

## **Buprenorphine: Evidence for effectiveness**

**Matteo Pacini<sup>1,3</sup> & Icro Maremmani<sup>1,2,3</sup>**

### *Summary*

In all cases, opiate addiction is best treated by the use of opiate agonist agents. A maintenance regimen based on an opiate agonist leads to a gradual dwindling of the subjective effects due to street opiates, thanks to the blockade achieved by these agents on the receptors that are reached by heroin.

Buprenorphine looms as the most useful of the latest generation of agonist agents for the treatment of opioid use disorders. It is equivalent to other opiates as regards retention rates and control of street opiate use. Apart from maintenance programmes for opiate addiction, buprenorphine has proved effective in short-term programmes for opiate detoxification.

Buprenorphine treatment should be regarded as first-line in subjects with low levels of craving and low severity of addictive behaviours, as long as: 1) it is documented that low methadone doses produced complete and stable remission; or 2) after a period of ongoing abstinence in drug-free conditions, the patient has recently relapsed into use of street opiates, so that their tolerance threshold is presumably still low. For subjects, whose tolerance is unknown, or when anamnestic or objective elements suggest there may be a high tolerance threshold, or else in cases comprising a recent history of unresponsiveness to low dose methadone treatments (below 60 mg), methadone should be the first choice for the therapy of opiate addiction. Subjects who have proved to be refractory to buprenorphine, even at higher dosages, can reasonably be directed to a methadone treatment programme.

Key words: Buprenorphine effectiveness - Opiate abuse - Predictors of outcome - Cocaine use - As antidepressant - Opiate withdrawal

In all cases, opiate addiction is best treated by the use of opiate agonist agents. This therapy calls for the administration of constant doses of an opiate agonist at constant time intervals, over a period of months or years. Historically, methadone and LAAM are the main agents that have achieved success in treating opiate addiction in therapeutical settings. A maintenance regimens based on an opiate agonist leads to gradual dwindling

of the subjective effects due to street opiates, thanks to the blockade achieved by these agents on the receptors affected by heroin. The vicious circle between intoxication and withdrawal which is bound to develop in heroin addicts, and which marks the revolving-door stage of their addictive careers, is itself showed and then broken. Agonist-maintained subjects display a satisfactory retention rate, have their neuroendocrine functions restored, from a condition of imbalance due to chronic opiate intoxication, and are kept off addictive behaviours (crime, spreading of HIV, pregnancy accidents). On this basis, former addicts are able to benefit most from concurrent psychosocial support facilities. On the whole, it can be stated that agonist maintenance effectively forestalls criminal behaviours, the abuse of street opiates and the risk of transmitting infective diseases, while guaranteeing quite a high retention rate.

Buprenorphine looms as the most useful of the latest generation of agonist agents for the treatment of opioid use disorders. It displays a unique pharmacological profile, which makes it suitable for various treatment strategies: in fact, it possesses a high binding-affinity for  $\mu$  and  $\kappa$  receptors, by acting as a partial agonist for  $\mu$  receptors and as an antagonist for  $\kappa$  receptors. Several studies provide evidence of its effectiveness on heroin abuse/dependence. On practical grounds, the usefulness of buprenorphine's properties can be described from a variety of viewpoints. It is equivalent to other opiates as regards retention rates and the limitation of street opiate use. Administration can take place daily or three times a week. Tolerability is acceptable. An optimization of buprenorphine's efficacy should be based on the identification of positive and negative predictors, to be used later as selection criteria for patients whose chances of responding positively may differ widely. Apart from maintenance programmes for opiate addiction, buprenorphine has proved effective in short-term programmes for opiate detoxification. Moreover, it has been indicated as probably being effective in cocaine abuse/dependence and as an antidepressant drug for refractory depression.

The present study aims to present a critical review of the buprenorphine-related issues outlined above.

