

## Buprenorphine Treatment: A Three-Year Prospective Study in Opioid-Addicted Patients of a Public Out-Patient Addiction Center in Milan

Edoardo Cozzolino, MD, Livia Guglielmino, MD, Pierluigi Vigezzi, MD, Paolo Marzorati, MD, Rosella Silenzio, MD, Margherita De Chiara, MD, Filomena Corrado, MD, Laura Cocchi, MD

Public Out-patient Addiction Unit, Local Health Administration, Milan, Italy

*The data shown here were collected with an open label prospective design from March 2001 to February 2004 while conducting routine recruitment and therapy of heroin-addicted patients. All of the data collected demonstrate the safety and efficacy of buprenorphine therapy and different characteristics observed in buprenorphine patients versus methadone patients. (Am J Addict 2006;15:246–251)*

The Dependence Departments of the Italian National Health Service provide specialized management of addicts through Out Patient Addiction Centers (Ser. T.). In each center, a multidisciplinary team of selected operators (physicians specializing in internal medicine, infectious diseases, and/or psychiatry; psychologists; social assistants; educators; and professional nurses) provide a double, contemporary approach, providing a medical treatment and psychosocial service. Throughout the country, there are 550 Out-Patient Addiction Centers (Ser. T.), which provide services to about 160,000 patients; 40% of these are in treatment with pharmacological substitutive therapy.

The main outcome of substitutive treatment is to decrease and eliminate heroin use to stabilize individuals with a better quality of life. Until a few years ago, the more widely utilized therapy for opioid addiction treatment in Italy—and all over the world—was methadone.<sup>1</sup>

For about four years in Milan, buprenorphine, a new substitutive drug for opioid dependence, has been utilized in clinical practice from Out-Patient Addiction Centers (National Health Service). Now, many studies report the efficacy of buprenorphine in maintenance treatment,<sup>2–8</sup>

and some authors highlight its similar or better efficacy compared with low or similar methadone dosages.<sup>4,7,9–14</sup>

This new synthetic oral opioid, available in 2 or 8 mg tablets for sublingual administration, has a partial agonist activity on  $\mu$  receptors that determines a lower abuse potential and dependence; its ceiling level on agonist activity limits adverse reactions at high dosages and protects against the danger of overdose. (Note, though, that its antagonist activity on  $\kappa$  receptors makes it more difficult to verify a respiratory depression.)

Its good bioavailability after sublingual absorption allows buprenorphine to reach maximum plasma levels after about two hours, and its long-lasting, substitutive effects remain for more than a day (about 48 or 72 hours, doubling or tripling the dose).

Considering these favorable characteristics, our service gave new patients the opportunity to have buprenorphine therapy according to inclusion-exclusion criteria.<sup>2</sup>

This new substitutive therapy was also provided to patients that were already in methadone maintenance treatment (MMT) and were asking to change drugs. Of course, our methadone therapies showed adequate dosage, including very high dosages for patient that manifested rapid methadone metabolism.

However, the opportunity to shift to buprenorphine was considered only when the methadone dosage was equal or inferior (below 25 mg/day) and if the patient would not agree to increase the methadone dosage to a therapeutically satisfactory dosage or showed no satisfactory experience with MMT. In these last cases, 25 mg/day MMT was simply a technical border dosage, over which it was more difficult for the patient to shift to buprenorphine for pharmacological Buprenorphine (BPF) action. Of course, the center also shifted to buprenorphine patients in MMT who had a much higher dosage (60–80 mg/day), but first the MMT dosage was rapidly

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Address correspondence to Dr. Marzorati, Public Out-patient Addiction Unit (SER.T), 25 via Boifava, ASL Città Di Milano, Italy. E-mail: pmarzorati@asl.milano.it.

decreased to 25 mg/day, a more favorable dosage to shift to BPF.

## MATERIALS AND METHODS

### Patients

Heroin-addict patients asking for the new pharmacological substitutive treatment were evaluated for the following concerns:

- the substance from which they were withdrawing—directly from free heroin or an MMT already in process
- their opioid dependence and tolerance level
- general clinical situation (with particular attention to renal and hepatic functionality): HIV-positive patients were routinely allowed to undergo BPF treatment<sup>15</sup>
- the established absence of pregnancy for female patients.

