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Effectiveness of buprenorphine in double diagnosed patients. Buprenorphine as psychothropic drug

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Summary

Opiate drugs were first proposed for the treatment of dysphoric syndromes, depression and psychoses many years ago. Even so, the usefulness of these compounds in psychiatry is supported by only a small corpus of data. The reasons given for the restrictions placed on opiate use are based on prejudice rather than scientific evidence. Buprenorphine, with its unique pharmacological profile, has proved to possess antidepressant, anti-dysphoric and antipsychotic properties in small groups of psychiatric patients. Moreover, it may turn out to be the opiate of choice in subjects affected by lower severity addiction coupled with dysthymic disorders, anxiety disorders and personality disorders. The best dosages appear to be those that ensure a combination of k-antagonism with high levels of μ-mediated stimulation.

Key Words: Buprenorphine - Treatment of mental disorders

Introduction: opiates and mental disorders

Since the Central Nervous System features opioid-related pathways with their own receptors and their own endogenous metabolic activity, every opiate drug, pure antagonists included, can be expected to possess psychotropic properties. Apart from this, therapeutic properties depend on how each drug interacts with the endogenous opioid system and other opioid-sensitive systems, whether through a fast-acting modality or a slow-acting one: the former corresponds to a major addictive risk and a destabilizing

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effect on endogenous functions, the latter to a potential therapeutic action and a neutral effect on the baseline endogenous metabolism. These categories do not relate to the molecular structure as such, but to its kinetics, so that the same molecule may act as a healing medication or as a drug that is toxic and liable to abuse, depending on how it is prepared (e.g. for quick absorption or by adopting a retard formulation) and how it is administered (e.g. intravenously or orally).

Opium was judged to be useful in treating states of dysphoria [5] and agitated depression as defined by Kraepelin [24], and approval of such observations can be found in textbooks of psychiatry until the late fifties [40]. More recently, other classes of drugs have been studied and assessed as useful in treating affective disorders and psychoses, while opiates have been overlooked, except for their use as anticraving agents in disorders induced by drugs belonging to the same class. This attitude is partly due to misunderstandings about the addictive risks associated with opiate drugs and about how to prevent prescription drug abuse.

As a result, little evidence is currently available to support the use of opiates in mental disorders [8-10, 26, 62], and most of it derives indirectly from populations of opiate addicts. Higher dosages of methadone are resorted to when symptoms of psychoticism, dysthymia, paranoia and somatic discomfort are a prominent feature or are particularly severe. Other psychopathological dimensions, such as anxiety, phobia, interpersonal sensitivity and obsessive-compulsiveness, seem to depend less on the amount of methadone needed to achieve stabilization [32]. Methadone dosage is higher in dual diagnosis patients, in polyabusers and in aggressive patients who display features of violence, anger, irritability and destructive behaviour [36].

The same conditions that are related to higher stabilization dosages in a methadone maintenance treatment programme [31] are predictors of dropout from a naltrexone maintenance regimen [34]. The administration of methadone to a group of dual diagnosis psychotic heroin addicts proved to induce remission both of addictive behaviours and psychotic symptoms [63].

Lastly, we may mention that an 8-year follow-up study of methadone-maintained subjects with a high prevalence of dual diagnosis showed that stabilization is not merely equally likely, but is even more likely for dual diagnosis subjects, as long as higher methadone dosages are attainable and stabilization is pursued as a longer term result. Thus, agonist-maintenance seems to favour a virtuous circle between therapy effectiveness and compliance, which seems to work best in subjects who are most severely impaired, as a result of their dual diagnosis condition [31, 35].

The restriction of medical opiate drug use to addiction and painful syndromes made them "unadoptable orphans", to quote Callaway's verdict on buprenorphine [4], when it comes to selecting primary psychotropic drugs for the treatment of other mental disorders. The reasons for this restriction are attributable to prejudice, because they have no scientific foundation. Before the opiate addiction epidemic, opiates could be prescribed in cases of persistent opiate-related dysfunction after the gradual withdrawal of opiate replacements (cf. National Conference on Opium, Geneva, Switzerland, 1924). It was

then permissible to restore or maintain somatic dependence on a drug, as long as that condition was judged to be preferable to an opiate-free condition in terms of rehabilitation and psychopathological adjustment. Therapeutic dependence is a feature common to several drugs, including psychotropic (benzodiazepines) and non-psychotropic ones (beta-blockers, thyroid hormone, insulin, cortisones), which can be lawfully prescribed. On the other hand, it is not prohibited to prescribe benzodiazepines to mentally ill people in the long-term, despite the fact that they induce somatic dependence, even if they are certainly liable to abuse, and even if benzodiazepine maintenance is not indicated, and is often counterproductive, in any mental disorder, with only a few exceptions. The view that mental disorders, such as affective ones, are not so severe as to call for maintenance strategies when a relapse-prevention approach is adopted, is open to criticism. Moreover, by contrast with what happens with benzodiazepines, withdrawal from opiates does not bring with it a lethal risk related to seizures. As withdrawal from opiate drugs is gradual, any major discomfort is avoided, whereas the need to abruptly interrupt an ongoing maintenance regimen usually reflects a lack of insight, or a patient's craving for heroin, in situations where the correct response is to increase dosages. The issue of iatrogenic tolerance to opiates also sounds inconsistent with current views on the nature of addiction as encoded in the DSM-IV[1]: addiction is diagnosed regardless of the state of opiate tolerance/dependence, so it is meaningless to exclude detoxified addicts from maintenance programmes, since agonist maintenance is the first-line treatment for opiate addiction as a relapsing behavioural syndrome, and not for opiate somatic dependence. It should be also remembered that, for addicts who enter treatment programmes in a state of physical dependence, methadone dosages are raised far beyond the current tolerance threshold, since opiate blockade and anticraving effectiveness can only be achieved by dosages higher than what is adequate for anti-withdrawal purposes.