### **Opiate abuse/addiction**

#### ***Effectiveness in opiate abuse***

Within a dose range of 2-32 mg, buprenorphine has proved as effective in controlling opiate use at low methadone doses (20-60 mg), with an equivalence relationship to be read as mirroring the corresponding  $\mu$ -opioidergic activity. Some time ago, its level of effectiveness was established on clinical grounds, by monitoring the level of its anti-withdrawal and anti-craving activity. More recently, the potency of these two agonists has been investigated by brain-imaging techniques, in terms of their respective rates of  $\mu$ -receptor occupation. These accounted for buprenorphine's greater affinity and methadone's higher potency. These two ways of defining dose-adequacy are in agreement: in other words, the effectiveness of buprenorphine at a certain dose is equal to that of methadone because it provides the same level of  $\mu$ -receptor stimulation [9; 30].

After accounting for the percentage of negative urinalysis, 8 mg of buprenorphine

are superior to 20 mg, but equal to 50/60 mg of methadone [11]. In addition, when patients are chosen so that their tolerance threshold is the same (by a pre-treatment evaluation based on a naloxone-challenge) [11], the superiority of buprenorphine may clearly be ascribed to its anticraving activity, rather than its anti-withdrawal effect. Otherwise, subjects treated with either of these two agonists at lower equivalent doses, but who are less tolerant at the beginning, show a poorer response. Moreover, after stabilization has been reached (i.e. within about four weeks) possible relapses into the use of street opiates, which are more likely than with low-dose methadone, cannot be justified on the grounds of persistent withdrawal symptomatology [11].

80 mg of methadone, which cannot be equalled by any buprenorphine dose, are superior to 8 mg of buprenorphine [17] – a dose that corresponds to about 50/60 mg of methadone. Likewise, craving is better controlled by 80 mg of methadone [17]. Even if higher buprenorphine doses were administered, no consistent gain in agonist activity would follow, due to the plateau reached on the dose-effect curve after an eight mg dose-level (known as the “ceiling effect”). One study has reported the equivalence, on clinical grounds, of 8-16 mg of buprenorphine and 50-90 mg of methadone, but it should be noted that the average doses administered are 9 mg and 54 mg, respectively, so that in the last analysis equivalence comes to stand for m-equipotent doses [28].

From the standpoint of ensuring a stable condition of abstinence, data from the literature do not agree in indicating a superiority of buprenorphine to equipotent methadone doses [11; 26]. The efficacy of treatment, when doses are kept stable, does not seem to vary through time, while an increase in doses results in efficacy enhancement [26].

Even if the final outcome is the same, methadone offers quicker progress to adjustment, (first month) [18], whereas the efficacy of buprenorphine builds up gradually. The fact that buprenorphine is characterized by a therapeutic gain which is progressive in the medium-term [28], though not wholly superior at the end of observation, does suggest that buprenorphine allows a satisfactory outcome in the medium-term, despite lower effectiveness in the early stages (as shown by rather high rates of early dropout) [19]. This property is dose-dependent, and probably reflects that combined blocking property (so-called antagonism) which favours the conditions needed for abstinence to begin. Although high methadone doses provide a blocking effect (80-120 mg), heroin reinforcement can usually be elicited at buprenorphine-equivalent doses of 20-60 mg.

Gradual dose-reduction worsens the opiate-use status [26], probably due to craving shooting up, since severe withdrawal symptoms during medically supervised tapering are very unlikely [20]. High buprenorphine doses are linked with a better outcome than lower doses, with a threshold as high as 8 mg for a satisfactory response. Some subjects, however, show a satisfactory outcome with lower doses: in a 16 week follow-up study, differences emerging from the use of high versus low doses during the early weeks tend to fade towards the end of the study [17]. At a 16 week term, 8 mg have the same effect as 1 mg; after 8 weeks 4 mg are no longer superior to 1; at 12 weeks, 16 mg are as effective as 1. This means that, amongst patients who are retained in treatment, there is

a subpopulation that responds to low doses. Other studies have, in fact, reported a good level of efficacy for 2-4 mg or 2-6 mg [13; 25]. In general addict populations, however, buprenorphine efficacy is dose-dependent, both in the whole sample, and in the responding subgroup [16].

