

Regular article

## Multimodal drug addiction treatment: A field comparison of methadone and buprenorphine among heroin- and cocaine-dependent patients

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### Abstract

**Aims:** Our objective was to compare the effectiveness of buprenorphine (BUP) and methadone maintenance treatment in opiate-addicted patients in a clinical nonexperimental setting. **Design:** We used a naturalistic observational prospective study of 24 months' duration. **Setting:** Subjects were enrolled and treated at a drug addiction outpatient clinic of the National Health System Local Unit in Milan, Italy. **Participants:** Two hundred fifty-seven subjects meeting the *DSM-IV* criteria for opioid dependence and opioid-seeking substitutive pharmacological treatment participated in the study. **Intervention:** One hundred twenty-one subjects received BUP at a mean daily dose of  $11 \pm 6$  mg (median = 8; range = 2–30) for a mean duration of 249 days. One hundred thirty-six subjects received methadone at a mean daily dose of  $54 \pm 29$  mg (median = 50; range = 4–140) for a mean duration of 267 days. **Measurements:** The main efficacy parameters were treatment retention rates and illicit substance abuse, as assessed by urinalysis. **Findings:** Retention rates were comparable in both treatment groups, but BUP-treated subjects had significantly lower rates of illicit opiate consumption ( $p < .0001$ ). **Conclusions:** The results confirm that, in a nonexperimental clinical practice setting, BUP is as effective as methadone in the treatment of heroin dependence, with significantly better opiate abuse control, thus possibly allowing longer and more effective treatment programs with reduced relapse rates. © 2006 Elsevier Inc. All rights reserved.

**Keywords:** Buprenorphine; Methadone; Treatment effectiveness

### 1. Introduction

The multiple problems of heroin-dependent patients require a complete rehabilitation program that utilizes both pharmacological substitution therapy and psychosocial support. At present, although cocaine addiction is increasing, the use of opiates continues to be widespread in Italy, with about 160,000 drug-addicted subjects (mainly heroin-addicted subjects) being followed by the National Health System Local Services. Only 40% of these subjects are

undergoing opiate substitution treatment, and even fewer are receiving psychosocial support.

The long-acting opiate agonist methadone has been used as the main agent for the detoxification of heroin-dependent patients. Many studies have demonstrated the efficacy of methadone maintenance therapy (MMT) in decreasing illicit drug consumption and criminal behavior, improving the rehabilitation of intravenous opiate-addicted patients, and lowering the prevalence of HIV infection (Newman, 1987; Plomp, Van der Hek, & Ader, 1996; Schottenfeld & Kleber, 1995). However, MMT is associated with several problems, including limited patient and community acceptance, and it appears not to be optimal for all subjects (Kolar, Brown, Weddington, & Ball, 1990; Schoenbaum & Selwyn, 1995).

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Since 2001, buprenorphine (BUP), an opiate  $\mu$ -receptor partial agonist, has been available for the treatment of heroin addiction, proving to be effective in reducing cravings for opiates and in blocking withdrawal symptoms, thus representing a useful alternative drug to methadone (Cozzolino et al., 2002, 2003; Ling et al., 1998; Pani, Maremmani, Pirastu, Tagliamonte, & Gessa, 2000). Recently, its efficacy in reducing concomitant cocaine and opiate abuse has been shown in a randomized placebo-controlled study (Montoya et al., 2004).

We were interested in the relative effectiveness of these two medications; thus, we performed this naturalistic, observational, prospective study with all new cases requiring opiate substitution therapies within our outpatient clinic from January 2002 to December 2003.

We compared the effectiveness of BUP and methadone in the treatment of opioid dependence in a clinical non-experimental setting.

## 2. Subjects and methods

### 2.1. Subjects

Beginning January 2002, all opiate-addicted patients requiring substitution pharmacotherapy were considered for admission to the study. Addiction diagnosis was established according to *DSM-IV* criteria. HIV patients were admitted even while undergoing highly active antiretroviral therapy.