After considering all these factors, we can conclude that buprenorphine, like other opiates, is useful in the treatment of opiate addiction because of its psychotropic properties, beyond withdrawal, so that a distinction between psychotropic properties in addiction and in other mental disorders is groundless and the hypothesis of employing it in non-tolerant individuals does not involve any conceptual leap.

Buprenorphine, with respect to other opiates, is safer, especially in the context of free prescription to psychiatric patients. First, withdrawal from buprenorphine, in cases of ineffectiveness, is quite easy, due to its longer half-life and slower elimination from the body. Its abuse potential may be limited by prescribing the naloxone-buprenorphine combination, in which possible buprenorphine highs are specifically blocked after improper injective use. Lastly, accidental overdosing is self-limiting, due to an early ceiling-effect, so that tolerant subjects do not run that risk [58, 59, 64].

Buprenorphine and psychopathology

Therapeutic effects on mental disorders can be expected from buprenorphine, in line with its distinctive receptorial profile. Buprenorphine combines μ-agonism, which is closely linked to its anticraving properties and is shared with methadone, with a k-antagonist activity [44]. This particular combination makes it easier to assess the psychotropic effects of k-antagonism, since retention rates are higher than those made possible by pure antagonists, such as naltrexone, which are poorly tolerated by heroin addicts, in general, and mentally ill ones, in particular [33, 34].

In a French sample (14), retention in a buprenorphine treatment programme was particularly low for mentally ill addicts, who received no further psychotropic treatment in response to their additional diagnosis. Retention in a buprenorphine treatment programme was predicted by the absence of a family history of affective disorders, and a high level of psychopathological discomfort, as assessed by the Addiction Severity Index [49], while MMPI-rated depression proved to be a negative predictor [49]. Depressive and paranoid symptoms rated by the SCL90 negatively affected retention in treatment for buprenorphine-treated subjects compared with a methadone-treated sample, at dosage levels of equal potency [46].

The Italian Multicentric study on quality of life (personal unpublished data) provided interesting evidence on the effects of buprenorphine upon psychopathology dependent on heroin abuse. This study evaluated a subgroup of subjects who had survived 3 months of attrition, i.e. who had stayed in treatment for at least 3 months. The comparison between the buprenorphine-treated group and the methadone-treated group was meaningful, since average dosages corresponded to similar levels of opiate agonism, 8 and 60 mg/day, respectively. After three months, the two groups showed similar levels of improvement, as assessed by the GAF-DSM-IV [1] and a similar reduction in their average SCL90 score (GSI) [7]. As treatment proceeded, the scores recorded for all psychopathological dimensions eventually decreased to a similar extent in the two groups. As expected, the gap from baseline to endpoint values during buprenorphine treatment turned out to be widest for opiate-related psychopathology, including anxiety, depression and aggressiveness. On the other hand, baseline psychopathology was more severe for methadone-treated subjects, for all SCL90-rated dimensions. Despite this, the following one-year observation revealed better adjustment for the buprenorphine group: therefore, as μ-agonism is the key factor in achieving psychopathological improvement, a full agonist such as methadone may be optimal in allowing drastic psychopathological improvement in severe cases, whereas buprenorphine may be preferable in the case of mild psychopathological pictures, which are best expressed through an unsatisfactory quality of life.

A higher level of psychopathology does not seem to favour buprenorphine abuse. Buprenorphine mishandlers do not seem to have a higher rate of specific mental impairment and are not concentrated in a high-psychopathology category of drug addicts [48, 61]. Although some authors [48] do not mention this while discussing results, the severity of addiction and the intensity of opiate craving seem to be the most likely factors

favouring buprenorphine abuse when no other therapeutic options (e.g. full agonists) are viable.

Buprenorphine as an antidote to dysphoria

Evidence of buprenorphine's psychotropic properties comes from two different kinds of population: the first consists of general drug addicts, whose response and outcome in terms of craving have often been described, so partly accounting for the course of psychopathological features during treatment.

For example, a group of 73 subjects who had survived one month of attrition, out of an original recruitment sample of 115, were made subject to additional observation during the next two months, while receiving buprenorphine at an average dose of 8.5±2.6 mg/day, with the aim of identifying possible outcome predictors. A positive outcome is predicted by a high level of psychopathological discomfort associated with addictive symptoms (psychopathological subscale of the Addiction Severity Index), a low susceptibility to boredom, low disinhibition scores on the Zuckerman scale, an absence of depression as rated by the MMPI but not by the Jouvent scale, the absence of alcoholism, no family history of addictive or affective disorders, and a low duration of addiction (less than 10 years) [49].

Some authors resorted to a pharmacological artefact in order to determine the psychotropic effects of k-antagonism alone (i.e. in the absence of any μ-agonism). In fact, Rothman and colleagues first carried out a three-month observation on a group of 15 subjects who were receiving a buprenorphine-naltrexone combination (4 mg/day of buprenorphine and 50 mg/day of naltrexone). K-antagonism induced by buprenorphine was the only significant effect on those subjects [52]. One third of the group were retained in treatment throughout the observation period; these patients were almost completely abstinent from both opiates and cocaine. Responders were male heroin addicts who were not tolerant to opiates at study entrance, with an average age of 41±7 years; these patients had been addicted for an average of 19±8 years. Isolated k-antagonism seems to yield better results than when coupled to μ-antagonism, as it happens with naltrexone. This evidence suggests that buprenorphine may exert an anticraving effect through its k-antagonist property. As an alternative, it could be hypothesized that k-antagonism acts by countering the dysphoric effects of naltrexone, so increasing the likelihood of retention in treatment. In other words, the same kind of dysphoria that can be handled at a later stage by the addition of fluoxetine to a naltrexone-maintenance regimen, with the aim of achieving better retention rates [37], can be prevented from the outset by using a naltrexone-buprenorphine combination.