### ***Retention in treatment***

Treatment retention, when calculated as the proportion of patients who stay in treatment at a certain term, can be read as an indirect index of effectiveness. This depends on the fact that retaining a patient in treatment makes it possible to achieve stabilization if the period is long enough; that is the main objective, along with the need to maintain the achieved results as long as possible. When doses remain unchanged, treatment duration provides no further benefit in terms of craving reduction, though longer treatments mean a lower risk of relapse when a patient is left drug-free. Retention does allow the resumption of psychosocial adaptation, which is a gradual process requiring stability over quite a long time, and develops alongside the maintenance of acquired abstinence. Buprenorphine has turned out to be an exception to this scheme, due to its combined agonist-antagonist properties at doses equipotent to 20-60 mg of methadone. If heroin use persists during buprenorphine administration, virtuous circle involving negative reinforcement can develop, so further decreasing opiate use through time, in association with expected social rehabilitation. An eight mg threshold seems to be definable for this phenomenon [18], corresponding to the threshold for a consistent receptor blockade. In general addict populations, however, a higher level of agonism than that made available by buprenorphine – as high as that provided by 80 mg of methadone – corresponds to a higher level of efficacy on craving, both in the short and long term. Retention in treatment with 8 mg of buprenorphine is comparable with that of equipotent doses of methadone [18] in the short term (4-6 mos). In only one study [12] a high early retention rate (72%) was documented for relatively low doses (2-6 mg), whereas most findings show agreement in describing the drop-out phenomenon with buprenorphine as coming earlier and as being more likely with low doses. Early retention does not relate to dosage, but a correlation is found with the degree of withdrawal symptoms [27]. We suggest this means that early retention depends on the effectiveness of treatment in suppressing withdrawal discomfort, which is not linked with dose as such, but with the adequacy of dose to the patient's tolerance threshold. In fact, other authors [27] reported a lack of correlation between agonist dose and retention, whatever the agonist, and, conversely, the importance of withdrawal control. High doses of buprenorphine bear a higher likelihood of retention than lower doses, around a threshold of 8 mg [16]. Isolated observations suggest a weaker effect on retention during the first weeks of treatment, along with the inadequacy of buprenorphine in cases with moderate-to-high tolerance levels. On the other hand, when subjects are directed to buprenorphine or methadone according to their level of tolerance, early retention with 8 mg of buprenorphine is even higher than with 60 mg of methadone [11]. A lack of differences in late retention between methadone and buprenorphine has been documented,

as far as equipotent doses are concerned [11]. Higher doses result in a greater likelihood of retention [17]. Recent results from a long-term high-dose maintenance study [5] document a 70% rate of retention at a two-year term, with 1.2% of successful completion of the programme. The absence of a massive early drop-out in this sample may be due to its being composed of heroin-addicts who were spontaneously asking their GP for treatment [27]. This justifies the supposition that they were a special subpopulation characterized by psychosocial adjustment and low severity of disease, that is, the category of patients who would be expected to benefit most from buprenorphine maintenance.

### ***Daily vs. three times a week administration***

When patients are started on buprenorphine, intermittent administration causes withdrawal symptoms to emerge within the 24-hr time windows between administrations. This phenomenon can easily be explained in terms of the inadequacy of the stimulation provided by buprenorphine against high tolerance thresholds, especially when blood levels tend to fall within a 24 hr time frame, as happens before a steady state is reached. A wider gap between maximum and minimum blood levels is recorded when buprenorphine is administered less often; in that case withdrawal symptoms display a consequent intermittent course towards extinction, which is only reached gradually [11]. Likewise, as far as maintenance is concerned, the intermittent administration of as much as 16 mg every second day may be associated with mild withdrawal-like symptoms during “free days”, or may show no difference from the corresponding daily administration schedule [10]. When doses twice as high as this (32 mg/two days) are used, minor withdrawal annoyance was not observed [23].