It is interesting to note that, increasing the authors' clinical experience, an ever-increasing number of patients were spontaneously asking for BPF treatment. About half of new patients since the summer of 2002 expressed a preference for treatment with BPF.

### Population

One hundred and thirty one consecutively recruited patients (107 males) underwent 150 treatments overall. The average age was  $34.0 \pm 6$  years, and the average length of dependence was  $12 \pm 6.4$  years. The highest level of education achieved was 10% primary school, 61% secondary school, 23.7% high school, and 5.3% university. Seventy-three patients were employed, seventeen were employed at a low level, 33 were unemployed, two were housewives, two were retired, and four were students.

In sorting by Hollingshead activity category classification,<sup>16</sup> one was second class, three were third class, thirty were fourth class, twenty-two were fifth class, six were sixth class, 63 were seventh class, and six were unidentified. Looking at Global Assessment Functionality (GAF), 64/100 (range 45–90) showed a medium beginning value.<sup>17</sup>

For HIV, 24 were positive patients, eighty were negative, and 27 were not identified. For HBV, 36 were negative patients, 46 were positive, eighteen were vaccinated, and 31 were unknown. For HCV, 67 were positive patients, 34 were negative, and thirty were unknown. Fifty-three patients had normal transaminases, 36 showed an increase, and 42 were unknown.

### Subgroups

#### *Dosage Subgroups*

Once started on BPF treatment, the dosage necessary to eliminate withdrawal signs and symptoms and stop

craving was judged as the optimal one to satisfy a clinical stabilized condition. If necessary, a medical doctor could utilize the Wang scale for withdrawal or VAS scale for craving detection.

Because 8 mg/day resulted in the median maximal dosage value, the authors obtained two numerically comparable groups, roughly 8 mg/day, according to main literature data.<sup>2–5</sup>

#### *Combined or not Subgroups*

Indications for psychosocial treatment were comprised of the following:

- Psychosocial treatment possibility relative to personal needs (social, psychological, educational, etc.) was offered to each patient during their first visit and talk.
- Psychosocial treatment was offered again later—during therapy already in course, if it was not satisfying in consideration of multiple positive urinary analyses, a clinically relevant negative change of patient behavior, and so on.
- In addition, all the patients with legal problems routinely underwent combined treatment.

#### *Opiate Molecule before BPF Subgroups*

The authors have determined two subgroups considering the opiate molecule before starting BPF treatment: a subgroup coming from free heroin (sixty patients), and a second one coming from MMT (68 patients). Various kinds of patients were part of this group:

1. Patients in MMT with an inadequate methadone dosage (often higher than 25 mg/day) but willing to have an adequate and therapeutical BPF therapy.
2. Patients with an already adequate MMT therapy and believing that they are being helped in ending substitutive treatment with BPF during the phase of reduction of the therapy.

Of course, in both kinds of patients, the MMT dosage was quite a bit higher than 25 mg/day, but patients were observed to have no problem in switching from methadone to BPF. The authors first arrived at 25 mg/day methadone dosage and then switched to BPF.

## METHODS

Addiction diagnosis was established according to DSM IV criteria,<sup>17</sup> considering accurate anamnestic evaluation, clinical objective evaluation, and positive urinary analysis for opiate metabolites. Each patient had to meet the following inclusion and exclusion criteria.

## Inclusion Criteria

- active opioid addiction following DSM IV criteria
- patients unwilling to reach an adequate methadone dosage but willing to have an adequate and satisfactory therapeutical dosage with BPF
- patients in MMT < 26 mg/day believing themselves to be helped in ending substitutive/treatment with BPF.

## Exclusion Criteria

- MMT  $\geq$  25 mg/day
- DSM IV I axis diagnosis<sup>17</sup>
- hepatic/renal failure in last six months
- ethilic or benzodiazepines addiction
- under eighteen years old
- pregnancy

Before beginning treatment, patients had to give written informed consent.

