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Selected issue 3

Buprenorphine — treatment, misuse and prescription practices

Overview

The use of pharmacological agents is one of the most common approaches in the treatment of opiate dependence. Early in the 20th century (Ministry of Health, 1926), authorities in some European countries realised the value of prescribing an opioid drug either as an aid to withdrawal or as a substitution medicine for patients who were addicted to heroin, morphine or opium. Today the most commonly used opioid substitution drug in Europe and the developed world is methadone, which was first introduced in the USA. A number of factors make this drug a popular therapeutic agent: it has a relatively long half-life (22 to 36 hours); it can be administered orally; and there is a strong scientific evidence base for its therapeutic efficacy. However, despite its popularity, the use of methadone continues to cause some concern, for example regarding the potential for it to be diverted to the illicit market, the level of withdrawal distress associated with cessation of the drug and the potential for overdose when used outside therapeutic settings. These concerns have been partly responsible for the development of interest in other withdrawal agents that can provide the same benefits as methadone but which may be more appropriate to some clinical settings or better suited to the needs of some client groups.

One drug that appears to deliver some of these benefits is buprenorphine. This mixed agonist/antagonist has historically been used for the short-term treatment of moderate to severe pain. Since the mid-1990s, buprenorphine has increasingly become available in Europe as an alternative to methadone for the treatment of opiate dependence. In this special issue, the reasons why clinicians are attracted to this drug, as well as the costs and benefits of buprenorphine in comparison with other treatment options, are explored in detail, and, for the first time, the increasing popularity of buprenorphine for the treatment of opiate dependence in many European countries is documented.

Introduction: legislation and pharmacological action

Buprenorphine is classified under Schedule III of the United Nations Convention of Psychotropic Substances of 1971, requiring all countries to place it under control. By comparison, methadone is classified under Schedule I

of the 1961 Convention, which places more restrictive measures on its control, distribution and use.

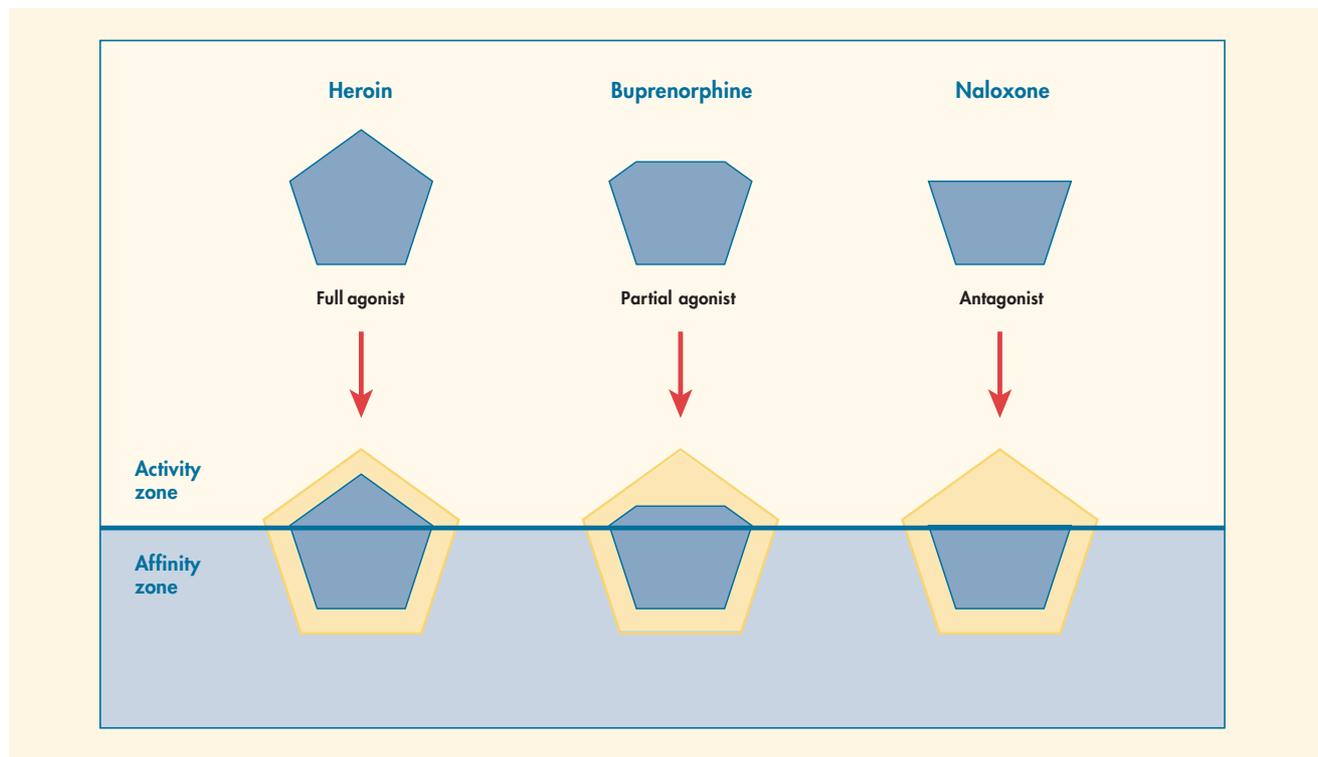
Buprenorphine is a derivate of the morphine alkaloid thebaine and, in contrast to methadone, which is a full opiate agonist, it is a mixed agonist/antagonist. This means that buprenorphine only partially activates the opiate receptors within the nervous system, producing a milder effect with both less euphoria and less sedation (Ridge et al., 2004).