### ***Safety and tolerability***

It can be stated that buprenorphine is mostly well-tolerated. Reported side effects appear during the induction phase and include sedation/drowsiness/giddiness [14], general discomfort (dizziness), dysphoria, nausea and headache. As long as such effects are tolerable and do not lead to drug discontinuation, they are likely to have dwindled by the time of stabilization. To favour early retention during the induction phase, it is advisable to temporarily stop administration during the next 24 hrs, when signs of opioid overstimulation, such as nausea, headache, sedation and constipation, may appear. No increase of dose is recommended before the above symptoms have disappeared. The number of side effects attributable to buprenorphine from 1st November, 1997 to 1st November, 2000, using FDA data, are 178, versus 170 for methadone and only 40 for LAAM. Considering that, so far, many fewer subjects have been started on buprenorphine, compared with the almost 450,000 on methadone and 10,000 on LAAM, the incidence of side-effects could loom rather large [15]. Buprenorphine overdosing is, however, very unlikely [15]. From 1994 to 1998, the overdose rate among 55,000 French buprenorphine-treated subjects was three times lower than that among 5,360 methadone-treated patients [1].

***Predictors of outcome: towards an optimal targeting***

Apart from the evaluation of tolerance threshold and intensity of craving, the choice between methadone and buprenorphine should be based on the assessment of specific outcome predictors. Cases of negative outcome with buprenorphine treatment tend to be characterized by more severe psychosocial maladjustment at the beginning of programmes [21]. When a maintenance programme with 8 mg of buprenorphine was compared with one employing 60 mg of methadone, predictors of negative outcome at a six-month term can be identified for buprenorphine-treated subjects that are not valid for methadone maintained probands: severe psychosocial maladjustment, high levels of craving for cocaine, and a high degree of psychopathology, especially of a depressive and paranoid kind. Conversely, no prognostic weight of baseline depressive symptomatology is reported for 4 mg-treated subjects. The contrast between the data might be explained by the fact that, when lower agonist doses (4 mg) are used, treatment failure is mostly due to its ineffectiveness on craving or withdrawal symptoms, whereas in higher dose programmes (8 mg), a positive response is likely except with mentally ill or severely maladjusted addicts, who tend to cluster among non-responders. Female gender has been also reported to favourably condition responses to buprenorphine, when 4 mg are compared with 20 or 65 mg of methadone [24]. Authors suggest that the difference is related to the documented higher analgesic sensitivity of women challenged with  $\kappa$ -opioid-agonists [7].

The optimum management of buprenorphine should therefore be based upon the selective enrolment of subjects displaying the following: psychosocial adjustment, absence of major psychiatric illness, especially of a depressive and paranoid quality, and low severity of addiction, as shown by a low tolerance threshold and a low level of craving. Concurrent cocaine use, despite suggestions about the possible effectiveness of buprenorphine in this matter, should represent a reason to direct patients to methadone maintenance. As a result, the selection criteria for buprenorphine treatment are intermediate between those of antagonist treatments, which fit cases of mild disease only, and full-agonist treatments, which fit any gravity of disease, including several cases of dual diagnosis.

***Buprenorphine as short-term treatment for opiate tolerant individuals (detoxification by buprenorphine)***

Buprenorphine is, predictably, as effective in detoxifying heroin addicts [2] as methadone, when  $\mu$ -equivalent doses are used. When compared with clonidine, it has proved to be less effective on tremors and on rising blood pressure, and it takes longer to control withdrawal symptoms as a whole. However, the longer latency for an anti-withdrawal efficacy is counterbalanced, after the first 24-48 hrs, by a more consistent healing pattern, and a greater impact on psychopathological items [4]. An apathetic-asthenic-abulic syndrome, which can develop with clonidine, is not found with buprenorphine administration. When withdrawal is due to the discontinuation of a long-

lasting agonist agent (e.g. methadone), and that agent is not available to be reintroduced and then tapered, buprenorphine should be preferred to any non-opiate chemical, since withdrawal from a long-lasting opiate does not require early buffering (which is needed in the case of rapid morphine-like opiates), but long-term buffering, though results are best if this starts soon after withdrawal. So treatment should begin as soon as withdrawal symptoms appear, but no earlier, in order not to elicit them as full-blown, and dosage should be increased in line with the patient's response.