## Medical Treatment

At the beginning of our experience, the authors started with 2 mg, increasing every 2–3 hours according to withdrawal symptoms of the patient until the clinical stabilization of the patient.

In this way, the patient remained at the Center under physician observation throughout the morning. The patient could return in the afternoon if he still was not well stabilized in his withdrawal symptoms. The following day, the patient condition was evaluated again, starting from the dosage reached the day before.

The treatment lasted from 1–1006 days. Most of the BPF treatments were long-term ones.

The substitutive opioid drugs were administered daily at our Addiction Center, taken home for the weekends, or taken home for six days if the patient abuse characteristics allowed it, according to regional guidelines. However, administration of the drugs took place at the Center at least once a week for all patients.

## Urinary Analyses

The author performed urinary analyses for opioid and cocaine metabolites once a week. Urine specimens were collected under control, sometimes with visual nurse control and always with temperature detection with thermometer (QUIKSITE 900 HB Instrument Company, USA). Specimens showing lower than 32°C or higher than 38°C temperature were excluded, as were those out of the range that showed a temperature difference  $> 1^\circ\text{C}$  with the oral one.

Collected specimens were put in the refrigerator at 3°C and then sent to the laboratories. Urine samples were analyzed by EIA assays, and, for particular cases with juridical problems, gas chromatographic assays were also performed in specific laboratories of other departments of ASL and the university.

Every positive result for each patient was followed by a visit with their own medical doctor with the following aims:

- modify BPF daily dosage, or, if a maximal dosage (32 mg) was already reached, switch to MMT.
- propose a combined treatment, if not already in place.
- motivate via a long talk, reinforcing the real motivation behind the chosen treatment, whether it was a therapeutical or simply a harm reduction one.

Note, though, that BPF substitutive treatment was not stopped.

## Global Assessment Functionality (GAF)

To globally evaluate the clinical, social and psychological performance of each patient, at the beginning and at the end of treatment, GAF (according to DSM IV) was performed. HIV patients (18% of our population) were accepted, even those undergoing to HAART.

## Statistics

Data underwent the following test: t-Student's, X-square, and odds-ratios, all performed in Microsoft Windows Office and Excel 2000.

## Endings

To evaluate the clinical efficacy of treatments, the following patient results were established:

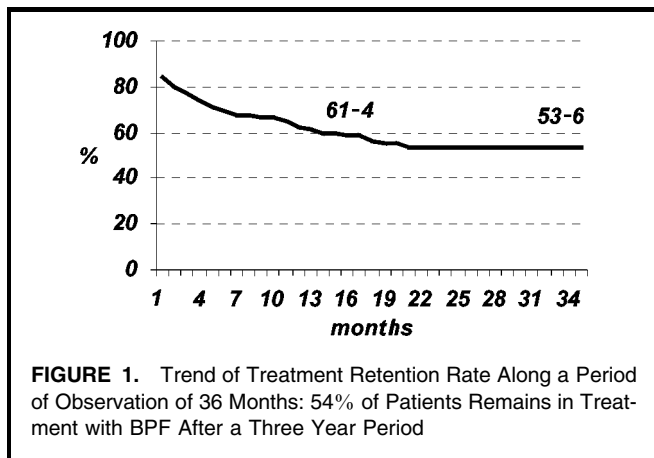
- still in treatment
- drop-out (fifteen days lacking therapy)
- shift to MMT
- regularly completed therapy
- jail
- transferred to other services or residential structures with rehabilitative-educational treatments

## RESULTS

### Patients

GAF initial mean value was  $64 \pm 10$  SD, while the mean final GAF value of patients completing treatment was 71 ( $t = 2.1$ ;  $p = 0.0004$ ).

Considering only the first treatment (131 patients) after 36 months of treatment, sixty patients were still in treatment, 31 dropped out, thirteen shifted to MMT, sixteen completed treatment, eight went to jail, and three were transferred to other services (see Fig. 1). Thus, a retention rate of 53.6% after two years was observed (see Fig. 2), while in all the treatments the percentage increased to 56.4% ( $\chi^2$ :  $p = 0.2$  NS).