We informed patients about the two (methadone and BUP) alternative pharmacological therapies, explaining their pharmacological and clinical characteristics. Then, patients were assigned to their pharmacological treatment of choice, taking into account a few exclusion criteria. Exclusion criteria for BUP were as follows: ongoing MMT of  $\geq 25$  mg/day; *DSM-IV* axis I diagnosis; hepatic/renal failure in the previous 6 months; addiction to alcohol or benzodiazepines; age of  $< 18$  years. However, patients with severe respiratory failure, symptomatic cholelithiasis, severe pancreatic disease, or previously clinically manifested methadone intolerance are normally excluded from MMT.

Patients were requested to give their written informed consent before enrolment into the study.

### 2.2. Pharmacological treatments

Methadone hydrochloride syrup (0.1%; Metadone Molteni) was administered at different dosages (according to patients' needs; starting with 20 mg), which could be increased following patients' withdrawal symptoms.

BUP was administered starting at a dose of 2 mg, which was increased every 2–3 hours to suit patients' withdrawal symptoms. The patients remained under a physician's observation at the center for the entire morning, and they were even allowed to return in the afternoon if their withdrawal symptoms have not been adequately stabilized.

The patients' condition was evaluated again on the next day, and the drug was administered starting with the dose reached the previous day, until the patient reached a stable condition.

For both BUP or MMT, the dosage was increased progressively until the elimination of withdrawal signs and symptoms. In BUP-treated subjects, the highest allowed dose was 32 mg: If this proved to be not adequately effective, the patients were switched to MMT. The individual effective dose was then adopted for maintenance therapy. For all subjects, long-term treatment was planned.

Both substitution drugs were administered daily at our addiction center or were taken home weekly on weekends for 6 days. However, all patients had to come to the center at least once a week to receive the drug.

### 2.3. Psychosocial support

Psychosocial treatment, according to the patients' personal needs (social, psychological, educational, and others), was offered to each patient during the first visit. Counseling was proposed even later, during the course of the pharmacological therapy, if the medication alone was not considered satisfactory based on multiple positive urinary analyses or clinically significant negative changes in patient behavior. All subjects with legal problems routinely underwent combined treatment.

### 2.4. Urinary analyses

We performed urinalyses for opioid and cocaine metabolites once a week. Urine specimens were collected under control (when possible, with visual nurse control and always with temperature control; QUIKSITE 900 HB thermometer; Instrument, USA). Specimens with temperatures below  $32^{\circ}\text{C}$  and specimens with temperatures above  $38^{\circ}\text{C}$ , with a difference of more than  $1^{\circ}\text{C}$  with oral temperature, were excluded. The specimens were placed in a refrigerator at  $3^{\circ}\text{C}$  and then sent to the laboratory. Urine samples were analyzed by enzyme immunoassay; in particular, cases with juridical problems were analyzed by gas chromatographic assay, performed in specific laboratories of the National Health System Local Unit or the university hospital. Every positive result for each patient was followed by a visit by the attending physician, which was aimed at adjusting the drug dosage and at proposing again the combined treatment (if not already ongoing).

### 2.5. Efficacy assessment

The main effectiveness criteria were: treatment retention rates (Fig. 1) and results of opiate- and cocaine-negative urinalyses. Moreover, the following treatment outcomes were established: (1) dropout ( $\geq 15$  days without therapy); (2) drug switch; (3) treatment completion; (4) patient transfer to other services or to a rehabilitative-educational residential structure; (5) patient imprisonment; (6) death.