During detoxification, it is fundamental to achieve discontinuation of street opiate usage, or at least to have possible street opiates made ineffective, so that tolerance is not kept high, and agonist doses can be tapered without any major withdrawal discomfort. This objective, which is granted by hospitalization, is uncertain when addicts undergo detoxification as outpatients. Buprenorphine may prove particularly useful in this context, due to its combined agonist-antagonist properties, at least at doses above 8 mg. It has been documented that 2 mg are less effective than 30 mg of methadone at blocking the effects of heroin [2]. It may therefore be suggested that a significant difference between receptor blockade with buprenorphine or with methadone, at equipotent doses, only emerges beyond an 8 mg dose threshold of buprenorphine. As regards frequency of administration, buprenorphine should not be administered less often than once a day in a detoxification regimen [6].

### ***Buprenorphine and cocaine use***

Buprenorphine's rate of effectiveness is negatively affected by concomitant cocaine use: when buprenorphine, at a dose of 8 mg, was tested, treatment retention for a general population of heroin addicts, where the frequency of cocaine use was as high as 66%, was lower than in a group of subjects selected to ensure the absence of concurrent cocaine use [18] (78% by 12 wks vs. 50% by 17 wks). While opiate usage tends to dwindle as buprenorphine doses increase, cocaine usage shows no such a trend [27]. The relationship between cocaine use and buprenorphine dose is not constant, but varies according to buprenorphine dose. 2 mg of buprenorphine enhances the pleasurable effects of cocaine, along with the faster heart beat that follows cocaine intake [22]. Doses of 4-8 mg do not block or enhance the same effects, and they leave cocaine highly distinguishable [29], as it is in natural conditions. For addicts maintained on 8 mg of buprenorphine, a higher baseline craving for cocaine is predictive of a drop-out outcome, whereas no increase in cocaine-related likelihood of drop-out is displayed by subjects treated with equipotent doses of methadone[19]. Recently, disulfiram has proved to be rather effective when targeted at cocaine-abusing heroin addicts as an add-on therapy to successful buprenorphine maintenance [8]. As no evidence of a toxic interaction between buprenorphine and cocaine has been documented so far, the safe use of buprenorphine for the treatment of heroin addiction can be viewed as feasible, even when cocaine use is concurrent. On the other hand, no data from the literature suggest there may be a specific effect of buprenorphine on cocaine use.

***Antidepressant properties of buprenorphine***

In heroin addicts, depressive symptoms may develop either as a result of opiate agonist undermedication, or a residual after detoxification, for individuals who are kept abstinent in a drug-free condition or on antagonist maintenance. Besides, depression may also appear during the maintenance phase of an opiate agonist treatment programme. In that case, it has not yet been assessed whether buprenorphine provides any specific benefits compared with those given by equipotent methadone dosages. However, when methadone doses are tapered down to a dose-range low enough to allow transition to equipotent buprenorphine treatment, this leads to the emergence of a depressive symptomatology due to current undermedication, besides which there is the risk of relapse into opiate addiction. Even when full-blown withdrawal symptoms are not elicited, a lowering of opioid stimulation matches with emerging symptoms of psychasthenia, which display a chronic course (delayed withdrawal). Kosten [12] reported the usefulness of buprenorphine in depressed patients in whom depression had developed along the tapering phase of a short-term agonist detoxification (from an average peak of 55 mg/die, down to 25 mg/die, with later transition, after a two-week stabilization interval, to buprenorphine, 3.2 mg/day on average). The therapeutic gain was worthwhile and came early (within the first week), but no evidence is available yet to justify the application of these results to the issue of depression in heroin addicts, let alone to depressive syndromes in the general populations, since this particular sample consisted of previously agonist-stabilized subjects who were later likely to experience a condition of undermedication.

While depression was assessed before subjects were started on buprenorphine, that is after preliminary methadone tapering, no information was gathered on the occurrence rate of depressive symptoms at study entrance, that is, during previous higher dose methadone treatment. Moreover, successful treatment with 55 mg/day average methadone dosages characterizes a low-craving subpopulation with moderate to low withdrawal thresholds, since standard methadone dosages capable both of controlling withdrawal phenomena and the craving for opiates have been reported to stand much higher, within a range of 80 to 120 mg/day. It should be also noted that the inadequacy of buprenorphine in buffering depressive symptoms as they emerge may not affect retention in treatment, at least as long as the soothing of early withdrawal symptoms – the feature that addicts are most concerned about – is guaranteed. Elsewhere, it has been reported that drop-out rates from buprenorphine treatments tend to turn higher for more depressed probands [19], while depressed heroin addicts fail to show greater benefits from buprenorphine treatment than from methadone treatment [21].