Buprenorphine is often described as a partial agonist (receptor stimulator)/antagonist (prevents receptor stimulation) (Jones, 2004) (Figure 1) because it has important actions on two types of opiate receptors in the brain. Many of the most common opioid effects, such as euphoria, respiratory effects and reduced pain sensation, are caused by stimulation of the mu receptor. Buprenorphine produces these effects because it stimulates the mu receptor, albeit at lower intensity than other opiates such as heroin or methadone. Additionally, however, as buprenorphine binds more strongly to the receptor than these drugs, it can displace them. As a result, an individual who takes buprenorphine while dependent on another opioid risks the development of withdrawal symptoms due to a reduction in stimulation of the receptor. In addition, disassociation of buprenorphine from the receptor is slow, accounting for the drug's long duration of action, one of the factors that makes it a versatile treatment option.

Buprenorphine is also an antagonist of another receptor associated with opioid effects. The kappa opioid receptor is associated with some of the negative effects experienced in withdrawal, particularly depression. As buprenorphine inhibits stimulation of this receptor it may produce feelings of well-being.

Studies have shown that buprenorphine can be effective for the treatment of opiate dependence. In addition, it has been argued that the pharmacology of buprenorphine provides a number of benefits: its mixed opioid stimulating/blocking action makes it a relatively safer option in terms of the risk of overdose; its properties make it a less attractive drug to the illicit user and it may therefore be less likely than other opiates to be diverted onto the illicit market; cessation of the drug is associated with milder levels of withdrawal distress; and the long duration of its action permits more flexible dispensing options. Taken together, these factors may make

Figure 1: Effects of buprenorphine, heroin and naloxone on the mu opioid receptor



NB: The mu receptor is one of the primary sites for the reward effects of opiate drugs in the brain. The opiate binds to the affinity zone of the receptor and stimulates the activity zone, thereby producing an effect. In the diagram, heroin, buprenorphine and naloxone are represented by blue polygons, and the receptors by yellow polygons. The stimulatory effect of each chemical is related to how it interacts with the affinity zone (represented here as filling a proportion of the affinity zone). Heroin, classified as a full receptor agonist (stimulator), almost fills the activity zone while buprenorphine, a partial receptor agonist, fills a smaller proportion of it and naloxone does not stimulate the receptor at all. The substances also differ in how strongly they bind to the receptors. A substance that binds more strongly to the receptor can displace a substance that binds less strongly. Thus, buprenorphine can displace both naloxone and heroin, and naloxone can displace heroin.

Source: Adapted from Jones, H. E. (2004), 'Practical considerations for the clinical use of buprenorphine', *Science and Practice Perspectives* 2, No 2, pp. 4–20.

buprenorphine a versatile therapeutic agent and provide clinicians with an important additional prescribing option, although questions about which client groups are best treated with buprenorphine and which clients may be better suited to a different treatment option remain unanswered. In particular, it has been suggested that the pharmacological action of buprenorphine may make it less attractive to some client groups and that other benefits have to be weighed carefully against the cost of the drug.

Common formulations

Buprenorphine is available as tablets to be taken sublingually (allowed to dissolve under the tongue), or as ampoules for intramuscular or subcutaneous injection. Low-dose tablets, containing 0.2–0.4 mg of the drug, are sold under the brand name Temgesic and are normally used for analgesic purposes, for relief from moderate to severe pain.

The most common formulation of buprenorphine used for the treatment of opiate dependence is high-dose tablets containing 8–16 mg buprenorphine hydrochloride and

available under the brand name Subutex. These tablets are specifically intended for the treatment of problem drug use in clients who are being maintained in medically assisted treatment; in the case of clients undergoing withdrawal treatment, they are administered in a gradually reducing dose. Low-dose tablets are sometimes used for the treatment of opiate dependence, in which case multiple tablets are prescribed in order to achieve the desired dose.