The same experiment was replicated by Gerra and colleagues in a small group of addicts (N=6) who had dropped out of a naltrexone maintenance programme after only days or weeks. The same subjects, in this study, were treated by a combination of buprenorphine (4mg/day) and naltrexone (50 mg/day), in line with Rothman and coll.'s study. Retention in treatment was as high as 83% in facing immediate attrition, and as long as 5.5±1.1 months on average. Retained patients reported better psychopathological adjustment (dysphoria, depression, irritability, depression, anxiety, asthenia,

nausea, sickness or stomach ache) than than they had experienced before dropping out of naltrexone maintenance [15].

Other authors investigated buprenorphine's beneficial effects on heterogeneous groups of psychiatric patients who shared what is generically referred to as dysphoria.

Resnick and Falk [50] studied two groups of patients with a high prevalence of DSM-III-rated borderline personality disorder (60%): the first group did not include heroin addicts, while the second consisted of abstinent heroin addicts. Among non-addicts, borderline patients only showed improvement after receiving buprenorphine stably for the first month of treatment (with a 30-50% reduction along the HAMD scale and a 43-50% fall in overall psychopathology). This short-term effect was placebo-controlled along a Pl-B-Pl 9-14 day schedule, or a Pl-B / B-Pl reverse switching schedule. Some limitations should, however, be recognized in this study. The second group was not suitable for an evaluation of the primary psychotropic properties of an opiate drug, because it consisted of former heroin abusers, whose current state of abstinence was not enough to qualify them as possessing a normal opiate metabolism. Moreover, the first group was suitable for evaluation, but the conclusive observation that symptoms re-emerged after the withdrawal of medication fails to provide any new evidence.

Morgan and Callaway [42] evaluated the effects of buprenorphine on a group of adult males treated with repeated buprenorphine 0.15 mg doses in a single session, until the effects became measurable. The sample comprised 8 subjects who were evaluated in a double-blind schedule, and 4 in an open-label fashion; it also included 11 mentally ill subjects, most of them diagnosed as depressed, but with a high rate of comorbidity, plus one non-mentally ill "control" subject. Six subjects suffered from some kind of chronic pain, and substance abuse was common in the history of the 11 mentally ill patients. All things considered, the data authorize the conclusion that buprenorphine exerts acute beneficial effects on patients with affective disturbances. On an anecdotal level, the only adverse reaction to buprenorphine (nausea and dysphoria) was reported by the "control" subject.

In addition, we can consider the maladjustment of heroin addicts as a residual state during stable abstinence or as a relapse precursor. Addicts who respond to anticraving treatment programmes benefit from a gradual improvement in, and broadening of, their environmental chances; this is commonly referred to as spontaneous rehabilitative potential. If rehabilitation is to succeed, it must be able to count on an increasing availability of resources, but it also means that an individual will be challenged by new duties and will have to enter into stressful experiences with no certainty of success. While normal individuals tolerate such stress and react by increasing their involvement in their duties, subjects with a history of opiate abuse are likely to feel distressed. Thus, a lower pain threshold, a lower tolerance of effort, and a blunted reactivity to outer stimuli may forerun relapse, signalling persistent opiate damage which will later find expression in an overshoot of craving [30, 38, 45].

In the case of agonist maintenance, the maintenance phase is meant to favour rehabilitation, since the level of opiate coverage can be adjusted to help patients stick to

their rehabilitative goals. Beyond its basic anticraving goals (abstinence), maintenance is meant to allow rehabilitative recovery, counteracting its burden of distress with an increase in opiate coverage which will allow detachment from abuse substances to continue.

Buprenorphine and Mental Disorders

Depression

Some data have suggested a link between depressive states and endogenous opioid dysfunction [13, 51, 65], whereas other studies have failed to support this theory [43].

Both opiate agonists with a prevalently μ-mediated action (morphine, methadone) and k-agonists (cyclazocine, pentazocine) have revealed antidepressant properties [12, 18], although psychotic effects were one possible outcome with the latter, so suggesting a manic effect rather than a specifically antidepressant one.

Buprenorphine combines the properties of partial μ-agonism , with an early plateau due to its high affinity, and k-antagonism, which curtails the risk of psychotomimetic effects. Some clinicians have issued warnings about possible manic effects, as in the case of other opiates [39], but those effects may be transient or may develop only in risk-prone subjects [20].

On the basis of the positive effects recorded in drug addicts, and the background body of evidence about the primary psychotropic properties of other opiates, buprenorphine has been administered to small groups of depressed patients without any history of drug abuse.

Emrich and colleagues performed a controlled double-blind study on a small group of patients with double depression, in most cases resistant to standard therapies, and reported rapid and major beneficial effects [9].

Bodkin and colleagues examined 10 patients with a depressive syndrome that had proved refractory to at least two classes of traditional antidepressant drugs (TCAs, SSRIs, MAO-Is). Six out of the seven patients who completed the study with no adverse reaction showed significant improvement by six weeks at an average dosage of 1.3 mg/day (which corresponds to a 60% response with an ITT correction). Depression was atypical in 9/10 cases, and the only subject with a typical picture was one of the responders [3].

Resnick and Falk reported a reduction in psychopathological symptoms in 9 out of 15 patients, and were able to identify borderline personality disorder rated according to the DSM-IIIR as a predictor of response. In borderline patients, the HAMD score fell by 30-50% during the first month of treatment, at dosages ranging from 0.3 to 12.3 mg/day, while other subjects performed the same as when on placebo [50].

Morgan and Callaway reported a 73% response in a small group of 11 male non-addicted psychiatric patients, with a variety of conditions, 8 of whom displayed an axis I depressive disorder [42].

In the multicenter Italian study, depression, anxiety and aggressiveness were the psychopathological dimensions which, as expected, benefited most from buprenorphine treatment. Buprenorphine's antidepressant action was preferentially expressed on

heroin addicts, who were depressed at treatment entrance (46). This effect is achieved at dosages ranging from 2 to 8 mg/day, by the end of the first month of treatment [23].