Ten non-addicted depressed patients, diagnosed as affected by Double Depression (Major Depressive Episode occurring against a background of dysthymia), mostly with atypical features, who had proved to be refractory to standard antidepressant agents, were quite responsive to buprenorphine, with a therapeutic gain displayed most strongly during the first week of treatment [3], in line with what Kosten reported for depressed heroin addicts [12]. It must, however, be noted that substance use disorders were present in this small sample, as well as comorbid anxiety disorders.

### **Buprenorphine for the treatment of opiate withdrawal**

When opiate withdrawal is to be treated in subjects whose tolerance threshold has not been ascertained, two practical rules should be followed: 1) using an agonist agent, start with low doses, so as to avoid overdosing in opiate-sensitive individuals; 2) choose an agent with such a dynamic profile as to be effective, by dose variation, within as wide a range of stimulating levels as possible, in order to ensure a feasibly high tolerance condition with adequate buffering. Anamnestic information about quantities of substance consumed, and time since latest intake, might be useful in estimating the tolerance threshold, so allowing the selection of subjects who, due to a moderate-to-low tolerance threshold, are likely to respond to low methadone doses, and, therefore, to equipotent buprenorphine treatment. Even so, considering methadone's wide range of agonist potency, it should be the first choice in the treatment of withdrawal states, unless these are due to the withdrawal of buprenorphine. Moreover, though buprenorphine's partial agonism precludes the risk of overdosing, when high dose buprenorphine is found to be insufficient to control high threshold withdrawal, the successive administration of a full agonist is likely to be awkward: due to the high binding affinity of buprenorphine to  $\mu$ -receptors, and its long half-life, buprenorphine displacement requires high doses of lower affinity full agonists, with a delayed risk of overdose as the buprenorphine level is reduced. Lastly, when buprenorphine is administered to highly tolerant addicts displaying initial withdrawal symptoms, with heroin levels still high enough to delay full-blown withdrawal, this latter may be precipitated due to displacement of heroin from  $\mu$ -receptors by stickier buprenorphine.

### **The role of buprenorphine in the treatment of opiate use disorders**

Buprenorphine treatment should be regarded as first-line in subjects with low levels of craving and low severity of addictive behaviors, as long as 1) it is documented that low methadone doses produced complete and stable remission; or 2) after a period of ongoing abstinence in drug-free conditions, the patient has recently relapsed into the use of street-opiates, so that their tolerance threshold is presumably still low. Moreover, the use of buprenorphine is indicated in the early phase of addiction, when tolerance is still low and craving levels have not yet peaked, so as to prevent craving from shooting up and the metabolic phase of addiction from being entered. During the "honeymoon" phase, as long as the patient is compliant, the antagonist property of buprenorphine may prove useful in moving them off heroin, in addition to the effect of its main anticraving action.

For subjects whose tolerance is unknown, or when anamnestic or objective elements point to a high tolerance threshold, or those with a recent history of unresponsiveness to low dose methadone treatments (below 60 mg), methadone should be the first choice for the therapy of opiate addiction. Subjects who have proven refractory to buprenorphine, even at higher dosages, can reasonably be directed to methadone treatment programmes. Buprenorphine, therefore, represents a possible

first-line agent instead of methadone, for subjects who display clinical features that make it likely that they will respond to low methadone doses (below 60 mg). This category of subjects, who can be enrolled in buprenorphine treatment programmes, may represent a self-medicating subpopulation of heroin addicts, who need low opiate doses and therefore develop low tolerance. Whether buprenorphine is preferable to methadone because of specific psychotropic properties is still a matter for research.

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*Received December, 10, 2001 - Accepted February, 1, 2002*