In some countries buprenorphine is also available in another formulation, under the brand name Suboxone; in this case, buprenorphine is combined in a 4:1 ratio with the opiate antagonist naloxone. Suboxone was developed to reduce the abuse and diversion potential of buprenorphine by making its injection undesirable (Chiang and Hawks, 2003). Naloxone, in contrast to buprenorphine, has little effect when taken sublingually. However, when injected, the antagonist properties of naloxone can precipitate a withdrawal syndrome in anyone who is opiate dependent. Not surprisingly, this is thought to make the drug less attractive to those who inject

drugs and thus lower the risk of diversion onto the illicit drug market. However, many problem opiate users in Europe do not inject drugs, and studies of illicit drug users have reported the use of non-prescribed Temgesic and Subutex tablets.

Treatment efficacy

Although the research literature is still developing, and questions remain regarding which patients are best suited to treatment with buprenorphine compared with other treatment options, a number of studies have suggested that buprenorphine can be effective in the treatment of opiate dependence. It should be remembered that prescribing for substitution or withdrawal management is likely to be only one part of a therapeutic intervention, and overall success rates are likely to be influenced by the overall package of care provided. Nonetheless, studies have suggested that buprenorphine can have a positive effect on a number of outcome measures, including reduced drug use, increased treatment retention rates and improved health status (Strain et al., 1994). Clinical approval of the drug also appears high. Studies have also shown that client acceptance of the drug is good, although questions remain about its attractiveness to all client groups and whether this has an effect on treatment uptake or retention (Schottenfeld et al., 1997). The question of which client groups are best suited to buprenorphine therefore remains an important one for further research.

Contraindications to buprenorphine treatment include a number of medical conditions (Jones, 2004) such as respiratory, kidney or gall bladder problems, mental disorders, head injury, adrenal or thyroid dysfunction, enlarged prostate and urination problems. Caution is also required in patients with hepatitis or impaired liver function as the impact of the drug on the liver requires further study. The suitability of buprenorphine for use by pregnant women remains open to debate. One study reported that the neonatal abstinence syndrome was less intense with buprenorphine than with methadone (Johnson et al., 2003), but again this is an area in which further studies are required.

Table 1 describes the pharmacological properties of buprenorphine and their clinical implications (Lintzeris et al., 2001).

The suitability of buprenorphine for use by pregnant women remains open to debate and the scientific evidence for the effects of buprenorphine use during pregnancy remains incomplete. In the USA, clinicians are currently advised to switch pregnant women from buprenorphine to a methadone prescription, partly because it seems clear that the therapeutic benefits of methadone are likely to outweigh any potential risks to the unborn child and this evidence base for buprenorphine is less complete. There are some concerns that, compared with methadone,

Table 1: Summary of the pharmacological and clinical properties of buprenorphine

Property	Clinical implication
Produces opioid effects	Reduces cravings for heroin and enhances treatment retention Less sedating than full agonists (heroin, morphine, methadone)
Prevents or alleviates heroin withdrawal symptoms	Can be used for maintenance or withdrawal treatment
Diminishes the effects of additional opioid use (e.g. heroin)	Diminishes psychological reinforcement of continued heroin use May complicate attempts at analgesia with other opioid (e.g. morphine)
Long duration of action	Allows for once-a-day to three-times-a-week dosing schedules
Ceiling on dose-response effect	Higher doses (e.g. >16 mg) may not increase the opioid agonist effects, while prolonging the duration of action Safer in overdose, as high doses in isolation rarely result in fatal respiratory depression
Sublingual preparation	Safer in accidental overdose (e.g. children) as poorly absorbed orally More time involved in supervised dispensing
No severe withdrawal precipitated by opioid antagonists	Treatment with naltrexone can be commenced within days of buprenorphine May complicate management of heroin overdose requiring high naloxone doses
Side-effect profile similar to that of the opioids	Generally well tolerated, with most effects transient

Source: Lintzeris et al. (2001).

buprenorphine may be more likely to induce abstinence syndrome in the neonate and it is thought to cause higher neonatal toxicity during breast feeding (Lintzeris et al., 2001). However, some studies have shown buprenorphine to be both effective and well tolerated by mother and foetus, and one study reported that the neonatal abstinence syndrome was less intense with buprenorphine than with methadone (Johnson et al., 2003). Clearly, further research in this area is required.

Buprenorphine costs considerably more than methadone but some economic analysis has suggested that the relative costs of methadone and buprenorphine treatment can be similar. This rests on the assumption that buprenorphine may allow the possibility for less frequent administration. As the total cost of the intervention will consist of both the drug cost and the cost of clinical resources necessary to administer the drug (staff time, use of facilities, etc.) this may generate savings in terms of the input of clinical staff and other resources. For example, Ridge et al. (2004) estimated the cost of buprenorphine treatment to be around 1.3 times higher than that of methadone treatment. However, the extent to which available studies are relevant to the European situation as a whole is unclear. Clinical costs vary considerably between countries and prescribing costs may be difficult to separate out in practice from other elements of the care package provided. Methadone prescribing practices also vary considerably between countries and may also differ according to patient characteristics. The extent to which buprenorphine costs are similar to or exceed methadone costs are therefore likely to vary according to both local factors as well as the extent to which different prescribing regimes are implemented for each drug. However, both methadone and buprenorphine are generally assessed as being cheaper than other pharmacological substitution options, such as lofexidine.