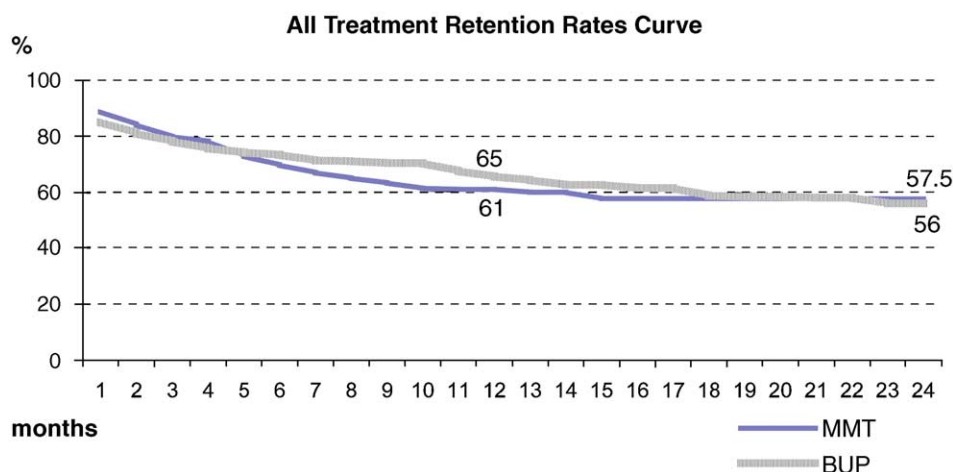


Fig. 1. Methadone and BUP retention rates curve of “all treatments.”

The subjects’ clinical, social, and psychological performances were evaluated by Global Assessment of Functionality (GAF), according to *DSM-IV*, at baseline and on completion of pharmacological treatment.

2.6. Statistical methods

Baseline characteristics were compared by Student’s *t* tests and chi-square tests.

Retention rates and positive urine samples were analyzed by chi-square tests and odds ratios.

3. Results

From January 2002 to December 2003, 257 patients began pharmacological substitution treatments in our

center. One hundred twenty-one patients underwent 135 BUP treatments, and 136 were treated with 156 separate methadone treatments. Detailed demography and other baseline characteristics are shown in Table 1.

The subjects in the two treatment groups were homogeneous for sex, age, educational level, and duration of drug addiction, but not for occupational level, according to the Hollingshead occupational classification (Fig. 2): The lowest occupational level and quality (Category 7) were significantly more common among subjects receiving MMT, whereas a higher level (Category 4) was significantly more represented in the BUP group. The number of subjects who are positive for HIV, hepatitis C virus, and hepatitis C virus was homogeneous in the two groups. The mean initial GAF was significantly higher in the BUP group.

Treatment duration ranged from 1 to 716 days (mean = 249) for MMT and from 1 to 708 days (mean = 267) for BUP. Twenty-nine (18.6%) and 27 (20%) treatments, were considered short term (<31 days); 57 (36.5%) and 31 (22.9%)

Table 1 Demographic and main baseline characteristics

Variables	Methadone patients (n = 136)	BUP patients (n = 121)	p
Sex			
Male	106	99	.36
Female	30	22	
Age (years; mean ± SD)	35 ± 7	34 ± 6	.2
Educational level			
Primary	21	12	
Middle school	87	76	.2
High school	22	28	
Degree	1	5	
Unknown	5	1	
Age at first use of heroin (years; mean ± SD)	20 ± 6	21 ± 5	.6
Heroin use (years; mean ± SD)	13 ± 7	12 ± 6	.2
HIV			
HIV-positive	29	21	.4
HIV-negative	71	74	.15
Declined testing	36	26	.4
Baseline GAF score (mean ± SD)	59 ± 9	64 ± 10	.001