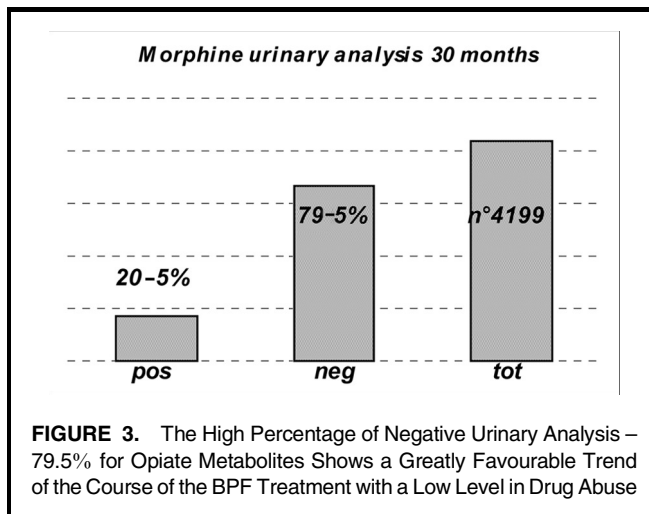
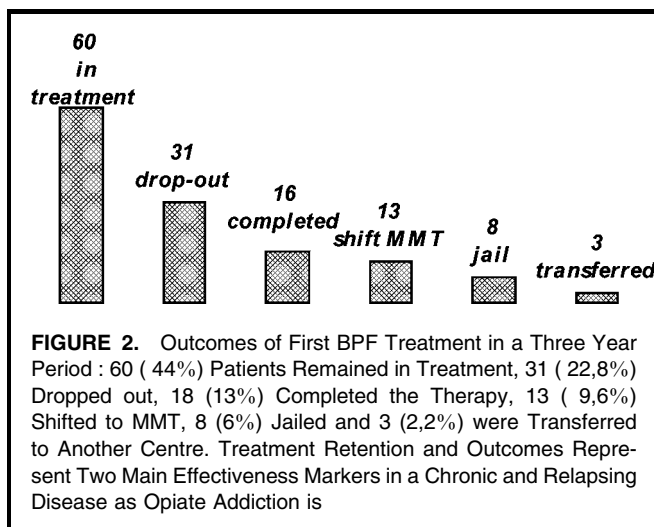
**Treatments**

Ten ± 6 (SD) mg/day was the mean max dosage (range: 2–30 mg/day).

The mean length of treatment was 305 days (range: 1–1006 days); twenty (23, considering all treatments) were short-term treatments, 25 (29) were medium-term, and 55 (57) were long-term treatments. Fifty-two percent were administered the drug daily at the center, 46% took it home once a week for six days, and 2% were administered only two or three times a week at the center, receiving a double or triple dosage each time.

**Sub-populations Outcomes**

As far as outcomes and treatment retention rates were concerned, no significant difference resulted whether treatments were integrated with psychosocial supports (53 patients;  $\chi^2: p = 0.69$  NS,  $\chi^2: p = 0.6$  NS, OR: 1.2) or in different groups concerning the dosage (>8 mg/day, 70 patients; ≤8 mg/day, 61 patients;  $\chi^2: p = 0.47$  NS,  $\chi^2: p = 0.6$  NS, OR: 0.8). A significant difference resulted only as far as the opiate molecule—methadone