Although there appears to be a growing consensus that the overall attractiveness of buprenorphine as a drug on the illicit European market is likely to be limited, and therefore diversion is potentially a smaller problem than with other opiates, this contention remains to a large extent speculative because of the limited evidence currently available. Buprenorphine, like all opiates, has the potential for misuse. Sources of harm include injection and combined use with other substances, in particular benzodiazepines and alcohol. As it is a relatively new substance in Europe, in many countries few data are yet available to inform a discussion on buprenorphine misuse and further research is therefore a priority.

Comparison with methadone

Some studies have compared the effectiveness of buprenorphine and methadone and found similar

outcomes in terms of retention rates and reduction in drug use (Strain et al., 1994; Schottenfeld et al., 1997). Some specific advantages of buprenorphine in the treatment of opiate dependence have also been reported. Compared with methadone, buprenorphine causes less sedation and users are more clear-headed; administration is also more flexible, which is useful in primary care settings (Fiellin et al., 2002) or at home, and the drug is well tolerated at high doses and has a safer profile. On the other hand, it has been suggested that methadone may be a more attractive drug (see, for example, Conférence de Consensus, 2004) to some client groups, especially those with long-term problems or a poor record of treatment compliance. This remains an important question for further study and should be seen as part of a broader debate on prescribing options for those with problems related to opioid dependence.

It remains unclear whether buprenorphine is superior to methadone regarding retention of clients in treatment and reduction of clients' additional consumption of illicit drugs. Some studies concluded that methadone is more effective than buprenorphine in retaining clients in treatment (Kosten et al., 1993; Ling et al., 1996), others have found no significant differences in retention rates (Strain et al., 1994; Schottenfeld et al., 1997). Similarly, claims that buprenorphine-maintained clients consumed significantly less additional opioids and cocaine than methadone-maintained clients (Giacomuzzi et al., 2003) must be weighed against research that found no significant differences between clients maintained on these two substances (Strain et al., 1994).

As buprenorphine is less hepatotoxic than methadone and is less likely than the latter to cause cardiac arrhythmias, renal disease and aggravate affective and psychotic disorders, buprenorphine may be particularly suitable for the following groups of patients:

- those with a short addiction history and good motivation (Kastelic and Scott, 1998);
- those with heart or renal disease;
- those with psychotic and affective disorders.

Historical development

American experts first suggested in 1980 that there was a scientific basis for the use of buprenorphine in the treatment of opiate dependence (Jasinski et al., 1978; Mello and Mendelson, 1980). Research work followed, and the drug was approved by the US Food and Drug Administration (FDA) as a narcotic for use in treating opioid dependence in men and non-pregnant women in 2002.

Buprenorphine had been used as an analgesic in Australia and Europe since the mid-1980s, but its role in the treatment of dependence came somewhat later. Typically in European countries, formal recognition of the drug as an approved approach in the treatment of opioid dependence followed a successful small experimental or ad hoc trial. For example, France, in the early 1990s, was one of the first European countries to use buprenorphine to any significant extent for the treatment of opiate dependence, but it was not until 1996 that a formal legal framework for its use was adopted. Similarly in Belgium, limited use of buprenorphine can be traced back as far as 1984, but the legal basis for its use was only put in place in 2004. More recently, the period between experimental and formal use appears to be decreasing as the evidence base for the effectiveness of the drug has grown; for example, Finland reports some limited use from around 1997 and a legal basis being put in place in 1999.

Substitution treatment in general increased in popularity in Europe during the 1990s, but for the most part the drug of choice for clinicians was methadone. Although high-dosage buprenorphine treatment was available in eight Member States by the year 2000, availability continued to be limited in comparison with methadone treatment (1).

By 2004, all of the old 15 Member States, except Ireland, reported some use of high-dosage buprenorphine treatment (HDBT) for opioid dependence — in Ireland, buprenorphine use is restricted to withdrawal treatment. Among the new Member States, the Czech Republic, Estonia and Lithuania reported the launch of HDBT in 2004, and in Slovenia it was implemented in 2005. In the Czech Republic, there are now more clients in HDBT than in methadone treatment.