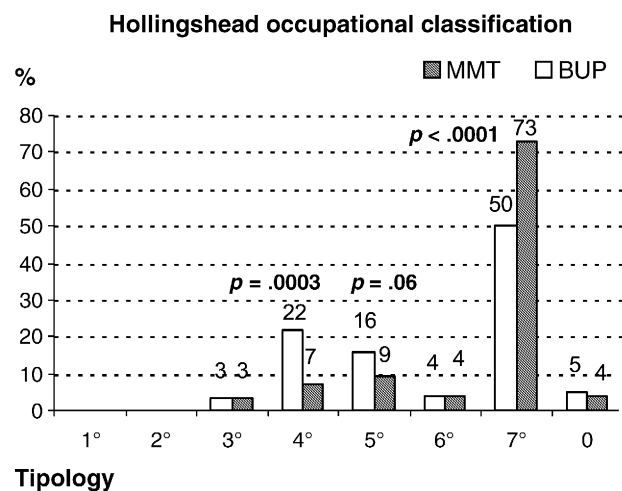


Fig. 2. Occupational level of BUP and MMT patients according to Hollingshead occupational classification: Employment level and quality decrease from 1 to 7.

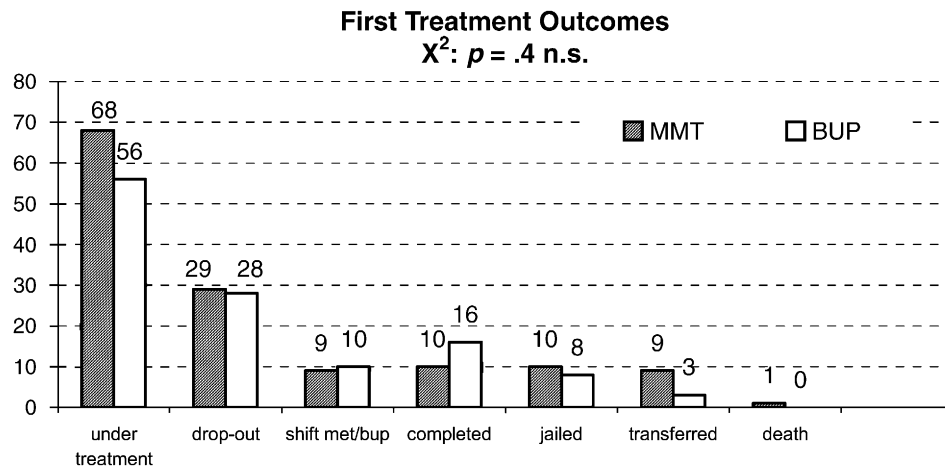


Fig. 3. Treatment outcomes of BUP or MMT at 2 years.

treatments were considered medium term (>30 days but <181 days); and 70 (44.9%) and 78 (57.8%) treatments were considered long term (>181 days) for MMT and BUP, respectively. The mean methadone maintenance dose was  $54 \pm 29$  (SD) mg/day (median = 50 mg/day; range = 4–140 mg/day) for MMT, and the mean BUP dose was  $11 \pm 6$  mg/day (median = 8 mg/day; range = 2–30 mg/day). Methadone was administered daily at the center in 56% of the patients, 36% were allowed to take their methadone home once a week for 6 days, and 8% received the drug twice or thrice a week for 2 or 3 days. BUP was administered daily at the center in 49.6% of the subjects, 46.2% were allowed to take the drug home once a week for 6 days, and 4.2% received it only twice or thrice a week, each time in double or triple dosage.

Forty-one percent of patients received combined psychosocial support in the MMT group, and 42% of patients received combined psychosocial support in the BUP group.

Treatment outcomes at 24 months are summarized in Fig. 3. The retention rates at 24 months were 58.6% for MMT and 54.9% for BUP ( $p = .4$ , *ns*). If only initial treatment episodes were considered, these figures were 57.5% for MMT and 56% for BUP ( $p = .5$ , *ns*) (Fig. 1). Urinalyses were negative for opiate metabolites in 63% and 80% of the samples collected in the MMT and BUP groups, respectively ( $p < .0001$ ).

Urine tests were negative for cocaine metabolites in 77.5% and 75.5% of specimens in the MMT and BUP groups, respectively (*ns*) (Table 2).

GAF values significantly increased in both treatment groups: from 59 at baseline to 64 on treatment completion in the MMT group ( $p = .008$ ) and from 66 to 71 ( $p = .0004$ ) in the BUP group. The difference between treatments was not statistically significant.