In a randomized controlled comparison with methadone, Dean and coll. reported an equivalent level of improvement along the BDI (Beck Depression Inventory) [6]. One hundred and fifty-four heroin addicts were assigned to two equal-sized treatment groups by Gerra and colleagues; methadone was administered at an average dosage of 81,5±36,4 mg/day vs. buprenorphine at 9,2±3,4 mg/day [16]. By the end of the third month, retention was similar, but after an intention-to-treat correction, depressive symptoms turned out to predict retention selectively for the buprenorphine group. Although no randomization was performed, depressive symptoms were linked both with longer retention and with lower rates of opiate use at the end of the observation period, so suggesting a buprenorphine-mediated effect.

Anxiety disorders seem to be sensitive to opiates even at low dosages. Anxious subjects require lower methadone dosages for stabilization, suggesting there may be a favourable interaction between opiate agonists, anxiety and retention in treatment [35].

Seifert and colleagues [56] compared two treatment regimens for opiate withdrawal, combining carbamazepine with either methadone or buprenorphine over a two-week period. Results indicate the superiority of the carbamazepine-buprenorphine regimen, even if one major limitation must be pointed out. Carbamazepine is, in fact, known to increase methadone metabolism by induction of the CYP3A4 enzyme system, an effect that develops in a period as short as 1-2 weeks [11], whereas no clear knowledge is available as regards its interactions with buprenorphine. It could be that the fall in methadone availability due to its increased metabolism is the real reason for the difference that was observed on clinical grounds. Despite this problem, the main features of the study design could be replicated, with the improvement of introducing a neutral combination.

Kosten and colleagues [23] assessed the antidepressant effects of buprenorphine in a group of 40 patients, of whom 35% were recruited from ongoing methadone programmes in which the average dosage was as low as 55 mg/day. After a preliminary methadone tapering phase, methadone dosage was kept stable at 25 mg/day for as long as two weeks before a switch to buprenorphine, simultaneously with that of the other 65% of probands, who had been recruited while in a drug-free condition. Interpretation of the results is awkward: no comparison with methadone is possible, since the mean buprenorphine dosages used were not equipotent with the methadone dosage (3.2 mg/day of buprenorphine is, indeed, comparable with 25 mg as far as withdrawal is concerned, but not to 55 mg, which was the latest known stabilization dose). Moreover, the recent tapering of methadone dosages does not justify ruling out possible late withdrawal as the cause of depressive symptoms which lasted no longer than a couple of weeks.

In conclusion, it appears to be difficult to provide a coherent interpretation of this corpus of data, since some studies indicate antidepressant properties for buprenorphine, whereas others identify depression as a dropout predictor in buprenorphine programmes.

The heterogeneity of depressive syndromes is the most likely explanation: depressive symptoms are featured in depressive episodes of varying severity, in chronic minor pictures (dysthymia), in states of intoxication due to a variety of substances, in depressive or mixed phases of bipolar syndromes and, frequently, during anxiety disorders. On one hand, therefore, major melancholic depression may be refractory to buprenorphine treatment, in either unipolar or bipolar pictures. On the other, dysthymia, anxiety disorders with secondary depression and personality-based chronic dysphoria (cluster B personality disorders) may show quick-acting and powerful sensitivity to buprenorphine. Moreover, buprenorphine may be able to improve the outcome of naltrexone-maintained subjects, who become depressed during successful treatment [55]. In opposition to the view that drug-free or agonist-free regimens should be the final objective of addiction treatment, we consider it to be preferable, mainly on ethical grounds, to switch from a badly tolerated, even if successful antagonist, to a better tolerated and, presumably, equally successful agonist. This sounds reasonable, especially considering that naltrexone-responders do, in any case, often require supplementary antidepressants. For those not receiving any specific treatment, buprenorphine alone should be preferred to any psychotropic treatment which fails to act on the opioid system, while possessing its own side-effects, in any case.

Psychosis

During the induction phase of opiate maintenance, μ-agonist drugs may induce hormonal variations resembling those elicited by classic neuroleptic agents [22]; these feature the suppression of hypophysis-controlled adrenal cortisol secretion [41] and hyperprolactinemia [22, 47]. Likewise, sedation and depressive symptoms may develop as a result of central nervous dopaminergic antagonism.

In mania [22], 10 mg of methadone, acting as a full μ and k-agonist, proved effective against symptoms of excitement. It should also be borne in mind that the abrupt withdrawal of methadone in tolerant individuals may be followed by psychotic outbursts [27, 57].

K-agonist opiates do possess psychotomimetic properties, especially when, as in the case of cyclazocine or pentazocine, k-antagonism is not linked to any μ-agonism [12,18,19]. Levels of the endogenous k-agonist dynorphin are related to psychopathological conditions in schizophrenic patients [17, 66].

It is reasonable to conclude that buprenorphine probably possesses antipsychotic properties deriving from its k-antagonist activity. Shmauss and coll. report some evidence of this kind in a small open-label study on 10 patients suffering from schizophrenic spectrum disorders, who were not receiving any antipsychotic treatment at the outset. The frequency of remission of psychotic symptoms was as high as 70% after single buprenorphine doses and lasted an average of about 4 hours [53].

Dosages and psychotropic effects

Buprenorphine's psychotropic profile varies with dosage. At lower (< 16 mg/day) dosages, μ-agonism is dose-related, showing a linear progression; k-antagonism is also exerted, and μ-blockade is incomplete. At over 16 mg/day, μ-agonism reaches its plateau [44, 59, 64], providing the same level of stimulation as 65 mg of methadone [21, 28, 60]; at this point μ-blockade becomes complete [2].