In addition to scientific evidence for the effectiveness of buprenorphine in the treatment of opiate dependence, other contextual factors contributed to its introduction in the European countries: insufficient availability of methadone treatment to meet the increased demand; irregular coverage of substitution treatment at national level in several countries; the spread of AIDS; and, finally, political debates on alternatives to methadone (2).

Treatment provision of buprenorphine

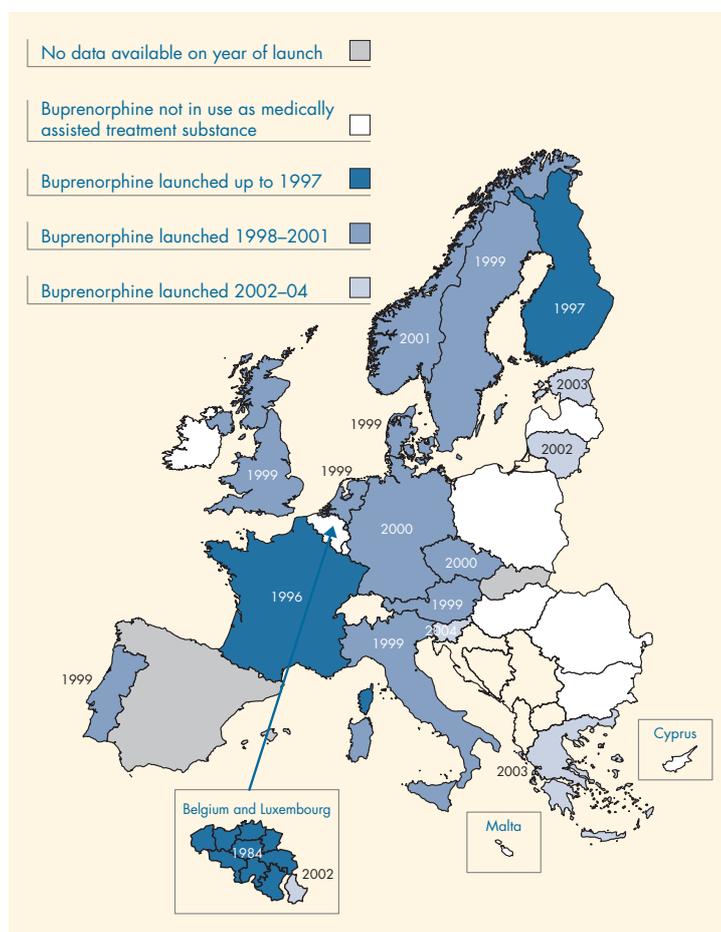
Figure 2 shows which countries use high-dosage buprenorphine treatment (HDBT), and when it was introduced, but it does not reveal anything about the extent or effectiveness of HDBT (for an overview of clients in HDBT see the section on opiate treatment in *Annual*

report 2005: the state of the drugs problem in Europe, Chapter 6).

The majority of Member States report the use of HDBT, mostly the old Member States. Thirteen of the old Member States (all but Ireland and Spain) report modest to extensive use of HDBT. Ireland uses buprenorphine only in withdrawal treatment, and Spain reports extremely low use, with a mere 36 clients receiving HDBT compared with 88 678 clients in methadone treatment, constituting a mere 0.04 % of the total treatment population.

Four of the 10 new Member States (the Czech Republic, Estonia, Lithuania and Slovenia) report use, or planned use, of HDBT but to a very limited extent (13 clients in Estonia in 2003, very modest use in Lithuania and no current clients in Slovenia). Only the Czech Republic reports relatively extensive use, with an estimated 1 400 buprenorphine clients being treated either in specialised units or at general practitioners.

Figure 2: High-dosage buprenorphine treatment in Europe (EU Member States, Bulgaria, Romania and Norway)

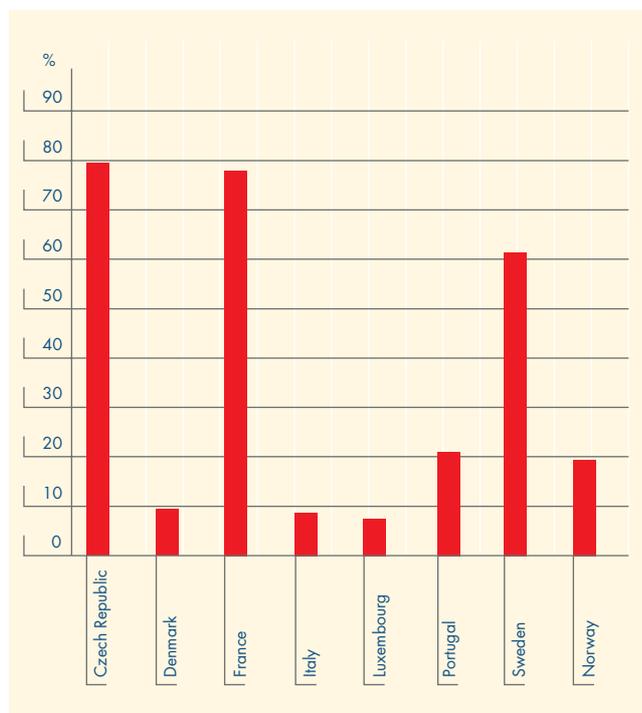


Source: Standard table on drug-related treatment availability.

