

Symptomatic treatment of opiate withdrawal syndrome by low-dose buprenorphine in an in-patient setting

**Andrea Fuscone ¹, Mariapia Correale ², Mauro Romualdo ²
and Walter Bianchi ²**

Summary

The present study aims to assess the effectiveness of buprenorphine treatment in countering predictable withdrawal from street opiates in 68 opiate-addicts who requested admission to an in-patient opiate detoxification facility. Buprenorphine was administered at flexible doses, on a patient-blind clinical basis. Withdrawal was assessed by scoring a range of symptoms at the start of treatment (T0) and three more times during treatment (T1-T3). The dropout rate was 14.7% and was not predicted by baseline clinical features. The average duration of treatment was 7.5 days. By then, buprenorphine had provided patients with quick-acting, stable protection against withdrawal symptoms and was well tolerated. Additional drugs were successfully resorted to when non-specific symptoms such as anxiety and insomnia were prominent. Buprenorphine proved effective in soothing withdrawal-related symptoms in a subgroup of mildly ill subjects. The short-term dropout in this population did not seem to be related to the severity of baseline withdrawal or to the absence of earlier improvement under buprenorphine.

Key Words: EEG - Heroin - Buprenorphine - Addiction -
Detoxification - Opiate withdrawal - Retention in treatment.

Introduction

Over the years the gravity and pertinence of the issue of drug addiction have risen. Both the APA and the WHO have agreed that addiction is a chronic relapsing disease^(1, 14), so bringing it to a higher level of attention in the public opinion. Given its chronic nature, addiction proceeds through phases of well-being alternatively with relapses of varying duration.

Most addicts, and, to their discredit, some healthcare workers too, generally mistake

a drug-free state for a sign of disease remission. Some addicts who have recently undergone detoxification apply for in-treatment at high-threshold centres, which would deny admission if any agonist-treatment was still ongoing. Other patients taper their methadone with a view to entering antagonist treatment with naltrexone, which requires them to be opiate-free before they can be enrolled.

No matter how strong their motivational drive, some patients fail to overcome withdrawal from their medication if they are left without pharmacological support. Moreover, some situations may require patients to taper quickly, so that special strategies to minimize discomfort are needed: in other words, patients may need an effective buffer against their complex withdrawal pictures.

Any healthcare operator dealing with addiction-related issues should know which symptoms may develop during opiate withdrawal. At the same time, it is quite uncommon to treat an opiate addict who is not also abusing other substances, as polyabuse is the rule in heroin addiction. Predictably, a polyabuser's withdrawal syndrome is of a more complex type, as it is rooted in a combined tolerance to different substances, with a variable grade for each.

Our aim in the present study has been to assess the effectiveness of buprenorphine (BUP), at low doses, against opiate withdrawal alone, regardless of what symptoms may be due to abstinence from other substances. Buprenorphine is a partial μ -agonist with a high receptorial affinity^(7,10): in fact, it soon establishes a sound opioid blockade⁽¹²⁾, while no room is left for further agonist input, due to massive receptor binding (ceiling effect)⁽¹³⁾. Thus, the agonist effect tends to reach a plateau quite quickly, and cannot equal that provided by full agonists, either in terms of therapeutic potency or toxicity⁽⁹⁾. Unlike other anti-craving opiate drugs, buprenorphine has a κ -antagonist effect^(7,11), which may be responsible for tolerance-related issues but also for therapeutic peculiarities⁽⁵⁾. Buprenorphine has proved effective both in medically supervised withdrawal from heroin⁽⁸⁾, and in treatment programmes for opiate-addicted individuals⁽⁶⁾.

Methods

Sixty-eight opiate-addicted patients, were enrolled after they have been referred to a Government-financed Clinic for inpatient opiate detoxification by their GPs or the local Addiction Treatment Unit. Their mean age was 32 (range 21-49) and 9.6%, (63 patients) were male.

All these patients had been addicted to opiates for over six years, and were essentially injectors, inhalation being an atypical mode of administration for all of them. 13% had been using cocaine irregularly, mostly by a snorting mode. All were habitual smokers and had been taking benzodiazepine at much higher doses than prescribed. Alcohol use was unremarkable, and was never reported at such a level as to create an expectation of specific withdrawal.

The therapeutic schedule was not fixed, but left flexible, to allow adaptation to each patient's needs. Treatment was started as soon as withdrawal symptoms emerged, by

administering 0.2 mg intravenous buprenorphine, followed by decreasing doses every 8-12 hrs.

Buprenorphine was administered intravenously into vessels leading to the upper caval system, in order to avoid the first-pass metabolism by the liver, which is responsible for an 80% conversion to the inactive 6-glycuronide metabolite ⁽²⁻⁴⁾.

Patients were blind to how much buprenorphine was being administered, since the amount of liquid vehicle did not vary with the buprenorphine dose, but was kept at around 100 ml of saline.