In subjects who are not tolerant to opiates, antidepressant effects were recorded at very low dosages (0.4 mg) [8, 9]. In heroin addicts, higher dosages are likely to be needed, since the baseline tolerance threshold is above zero, and dosages must therefore be raised to achieve the remission of addictive behaviour, independently of depression. Even those dosages, however, are lower than the standard recommended for the treatment of heroin addiction (2-32 mg/day). Also, the effects of buprenorphine on psychopathology, especially of a depressive kind, do not appear to be dose-related: in fact, mean effective dosage is 8.5 mg/die over a wide 3-16 mg/day range [25, 49].

Data discussed by Schottenfeld and colleagues [54] suggest that buprenorphine's effects on depression may be biphasic, with lower dosages (around 4 mg/day) corresponding to a sharply favourable effect, and higher, blocking dosages corresponding to a less favourable or even an adverse effect. Two types of depression may, in fact, be distinguished: one is usually associated with severe addiction and sensation-seeking traits; it tends to have a poor outcome and is refractory to low potency opiates. The other is milder (dysthymia), is often associated with anxiety disorders and is highly sensitive to buprenorphine. The course of substance use during depression may address towards the best treatment option as suggested by data from Gerra and colleagues [16]: their depressed patients do better on buprenorphine; these are cases in which depression is associated with lower rates of positive urinalysis. Conversely, depressed peers in the methadone group are not characterized by a higher retention rate, or by a lower abuse rate as evaluated/tested by urinalyses. It may just be that the two groups correspond to two different longitudinal diagnostic clusters, according to the distinction previously hypothesized.

Patient-treatment matching.

The assignment of patients to buprenorphine programmes should take into account two different factors: the severity of addiction and the severity of psychopathology, on grounds of behavioural stability and reliability. Less severe psychpathology can be taken to include non-bipolar anxiety disorders, dysthymia, obsessive-compulsive disorder and personality disorder in the absence of major affective disorders. As for addiction, severity can be understood to comprise intense cravings, shorter-term relapsing behaviour, habitual polyabuse and multiple concurrent addictions.

The position of buprenorphine with respect to other better-known options (opioid agonists and antagonists), should first be thought of in terms of retention in treatment. In this connection, widely effective options should be chosen first. Patients who are re-

sponders to other agonist treatments can be switched later to buprenorphine programmes, depending on the degree to which a switch is thought to be feasible and preferable.

Let us first consider the case of naltrexone maintenance; short-term naltrexone treatment is out of the question, since it is non-specific towards addiction. Some responders to naltrexone need supplementary medication due to affective disturbance (SSRIs) [37] or resort to non-opiate substances (benzodiazepines, alcohol) in order to keep a balance, while others simply fail to respond and continue to use opiates, or actually drop out [29]. Non-responders or dropouts, as well as dysphoric responders or non-opiate abusing responders could be switched to buprenorphine treatment. On the other hand, full responders, ex juvantibus, may satisfactorily be kept on naltrexone.

To the extent to which the minimization of dropout rates is a goal, buprenorphine could be chosen for those who would fit the criteria for enrolment into naltrexone programmes: in other words, naltrexone treatment may be abandoned in favour of buprenorphine maintenance, which allows the average heroin addict a higher retention rate and a better psychopathological balance.

As to the role to be assigned to methadone, it is useful to classify addicts by applying two criteria: severity of their addictive symptoms, and the severity of other types of psychopathology:

- averagely-to-severely ill addicts (expected to be responders to high dosages of methadone and to be refractory to naltrexone) who are also affected by mental disorders of average severity.
- mildly-to-averagely ill subjects (expected to respond to lower dosages of methadone, with unpredictable reactions to naltrexone), who are also affected by mental disorders of low severity.
- mildly-to-averagely ill subjects (expected to respond to lower dosages of methadone, with unpredictable reactions to naltrexone), who are also affected by mental disorders of high severity.

The first category should be treated by methadone maintenance, with a perspective of complete or partial response. Those who are actually resistant to higher dose, long-term methadone maintenance may thus be labelled as treatment-resistant.

The second group may be started on buprenorphine or, if already on methadone, switched to μ-equipotent buprenorphine dosages, with a perspective of achieving an improved quality of life, fewer and milder side-effects, and a better endocrine function. The transition should only be chosen with stabilized patients, who are almost balanced on psychopathological grounds.

The third group may be preferentially assigned to buprenorphine, as a first-line option. In other words, buprenorphine may be preferable for them, not merely equivalent, in terms of their cost/benefit ratio.

The higher the ratio between psychopathology and addiction, the lower the expected level of effectiveness of buprenorphine on the clinical course will be. In other words, buprenorphine is expected to work best in forms of addiction that are mild-severe and have a short duration. It should be added that buprenorphine may also be effective in

Table 1. Buprenorphine as psychotropic drug. Review of the studies.

Authors	Year		Design	Diagnosis	Dosages (mg/die)	Results
Emrich et al	1982	10	Pl^1-Bup-Pl^2 (5-8 gg) pc, db crossover	Double DEP (Refractory)	0,4	50% response Rapid effect (HAMD)
Resnick & Falk	1989	15 (a) + 20 (b)	Pl-Bup-Pl (a) 9-15 days Pl-Bup / Bup-Pl (b) 1 days * 2	Psych (a) Add (b)	0,3-1,2 (a) 0,2 (b)	9 responders. Borderline 9/9 vs. 0/6 HAMD
Morgan & Callaway	1990	12 (11 vs. 1)	Bup-Pl (db) n=8 Open n=4 1 day	12 Psych (8 DEP) 1 control (6 pain)	0,15 * n	9 positive effect, 1 (control) dysphoria
Kosten et al	1990	40	35% of patients: Decrease from 55 mg meth (av.) by -10 mg/wk down to 25 mg, stable for two wks, then switch to Bup	Add DEP Vs. Add	2-8 mg 3,2 av.	Positive effect ITT-corrected
Bodkin	1995	10	Open, 6 wks	DEP (Refractory)	1,3 (av.)	86% (60% ITT) Nausea, dysphoria in 30%
Pani et al	2000	72	Rc, db multicentric Meth 60 mg vs Bup 8 mg	Add	8	Negative predictors: severe psychopathology, paranoid and depressive symptoms (SCL90)