(1) Belgium, Denmark, France, Germany, Italy, Austria and the UK (EMCDDA, 2000).

(2) http://www.anit.asso.fr/docs/subutex_1.php.

Figure 3: Buprenorphine clients as a percentage of all medically assisted treatment clients



Source: Standard table on drug treatment.

Neither of the candidate countries, Romania and Bulgaria, reports the use of buprenorphine, although it has been allowed in Romania since 2000.

Clients and coverage of high-dosage buprenorphine treatment (HDBT)

Analysis of the proportion of clients being treated with buprenorphine out of the total number of clients in medically assisted treatment (MAT) reveals two distinct groups of countries (Figure 3). In the first group (which comprises the Czech Republic, France and Sweden), clients receiving HDBT account for more than 60 % of the national aggregated number of clients in MAT. In France, in particular, buprenorphine treatment spread quite rapidly, because of some restrictions in methadone access (strict requirement for access, few places, reluctance of doctors in providing methadone) and because buprenorphine was judged as a safer and effective alternative to methadone. The second category comprises countries where HDBT accounts for less than 25 % of the total MAT (Denmark, Italy, Luxembourg, Norway). In both cases, it must be kept in mind that these figures are only relative and reveal nothing about the overall national provision of MAT or HDBT.

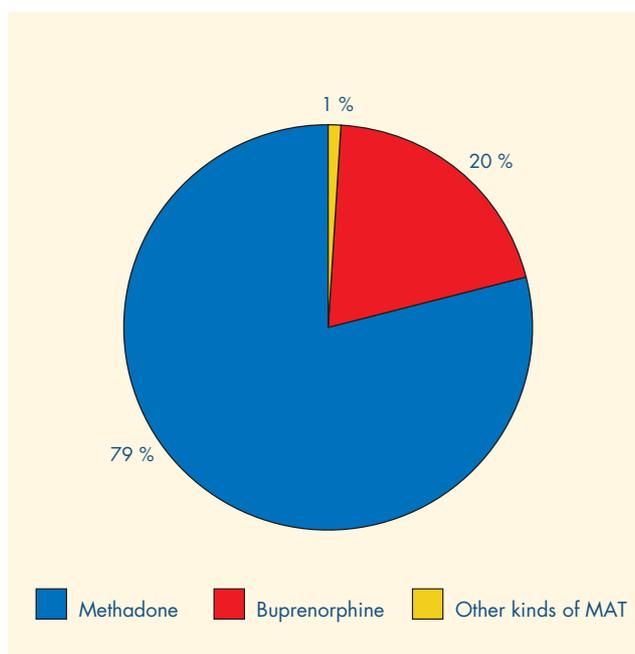
Taking the countries in the first group (>60 % in HDBT), the detailed figures are as follows. France reports

13 000 clients being treated with HDBT in specialised units and 70 000 at general practitioners, a total of 83 000 HDBT clients. The most recent prevalence estimate of problem drug use in France is around 180 000, giving a coverage rate for HDBT of about 46 % (there are also clients in methadone treatment). The same calculation for the Czech Republic gives an HDBT coverage rate of between 10.8 and 15.6 % (1 400 clients in HDBT divided by somewhere between 9 000 and 13 000 opiate problem drug users).

Out of the second group of countries, Norway aims to have buprenorphine on ‘equal terms’ with methadone, but this has not yet been achieved.

Looking at an aggregated European level, the following picture of HDBT clients as a proportion of MAT emerges. Overall, around 20 % of clients in MAT in the EU today receive buprenorphine (Figure 4). However, around 77 % (83 000 of 107 156) of these clients are in France. After subtracting the figures for France, the number of clients in HDBT constitutes a mere 5 % of the total (24 156 of 441 046). Thus, although buprenorphine treatment is now available in many EU countries, in the vast majority of Member States the actual number of HDBT clients is still very small. The expansion of HDBT is in fact very ‘superficial’ and its geographical distribution very uneven. Even in France, the geographic distribution of HDBT is rather unequal (Feroni et al., 2004).

Figure 4: Breakdown of medically assisted treatment (MAT) including high-dosage buprenorphine treatment in Europe (EU Member States, Bulgaria, Romania and Norway)



Source: Standard table on drug treatment.