Withdrawal symptoms were assessed by a self-evaluation scoring system ranging from zero to five (0-5), zero corresponding to no symptom, and five to a subjective level of high intensity. Rated symptoms included sweating, tremor, muscular pain/spasms, running nose and nausea/vomiting. The self-evaluation scoring form was administered to patients at the start of the treatment schedule (T0-score), on the 2nd and 4th days of buprenorphine treatment (T1- and T2-score, respectively) and before discharge (T3-score) (Table 1).

All of our patients received benzodiazepine treatment to treat insomnia and anxiety: fast-acting, high potency benzodiazepines were chosen as hypnotics, whereas low potency, long-acting compounds were resorted to for an anxiolytic effect.

Results

Of the 68 patients admitted, 10 (14.7%) asked to be discharged on their own responsibility. Two of these had never started buprenorphine at all, while 8 others discontinued it, mostly on the 2nd or 3rd scoring day on the schedule.

Drop-outs did not differ from completers as regards age, sex or T0-score (Table 2- Figure 2).

Significant improvement was recorded between T0- and T1-score, both for drop-outs and treatment completers, while the two groups scored similarly at time 1 (Table 2). Score reductions were below significance into the two groups from T1 to T2, and from T2 to T3 (Figure. 1).

The baseline withdrawal-related conditions, as rated by T0-scores, do not seem to foretell either retention in treatment or treatment effectiveness.

On average, programme completers were hospitalized for 7.5 days (range 4-11) and were given an average cumulative dose of 235.5 ± 14.7 mcg.

No major side-effects ascribable to the medication were observed. One patient experienced vomiting throughout the second day of treatment, and was given standard anti-emetics. Another patient reported a headache, which spontaneously disappeared on the 2nd day, and was thus of uncertain origin.

To sum up, the therapeutic schedule proved safe, and no major side-effects calling for treatment discontinuation were observed.

Table 1. Self-evaluation rating scale for opiate withdrawal symptoms							
Symptom	Score						
	absent ← → intense						
Sweating	0	1	2	3	4	5	
Tremor	0	1	2	3	4	5	
Muscular pain/spasms	0	1	2	3	4	5	
Running nose	0	1	2	3	4	5	
Nausea/Vomit	0	1	2	3	4	5	
	TOTAL						