Callaway	2001	5	Case series	DEP (3) Panic (1) Dysthymia (1)	1,2	Rapid response, stable for several years
Poirier et al	2004	73	3 mos observation	Add	8,5 (av.)	Positive predictors: Low boredom and dishinibition (Zuckerman) High pychopathology (ASI) Absence of depression (MMPI) No family history for affective disorders or addiction
Gerra et al	2004	154	12 weeks observation Meth 80 mg vs. Bup 9 mg	Add	9 (av.)	Depression is a positive predictor of abstinence and retention with Bup
Seifert et al	2005	26	Rc, 2 wks detoxification: CBZ-Meth vs. CBz-Bup (low-dose)	Add	Low-dose	Similar dropout More severe affective disturbance in Meth
Maremmani et al	2005	138	Observation after early attrition Meth 70 mg vs, Bup 7 mg	Add	8 (av.)	Positive effect equivalent to methadone upon SCL90 dimension, among less severely addicted subjects

Legend:
Add = Addicted patients; av. = average; Bup = Buprenorphine; CBZ = Carbamazepine
db = Double-Blind DEP = Depression ITT = Intention-to-treat Meth= Methadone
mos = months Pl = Placebo Psych = General psychiatric patients
Rc = Randomized-controlled vs. = versus wk,wks = week, weeks Open = Open-label study

treating severe psychopathology, as long as comorbid addiction is approached very early and is not accompanied by intense cravings.

Conclusions

Opiate drugs were first proposed for the treatment of dysphoric syndromes, depression and psychoses many years ago. Even so, the usefulness of these compounds in psychiatry is supported by only a small corpus of data. The reasons given for the restrictions placed on opiate use are based on prejudice rather than scientific evidence. Buprenorphine, with its unique pharmacological profile, has proved to possess antidepressant, anti-dysphoric and antipsychotic properties in psychiatric patients. Moreover, it may turn out to be the opiate of choice in subjects affected by lower severity addiction coupled with dysthymic disorders, anxiety disorders and personality disorders. The best dosages appear to be those that ensure a combination of k-antagonism with high levels of μ-mediated stimulation.

References

1. A.P.A. (1994): DSM-IV. Diagnostic and Statistical Manual of Mental Disorders. American Psichiatric Association, Washington.
2. BICKEL W. K., STITZER M. L., BEGELOW G. E., LIEBSON I. A., JASINSKI D. R., JOHNSON R. E. (1988): Buprenorphine: dose-related blockade of opioid challenge in opioid dependent humans. . J Psychopharmaco Exper Ther (247) 47-53.
3. BODKIN J. A., ZORNBERG G. L., LUKAS S. E., COLE J. O. (1995): Buprenorphine treatment of refractory depression. . J Clin Psychopharmacol 15:(1) 49-57.
4. CALLAWAY E. (1996): Buprenorphine for depression: the un-adoptable orphan. Biol Psychiatry. 39:(12) 989-990.
5. CARLSON E. T., SIMPSON M. M. (1963): Opium as a tranquilizer. Am J Psychiatry 120 112-117.
6. DEANA. J., BELL J., CHRISTIE M. J., MATTICK R. P. (2004): Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. Eur Psychiatry. 19:(8) 510-513.
7. DEROGATIS L. R., LIPMAN R. S., RICKELS K. (1974): The Hopkins Symptom Checklist (HSCL)--A self report symptom inventory. Behav Sci. 19 1-16.
8. EMRICH H. M., VOGT P., HERZ A. (1982): Possible antidepressive effects of opioids: action of buprenorphine. In: VEREBEY K. (Ed.) Opioids in mental illness: theories, clinical observations and treatment possibilities. Ann. N.Y. Acad. Vol. 398. The New York Academy of Sciences, New York, N.Y. pp.
9. EMRICH H. M., VOGT P., HERZ A., KISSLING W. (1982): Antidepressant effects of buprenorphine. . Lancet. 25:(2-8300) 709.
10. EXSTEIN I., PICKARD D., AL. E. (1981): Methadone and morphine in depression. Pharmacol Bull. 17 29-33.