Prescription practices, admission criteria and guidelines for treatment

Although prescription practices are complex and can vary considerably even within a Member State, some common features can be identified. HDBT will typically be provided through two main channels: specialised units (which can be independent units or wards linked to a mental health centre or hospital) and general practitioners. Very often complete and fully reliable quantitative data regarding the provision of HDBT are not available, but reports from Member States suggest the following general trends.

In some countries (Denmark, Estonia, Greece, Spain, Italy, Finland, Sweden, Norway) HDBT is provided predominantly, if not exclusively, by specialised units, whereas in other countries (the Czech Republic, Germany, France, Luxembourg) HDBT is provided mainly by general practitioners. In a third group of countries (Belgium, Lithuania, Austria) it is not possible to establish the main provision channel. The role of general practitioners varies greatly among Member States; in some countries (Denmark, Greece, Sweden) general practitioners have no involvement while in others (Czech Republic, France) they are the main provider.

Admission criteria and/or rules related to the prescription and delivery of HDBT also vary among Member States. For example, the minimum age for treatment is 16 years in the UK, 18 years in Portugal, 20 years in Greece and Sweden, and 25 years in Norway.

Other admission criteria for the provision of buprenorphine include the following: buprenorphine should not be given to heroin injectors (Belgium), clients should be more motivated than others to quit drugs (Italy), the user should be dependent on opiates (France), users must meet the criteria of WHO's ICD-10 (Denmark). As discussed earlier, no clear consensus exists on the prescription of buprenorphine during pregnancy. The clinical practice in Belgium, the Netherlands and Portugal is to avoid prescribing buprenorphine to pregnant women while in contrast, in Austria and Norway, it is recommended.

Misuse of buprenorphine

Buprenorphine, like all opiates, has the potential to be misused and, despite its relatively safer profile (Greenstein et al., 1997), cases of buprenorphine misuse have been reported. The combination of buprenorphine and other sedatives (such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants or major tranquillisers) can cause

serious interactions that can result in respiratory depression and overdose.

Buprenorphine is readily injected if the tablets are crushed and dissolved in water, with the related risks of viral contamination; in addition, since it is not completely soluble in water (Guichard et al., 2003), injection is associated with specific risks such as skin infections, abscesses, oedema and vascular infections. Finally, injection of buprenorphine that has already been in the mouth can result in systemic fungal or bacterial infections (Lintzeris et al., 2001).

Prevalence of buprenorphine misuse

Data on buprenorphine misuse are scarce and not harmonised at European level. In 2004, the EU Member States provided specific information on buprenorphine misuse ⁽³⁾: out of 17 countries where buprenorphine treatment is available, 12 reported some misuse of buprenorphine, albeit often extremely rare.

The two countries where the problem is most visible are Finland and France. In Finland, 28 % of persons entering drug treatment and 90 % of opiate users reported that they had buprenorphine as a primary drug leading to treatment; in France the corresponding figures were 5.8 % and 8.3 %.

Elsewhere, the number of buprenorphine misusers is much lower; in the Czech Republic, Denmark, Germany and Sweden, buprenorphine misuse is referred to only in informal sources; in the other countries, misuse is reported to be extremely rare (close to zero).

Very little information is available on trends in buprenorphine misuse in European countries, although there are some indications of a recent increase. The prevalence of buprenorphine misuse is highest in Finland, which has reported a steady increase of drug clients among persons entering drug treatment over the last four years (+170 %).

Studies carried out among specific populations have revealed that the proportion of buprenorphine misusers is higher among patients of low-threshold services (up to 41 % in France), among substitution treatment clients (Norway) and among disadvantaged and marginalised young people. Misuse of high-dose buprenorphine is also reported to be quite common among homeless people living in urban regions, partly because the combination of greater flexibility of administration and easy access to the substance can play a role in attracting users who

⁽³⁾ The TDI European protocol on people demanding treatment for their drug use provides information on clients using opiates as substitution treatment or as a primary and secondary drug of abuse; buprenorphine is included in the 'other opiates' category and only occasionally is the type of opiate specified. Specifications and qualitative information on buprenorphine were requested from the EU Member States in the 2004 Reitox national reports.

do not want a regular setting for care and partly because drug users who have received buprenorphine treatment sometimes switch to misusing the drug (Blanchon et al., 2003).

According to the available information, buprenorphine misusers seem to differ from other opiate users in several respects: they are reported to be younger, enter treatment earlier, start injecting sooner, and inject more often (Reitox national reports, 2004).

Two distinct groups of buprenorphine misusers are reported:

- those who self-medicate with the aim of stopping using other opiates; reasons for this type of misuse might be insufficient availability of substitution treatment or the desire to remain anonymous and keep away from the public health system (OFDT, 2004);
- drug addicts who use buprenorphine as drug of abuse, either as replacement for heroin (if heroin is not available or as a breakdown product) or as a primary drug of choice; reasons for this type of misuse may include the specific desirable effects of the substance, its accessibility and the opportunity to evade urine analysis in countries where it is not possible to measure buprenorphine in urine samples (e.g. Denmark).