The analyses of dose subgroups showed that the retention rates and the percentages of opiate-negative urine specimens were significantly higher in the MMT higher dose subgroup

(>50 mg/day) than in the MMT lower dose subgroup ( $\leq 50$  mg/day). Similarly, retention rates were also different between these two groups (65.2% vs. 52%,  $p = .0006$ ) as were cocaine-negative urinalyses (68.5% vs. 56.4%,  $p < .001$ ). Among BUP patients, the difference between the higher dose (>8 mg/day) and the lower dose ( $\leq 8$  mg/day) was significant only for cocaine urinalyses (81.4% vs. 78.1%,  $p < .0001$ ).

In both treatment groups, the rates of opiate-negative urinalyses were significantly higher in patients receiving combined pharmacological and psychosocial treatment than in those receiving medications only (BUP: 82.3% vs. 77.5%,  $p = .0004$ ; MMT: 69.1% vs. 57.8%,  $p < .0001$ ). Retention rates were not influenced by psychosocial support in either treatment group (BUP: 56.1% vs. 54%,  $p = .9$ ; MMT: 52.4% vs. 62.2%,  $p = .2$ ).

#### 4. Discussion

In our 2-year experience, we found very good retention in care and very significant improvements in opioid and cocaine use among our opiate-dependent patients treated with either methadone or BUP substitution treatments. We

Table 2  
Effect of BUP and methadone on retention rates, urinalyses, and GAF scores

Variables	"All treatments"		<i>p</i>
	BUP	Methadone	
Treatment retention (%)	56	57.5	.5
Negative urinalyses (%)			
Morphine	80	63	<.0001
Cocaine	75	77.5	.1
GAF score			
Basal	66	59	.97
Final (in patients who completed treatment, $n = 26$ )	71	64	

found no differences in retention or in cocaine use between the two treatments. These findings are in agreement with previous studies demonstrating no difference in retention measures between MMT and BUP (Farre, Mas, Torrens, Moreno, & Carni, 2002; Gerra et al., 2004; West, O'Neal, & Graham, 2000), but differing from some other older articles reporting better retention rates with MMT than with BUP (Fischer et al., 1999; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Mattick, 2003; Mattick et al., 2003). This is possibly due to the relatively higher doses of methadone than of BUP that were used in those trials. Moreover, in our experience, higher doses of MMT (>50 mg/day) gave better retention rates than lower doses of MMT, whereas BUP showed to be equally effective on retention at both higher (>8 mg/day) and lower ( $\leq$ 8 mg/day) doses.

Significantly higher percentages of negative morphine urinalyses in the BUP group suggest that opiate abuse may be better controlled by BUP treatment than by MMT. Gerra et al. (2004) and Giacomuzzi et al. (2003) have also reported significantly less consumption of opioids in BUP-maintained patients. However, cocaine abuse did not differ between the two substitution treatments.

BUP patients might have been positively influenced by higher motivation and stronger intention to abstain from illicit drug abuse, but we have no proof of this.

Moreover, the different pharmacological mechanism of action of BUP, in comparison with methadone, seems to favor abstinence from opiate abuse, which allows concomitant heroin consumption. All these factors might have influenced the significantly lower opiate abuse during BUP therapy.

The greatest level of effectiveness was seen with combined pharmacological and psychosocial treatments in both MMT and BUP groups, perhaps because these patients decided to face every aspect of their dependence, including the psychosocial-educational aspect.

Although it is important to note that this study was performed in the real world, this clinical study that did not use random assignment; the results appear to confirm that BUP is as effective as MMT in the treatment of heroin dependence and may even offer better opiate abuse control. It is possible that better substance abuse control from substitution therapy allows longer and more effective treatments, prolonging benefits and reducing relapse danger after pharmacological therapy. This hypothesis is worth testing in specifically designed follow-up studies.

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