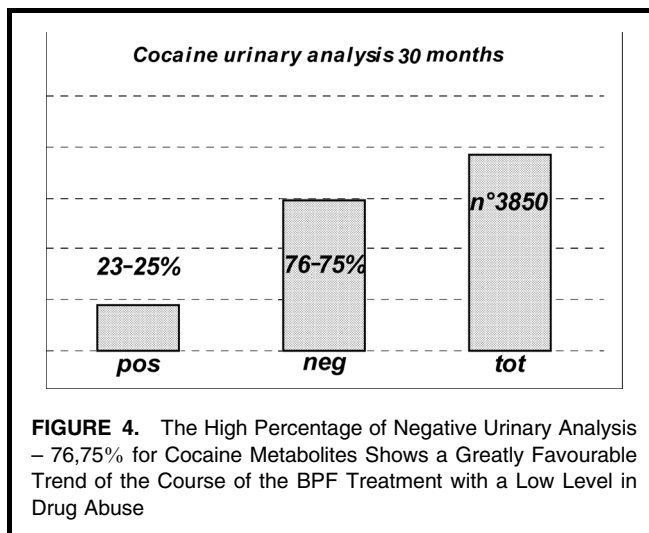
(68 patients) or free heroin (sixty patients)—before substitutive buprenorphine therapy ( $\chi^2: p = 0.034$ ,  $\chi^2: p = .0017$ , OR: 3.5). In particular, the patients coming from MMT dropped out less than patients coming from free heroin ( $\chi^2: p = 0.0017$ ).

**Urinary Analyses**

Samples showed 79.5% negative results for opiate metabolites and 76.7% for cocaine (see Figs. 3 and 4).

Patients in integrated therapy groups providing psychosocial support were observed to have a higher percentage both of negative morphine ( $\chi^2: p = 0.0007$ , OR = 1.3) and cocaine urinary analyses ( $\chi^2: p = 0.026$ , OR = 1.2). A significant difference resulted among negative samples for both opiate metabolites ( $\chi^2: p = 0.0001$ , OR = 1.8) and cocaine metabolites ( $\chi^2: p = 0.0046$ , OR = 1.25) in the two groups coming from heroin or methadone.

As far as maximal dosage, no significant difference was observed for opiate negative urinary samples ( $\chi^2: p = 0.9$



NS, OR = 0.99), while a significant difference resulted for negative cocaine urinary analysis ( $\chi^2$ :  $p < 0.0001$ , OR = 2.15).

## DISCUSSION

The positive results obtained in this clinical practice with buprenorphine were related to several different reasons.

At first, attention was paid to the beginning of therapy: receiving the patient during the first induction day in the physician's study, creating a comfortable setting, and monitoring in this way each psychophysical sign and symptom that could be properly treated.

The authors realized a lower number of drop-outs by increasing the dosage until stabilization—without previously established maximal dosage limits at the first day of therapy—than with a maximal daily dosage in induction phase, as previous clinical guidelines advised. Increasing buprenorphine dosage combined with a psychosocial supportive aid succeeded in solving many difficult moments characterized by relapse danger or directly by relapse in heroin and cocaine abuse.

Spontaneously selected patient populations showed a high educational and occupational level. The main aim of patients was not oriented to a simple harm reduction program but to a therapeutic program to stop substance use and face every psychosocial individual side effect in determining their own dependence condition. In these incident patients, two main observations were made:

1. a higher percentage of psychosocial integrated treatments were also observed in incident patients in methadone therapy (ie, the reality not occurring in prevalent patients when methadone alone was utilized)
2. the greater sensitivity they demonstrated toward their own general medical condition (ie, undergoing serodiagnostic examinations more frequently than before) and toward multiple treatments utilizing a multidisciplinary program.

These new attitudes could be explained by the following considerations: if it is possible to recognize a new trend in all populations of addicted patients—supported by a positive input given by the treatment with buprenorphine—it is reflected by a new attitude of all specialists of our Center in therapeutic setting. This last point concerns a multidisciplinary and greater support, expressed in a particular way at the beginning of substitutive therapy. These characteristics appeared to us as a favorable prognostic factor for the effectiveness of treatment, and the following results in BPF treatment were actually reached:

- satisfying retention rate in treatment
- high percentage of negative urinary analysis for opiate and cocaine metabolites
- high percentage of psychosocial integrated treatments
- high number of serum diagnostic analyses, intended to screen prospective co-morbidities such as infective pathologies

The results of this study show that buprenorphine maintenance treatment was confirmed to be an effective pharmacological option for opioid dependence substitutive therapy.

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