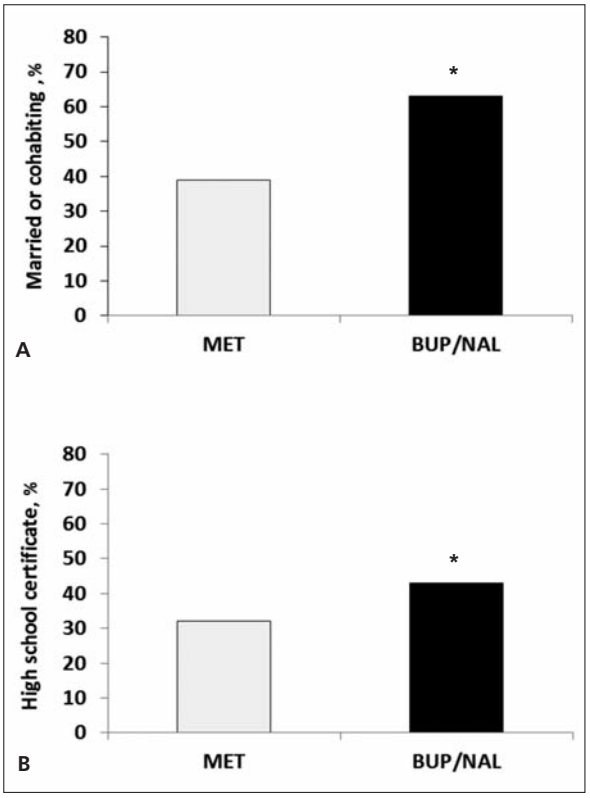

Figure 1. Social status (married or cohabiting) and educational level (high school degree) in methadone- versus buprenorphine/naloxone-treated patients. Grey bars, methadone (MET); black bars, buprenorphine/naloxone (BUP/NAL). *p<0.05 (χ^2 test on percentages).

Toxicology tests for 11% of subjects treated with buprenorphine/naloxone were not performed in the last 6 months of the study. The relative percentages of these data are reported in Figure 2.

Discussion

These preliminary data suggest that buprenorphine/naloxone treatment of opioid dependence produces a similar reduction to methadone in the number of subjects who need treatment. This finding may be clinically relevant, because it has been shown recently that a higher proportion of patients (especially adolescents and young adults) treated with intravenous buprenorphine reported drug misuse, compared with those receiving methadone[6]. The current study also confirms previous evidence on the efficacy of buprenorphine/naloxone for detoxification treatment in opiate-dependent patients[8]. The assessment of the safety profile of buprenorphine/naloxone was beyond the purpose of this study. However, a favourable safety profile has been demonstrated for this drug combination in previous reports[8,9], with the main treatment-related adverse events being anxiety, sweating and insomnia[9].

One of the novel findings of this study is that the combination therapy appears to be associated with an improvement in social life and progression in educational level, i.e. to have an influence on the global social status of the treated subjects. This finding may somehow correlate with previ-

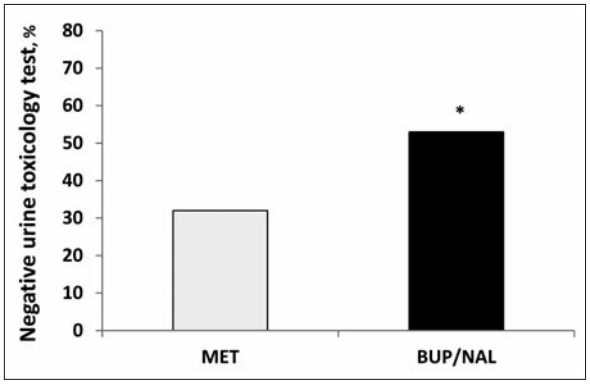

Figure 2. Percentages of negative urine toxicology test in methadone- versus buprenorphine/naloxone-treated patients. Grey bars, methadone (MET); black bars, buprenorphine/naloxone (BUP/NAL). *: p<0.05 (χ^2 test on percentages).

ous preliminary data, which showed that a high percentage of buprenorphine/naloxone-treated patients reported improved psychosocial functioning, which could contribute to better reintegration into the community, and to enhanced social interactions[10].

Last, buprenorphine/naloxone combination therapy seems to stabilize the toxicological status of patients, providing a significant advantage over the methadone alone. In fact, more than one-half of the buprenorphine/naloxone-treated subjects had opioid- and cocaine- negative urine tests at the end of the observational period, compared with about one-third of the methadone-treated individuals. Although this finding may be clinically relevant, we cannot exclude that the Ser.T. physicians could have decided to switch to buprenorphine/naloxone treatment those patients who were more likely to stabilize the opiate dependence. However, in our setting is difficult to avoid this selection bias, due to ethical reasons. Another relevant limitation of the present analysis is represented by its observational nature.

Given the limitations, the results of the present study should be regarded as preliminary, and further studies will be needed to better characterize the psychological profile of the patients. Moreover, these data need to be integrated with a more complete evaluation of the safety and efficacy of buprenorphine/naloxone combination therapy, which should include a more extensive evaluation of laboratory parameters, and a screening for viral infections.

Acknowledgements

Editorial assistance was provided by inScience Communication, a Wolters Kluwer business. This assistance was funded by Reckitt Benckiser Healthcare SpA, Milan, Italy.

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