11. FERRARI A., COCCIA C. P. R., BERTOLINI A., STERNIERI E. (2004): Methadone-metabolism, pharmacokinetics and interactions. Pharmacological research, YPHRS, in press.
12. FINK M., SIMEON J., ITIL T. M., FREEDMAN A. M. (1970): Clinical antidepressant activity of cyclazocine--a narcotic antagonist. Clin Pharmacol Ther:(11) 41-48.
13. FRECSKA E., PERENYI A., ARATO M. (2003): Blunted prolactin response to fentanyl in depression. Normalizing effect of partial sleep deprivation. Psychiatry Res. 118:(2) 155-164.
14. GASQUET I., LANCON C., PARQUET P. (1999): Predictive factors for patient maintenance on buprenorphine high dosage treatment: a naturalistic study in primary care. . Encephale. 25:(6) 645-651.
15. GERRA G. (2002): Buprenorfina in associazione a trattamento prolungato con naltrexone in soggetti affetti da grave dipendenza da eroina. In: A L. (Ed.) L'uso della buprenorfina nel trattamento della tossicodipendenza. FrancoAngeli, Milano. pp.
16. GERRA G., BORELLA F., ZAIMOVIC A., MOI G., BUSSANDRI M., BUBICI C., BERTACCA S. (2004): Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. Drug Alcohol Depend. 75:(1) 37-45.
17. HEIKKILA L., RIMON R., TERENIUS L. (1990): Dynorphin A and substance P in the cerebrospinal fluid of schizophrenic patients. Psychiatry Res. 34:(3) 229-236.
18. HOLTZMAN S. G. (1982): Phencyclidine-like discriminative stimulus properties of psychotomimetic opioids. . Ann NY Acad Sci:(398) 230-239.
19. JAFFEE J. H., MARTIN W. R. (1990): Opioid analgesics and antagonists. . In: IN GILMAN A. G., RALL W. R., NIES A. S., TAYLOR P. (Eds.): Goodman and Gilmans: the pharmacological basis of therapeutics. 8th ed. Pergamon Press, New York. pp. 488-521.
20. JAGADHEESAN K., MUIRHEAD D. (2004): Possible manic potential of buprenorphine. Aust N Z J Psychiatry. 38:(7) 560-561.
21. JOHNSON R., JAFFE J., FUDALA P. (1992): A controlled comparative trial of buprenorphine and methadone treatment for opioid dependence. JAMA. 267 2750-2755.
22. JUDD L. L., PARKER D. C., JANOWSKY D. S., SEGAL D. S., RISCH S. C., HUEY L. Y. (1982): The effect of methadone on the behavioral and neuroendocrine responses of manic patients. Psychiatry Research. 7:(2) 163-170.
23. KOSTEN T. R., MORGAN C., KOSTEN T. A. (1990): Depressive symptoms during buprenorphine treatment of opioid abusers. . J Subst Abuse Treat. 7:(1) 51-54.
24. KRAEPELIN E. (1921): Manic-Depressive Illness and Paranoia. Livingstone, Edinburgh.
25. LAQUEILLE X., POIRIER M. F., JALFRE V., BOURDEL M. C., WILLARD D., OLIE J. P. (2001): Predictive factors of response to buprenorphine in the substitutive treatment of heroin addicts. Results of a multicenter study of 73 patients. Presse Med. 30:(32) 1581-1585.
26. LEHMANN H. E., J.V. A., A. G., T.A. B. (1971): Treatment of depression with

dexedrine and demerol. Cur Ther Res:(13) 42-49.
27. LEVINSON I., ROSENTHAL R. N. (1995): Methadone withdrawal psychosis. J Clin Psychiatry. 56:(2) 73-76.
28. LING W., WESSON D. R., CHARUVASTRA C., KLETT C. J. (1996): A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 53:(5) 401-407.
29. MAREMMANI I., BALESTRI C., SBRANA A., TAGLIAMONTE A. (2003): Substance (ab)use during methadone and naltrexone treatment. Interest of adequate methadone dosage. Journal of Maintenance in the Addictions. 2:(1-2) 19-36.
30. MAREMMANI I., CANONIERO S., PACINI M. (2002): Psico(pato)logia dell''addiction'. Un'ipotesi interpretativa. Ann Ist Super Sanità. 38:(3) 241-257.
31. MAREMMANI I., CANONIERO S., PACINI M., LOVRECIC M., TAGLIAMONTE A. (2001): An eigh year longitudinal study of psychiatric patients on methadone maintenance treatment. Odvisnosti. 2:(1-2) 22-24.
32. MAREMMANI I., DAINI L. (2000): Sintomi di Comorbidità Psichiatrica durante il trattamento della dipendenza da eroina. Bollettino per le Farmacodipendenze e l'Alcolismo. 23:(1) 29-38.
33. MAREMMANI I., MARINI G., FORNAI F. (1998): Naltrexone induced Panic Attacks. Am J Psychiatry. 155:(3) 447.
34. MAREMMANI I., PACINI M., GIUNTOLI G., LOVRECIC M., PERUGI G. (2004): Naltrexone as maintenance therapy for heroin addiction: Predictors of response. Heroin Add & Rel Clin Probl. 6:(1) 43-52.
35. MAREMMANI I., PACINI M., LOVRECIC M., LUBRANO S., PERUGI G. (2003): Maintenance Therapy with opioid agonist for heroin addicted patients. Usefulness in the treatment of comorbid psychiatric diseases. In: WAAL H., HAGA E. (Eds.): Maintenance Treatment of Heroin Addiction. Evidence at the Crossroads. Cappelen Akademisk Forlag, Oslo. pp. 221-233.
36. MAREMMANI I., ZOLESI O., AGUECI T., CASTROGIOVANNI P. (1993): Methadone Doses and Psychopathological Symptoms during Methadone Maintenance. J Psychoactive Drugs. 25(3) 253-263.
37. MAREMMANI I., ZOLESI O., DAINI L., CASTROGIOVANNI P., TAGLIAMONTE A. (1995): Fluoxetine improves outcome in Addicted Patients Treated With Opioid Antagonists. Am J Addict. 4:(3) 267-271.
38. MARTIN W. R. (1979): History and development of mixed opioid agonists, partial agonists and antagonists. Br J Clin Pharmacol. 7 Suppl 3 273S-279S.
39. MATUSSEK N., HOEHE M. (1989): Neuropsychobiology. Investigations with the specific mu-opiate receptor agonist fentanyl in depressive patients: growth hormone, prolactin, cortisol, noradrenaline and euphoric responses. J Neuropsychiatry Clin Neurosci. 1:(3) 291-295.
40. MAYER-GROSS W., SLATER E., ROTH M. (1956): Clinical Psychiatry. . Williams & Wilkins, Baltimore.
41. MENDELSON J. H., TEOH S. K., MELLO N. K., ELLINGBOE J. (1992):