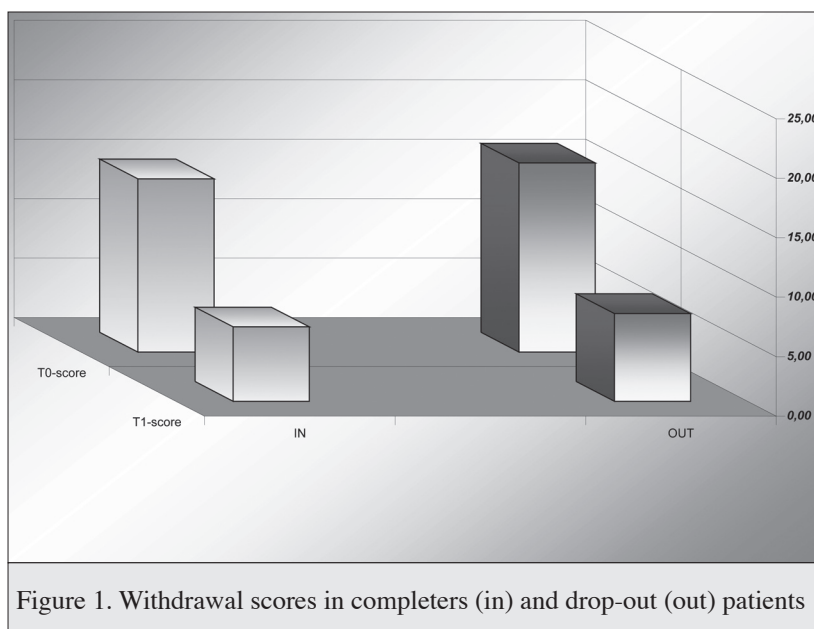


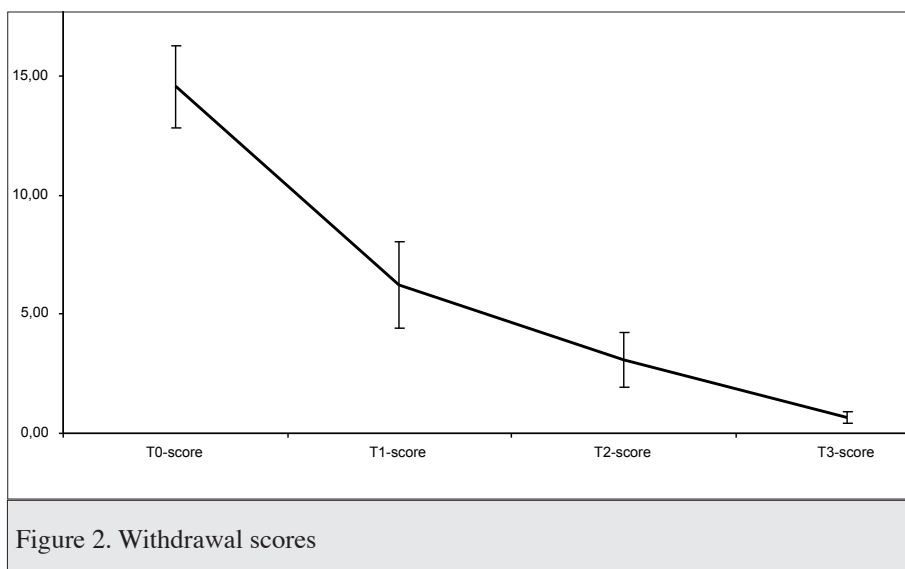
Figure 1. Withdrawal scores in completers (in) and drop-out (out) patients

Discussion

As a premise, it must be noted that buprenorphine detoxification was intentionally practised for a subgroup of opiate addicts, who had absent/very low craving when applying for detoxification, and were highly motivated to undergo it because of their urgent need to discontinue agonist treatment, and/or to be enrolled in drug-free residential programmes.

Variable	Responders (n = 58)	Drop-outs (n = 10)	Significance (p < 0.05)
Sex (male)	93.1 %	90.0 %	ns
Age	31.98 ± 6.01	35.20 ± 7.80	ns
T0 Score	14.57 ± 1.72	15.90 ± 1.91	ns
T1 Score	6.26 ± 1.82 *	7.38 ± 2.54 *	ns

* T0-score vs T1-score: p < 0.001



Compliance was high: 58 out of 68 enrolled patients (85%) completed treatment as scheduled, experiencing a satisfactory resolution of most withdrawal symptoms.

Typical opiate withdrawal symptoms (vomiting, painfulness, sweating, runny nose and tears/weeping) markedly dwindled throughout the treatment period. A 30% reduction in global withdrawal discomfort was reported, which in itself was enough to classify the treatment as beneficial.

Anxiety and insomnia, which were challenged by anxiolytic and hypnotic drugs, must be considered separately: such symptoms are quite common during opiate withdrawal, but are usually a consequence of continued opiate use, too. In other words, they are a feature of opiate abuse regardless of ongoing withdrawal, and are best described as a

harmful result of addiction itself, rather than as an outcome of acquired tolerance.

Despite the apparently strong motivation declared by all patients, 15% of them failed to continue after hospitalization, and dropped out. It remains unclear whether dropping out can be related to a flaw in motivation, or is a result of previously latent craving, evoked by the new perspective that the substance would no longer be available while on treatment. Moreover, personality traits may have played a role in favouring treatment discontinuation because of subjects failing to adapt to the environment of our Clinic. A subject with a borderline personality disorder, for instance, may feel coerced and victimized within that environment, even if admission has been voluntary. Future studies are now needed to evaluate the influence of psychiatric conditions, as assessed at baseline, on treatment retention. On the other hand, programme completers showed they were able to overcome the psychological discomfort raised by the withdrawal they had to face, and while in hospital they found greater support than that provided by pharmacological treatment alone. There is no doubt that environmental factors do weigh on the quality and intensity of opiate withdrawal as a subjective experience.

It is striking that 85% of patients completed their treatment schedule in spite of the persistence of some unpleasant symptoms, such as anxiety and insomnia, which made it necessary to maintain specific pharmacological treatment after discharge. However, without a placebo control, the contribution of psychological factors rather than pharmacological agents to success in overcoming opiate withdrawal cannot be clarified. It should be borne in mind that buprenorphine was administered at low dosages, and that no significant differences between T0- and T1-scores emerged in comparing completers and dropouts, so no clear treatment effect can be identified. As many as 85% of treatment starters completed the programme, so various different factors could have contributed to this result. The combination of a minor pharmacological effect, provided by buprenorphine, and a reassuring environment is likely to ensure that patients achieve a satisfactory outcome, but no clue is available so far to allow the relative weight of either component to be determined.

Conclusions

Parenteral low-dose buprenorphine administered along a short-term decreasing-dose schedule proved effective in the treatment of opiate withdrawal in an in-patient setting, for as many as 85% of the patients admitted. Treatment was considered viable for patients who showed a low level of craving or none at all, and a strong need to discontinue agonist treatment in view of a drug-free residential treatment. Safety was high, since side-effects were never such as to require treatment interruption. Hospitalization may have been a key factor contributing to a positive outcome. Although a minority of patients experienced notable anxiety and/or insomnia, these symptoms were successfully treated by adding on benzodiazepines. With these features, an 85% retention rate was achieved throughout the study. The schedule adopted showed it was suitable for the treatment of opiate withdrawal in a subgroup of patients selected by

the above criteria at study entrance.

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