Buprenorphine attenuates the effects of cocaine on adrenocorticotropin (ACTH) secretion and mood states in man. Neuropsychopharmacology. 7:(2) 157-162.
42. MORGAN L., CALLOWAY E. (1990): Buprenorphine responders. Biol Psychiatry:(28) 1078-1080.
43. NABER D., JUNGKUNZ G. (1986): Opiate receptor sensitivity in depressed patients before and after clomipramine treatment. J Affect Disord. 11:(1) 59-62.
44. NUTT D. J. (1997): Receptor pharmacology of buprenorphine. Research and Clinical Forums. 19:(2) 9-15.
45. PACINI M., MAREMMANI I. (2005): Medical meaning of psychosocial issues of heroin addiction. Heroin Add & Rel Clin Probl. 7:(2) 37-48.
46. PANI P. P., MAREMMANI I., PIRASTU R., TAGLIAMONTE A., GESSA G. L. (2000): Buprenorphine: A Controlled Clinical Trial on the Efficacy in the Treatment of Opioid Dependence. Drug Alcohol Depend. 60 39-50.
47. PENDE A., MUSSO N. R., MONTALDI M. L., PASTORINO G., ARZESE M., DEVILLA L. (1986): Evaluation of the effects induced by four opiate drugs, with different affinities to opioid receptor subtypes, on anterior pituitary LH, TSH, PRL and GH secretion. Biomedicine and Pharmacotherapy. 40:(5) 178-183.
48. PHAN O., SANCHEZ M., BOUTHILLON-HEITZMANN P. (2005): Absence of correlation between mental disorders and high-dose buprenorphine. A case-control study. Presse Med. 34:(10) 711-718.
49. POIRIER M. F., LAQUEILLE X., JALFRE V., WILLARD D., BOURDEL M. C., FERMANIAN J., OLIE J. P. (2004): Clinical profile of responders to buprenorphine as a substitution treatment in heroin addicts: results of a multicenter study of 73 patients. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 28:(2) 267-272.
50. RESNICK R. B., FALK F. (1987): Buprenorphine: pilot trials in borderline patients and opiate dependence: treatment of a common disorder? In: HARRIS L. S. (Ed.) NIDA Research Monograph: Problems of drug dependence. US Governement Printing Office, Washington DC. pp.
51. ROBERTSON A. G., JACKMAN H., MELTZER H. Y. (1984): Prolactin response to morphine in depression. Psychiatry Res. 11:(4) 353-364.
52. ROTHMAN R. B., GORELICK D. A., HEISHMAN S. J., EICHMILLER P. R., HILL B. H., NORBECK J., LIBERTO J. G. (2000): An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. J Subst Abuse Treat. 18:(3) 277-281.
53. SCHMAUSS C., YASSOURIDIS A., EMRICH H. M. (1987): Antipsychotic effect of buprenorphine in schizophrenia. Am J Psychiatry. 144:(10) 1340-1342.
54. SCHOTTENFELD R. S., PAKES J. R., KOSTEN T. R. (1998): Prognostic factors in buprenorphine- versus methadone-maintained patients. J Nerv Ment Dis. 186:(1) 35-43.
55. SCHURKS M., OVERLACK M., BONNET U. (2005): Naltrexone treatment of combined alcohol and opioid dependence: deterioration of co-morbid major depression. Pharmacopsychiatry. 38:(2) 100-102.

56. SEIFERT J., METZNER C., PAETZOLD W., BORSUTZKY M., OHLMEIER M., PASSIE T., HAUSER U., BECKER H., WIESE B., EMRICH H. M., SCHNEIDER U. (2005): Mood and affect during detoxification of opiate addicts: a comparison of buprenorphine versus methadone. Add Biol:(2) 157-164.
57. SHREERAM S. S., MCDONALD T., DENNISON S. (2001): Psychosis after ultrarapid opiate detoxification. Am J Psychiatry. 158:(6) 970.
58. STITZER M., SCHUH K., WALSH S., PRESTON K., BIGELOW G. (1994): The effects of buprenorphine in morphine-maintained subject. In: HARRIS L. (Ed.) Problems of drug dependence 1993. NIDA Research Monograph Series. NIDA, Baltimore. pp. 383.
59. STITZER M., WALSH S., PRESTON K., CONE E., BIGELOW G. (1994): Clinical pharmacology of buprenorphine: ceiling effects at high doses Clinical Pharmacology and Therapeutics. 55 569-580.
60. STRAIN E. C., STITZER M. L., LIEBSON I. A., BIGELOW G. E. (1996): Buprenorphine versus methadone in the treatment of Opioid Dependence: Self-reports, urinalysis and Addiction Severity index. J Clin Psychopharmacol. 16:(1) 58-67.
61. TORRENS M., SAN L., CAMI J. (1993): Buprenorphine versus heroin dependence: comparison of toxicologic and psychopathologic characteristics. Am J Psychiatry. 150:(5) 822-824.
62. VARGA E., SUGERMAN A. A., APTER J. (1982): The effect of codeine on involutional and senile depression. In: VEREBEY K. (Ed.) Opioids in mental illness: theories, clinical observations and treatment possibilities. Ann. N. Y. Acad. V. 398. The New York Academy of Sciences, New York, N.Y. pp.
63. WALBY F. A., BORG P., EIKESETH P. H., NEEGAARD E., KJERPESETH K., BRUVIK S., WAAL H. (2000): Use of methadone in the treatment of psychotic patients with heroin dependence. Tidsskrift for Den Norske Laegeforening. 120:(2) 195-198.
64. WALSH S. L., PRESTON K. L., STITZER M. L., CONE E. J., BIGELOW G. E. (1994): Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 55:(5) 569-580.
65. WEIZMAN A., GIL-AD I., GRUPPER D., TYANO S., LARON Z. (1987): The effect of acute and repeated electroconvulsive treatment on plasma beta-endorphin, growth hormone, prolactin and cortisol secretion in depressed patients. Psychopharmacology (Berl). 93:(1) 122-126.
66. ZHANG A. Z., ZHOU G. Z., XI G. F., GU N. F., XIA Z. Y., YAO J. L., CHANG J. K., WEBBER R., POTKIN S. (1985): Lower CSF level of dynorphin(1-8) immunoreactivity in schizophrenic patients. Neuropeptides. 5:(4-6) 553-556.

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