Younger people are reported to use the drug more often as the primary drug of choice, whereas older users more often use buprenorphine as 'self-medication' (Table 2).

Patterns and consequences of buprenorphine misuse

When buprenorphine is misused, it is often injected in combination with other substances, particularly benzodiazepines and other sedatives, alcohol and, to a lesser extent, cocaine and other stimulants.

Table 2: Frequency of reasons for use of HDB in the past month, in 2003, among participants in the '2003 low-threshold' survey by age group in France

Reason for use	Age (years)			
	15-24 (%)	25-34 (%)	35 and over (%)	All (%)
As treatment	47	50	66	54
To 'get high'	20	10	13	13
Both	33	40	21	34
Total	100 (n=80)	100 (n=209)	100 (n=100)	100 (n=389)

Sources: TREND/OFDT (Escots and Fahet, 2004).

Table 3: Frequencies and odds ratios (ORs) of risks associated with the injection of Subutex or other substances during the past month in France

	Subutex injectors (%)	Injectors of other substances (%)	OR and 95 % confidence interval	
Abscess	31	19	1.9	[1.2-3.1]
Injection difficulties	68	55	1.7	[1.1-2.6]
Blocked vein, thrombosis, phlebitis	42	30	1.7	[1.1-2.5]
Swelling of hands or forearms	44	26	2.3	[1.5-3.5]
Febrile episodes	27	22	1.4	[0.9-2.1]
Haematoma	44	36	1.4	[0.9-2.1]

Sources: TREND/OFDT (Escots and Fahet, 2004).

Data on route of administration of buprenorphine misuse are very limited; in Finland and France, where the problem is more common, most buprenorphine misusers inject the substance (90 % of Finnish drug clients). In France, it is reported that injection is more common among less socially integrated people. Nevertheless, indications of a decrease in buprenorphine injection in recent years are reported.

French studies reveal that buprenorphine injection increases the risk of respiratory depression, overdose, skin and vascular infections and is more likely than some other drugs to cause abscess, thrombosis and haematomas (Table 3) (Escots and Fahet, 2004; OFDT, 2004).

Specific risk factors for buprenorphine injection are reported to be polydrug use, precarious economic conditions and insufficient doses of buprenorphine for people in treatment setting (Vidal-Trecan et al., 2003).

Deaths

Deaths due to buprenorphine misuse are very rare, and it is thought that the risk of overdose is lower with buprenorphine than with other opioids because of its agonist/antagonist pharmacological characteristics (i.e. beyond a certain dose a further increase does not result in any further increase in effect) and because its usual administration is sublingual (see also the introduction).

Despite this, some deaths have been reported in the scientific literature and by some European countries. However, data are very limited and in most cases buprenorphine is detected in the blood together with other substances, often benzodiazepines or alcohol. It is thought

that the risk of overdose is highest with intravenous injection and concomitant use of alcohol and sedatives.

Five European Member States in 2003 reported post-mortem findings of buprenorphine in the blood. Eight reported cases in France, and 44 in Finland, were linked to Subutex. The difference between the two countries is striking given that in France between 72 000 and 85 000 people were receiving buprenorphine substitution treatment, whereas in Finland 460 patients were treated in 2004 with buprenorphine. In Finland, buprenorphine is frequently used as a substance of abuse, and in 2003 90 % of users entering treatment were injecting it. But in France too about one third of those using buprenorphine outside a protocol injected the substance. Finally, two deaths associated with buprenorphine were reported in Luxembourg and two in Sweden (4).

Comparing data on the number of deaths related to methadone misuse and the number of deaths related to buprenorphine misuse, buprenorphine appears to be associated with a lower risk than methadone. For instance, in France in 2003, eight deaths related to buprenorphine were reported, out of 72 000 to 85 000 people receiving buprenorphine substitution treatment; by comparison, there were also eight deaths related to methadone, out of a total of 11 000 to 17 000 treatment clients (French national report). However, data limitations should be taken into account (Pirnay et al., 2004).

Very little information is available on the measures adopted by European countries to reduce harm from buprenorphine misuse. Generic measures targeted at all drug users, but especially those who use opiates, including buprenorphine, include counselling, needle exchange and the use of filters.

The use of naloxone combined with buprenorphine (Suboxone) is mentioned as a specific measure to prevent overdoses, decreasing the likelihood of abuse (CESAR Fax, 2003).

Illicit market

Information on the availability of buprenorphine on the black market is also very limited. Diversion of buprenorphine to the illegal market is reported in Austria (where it is very rare), the Czech Republic, Estonia, France and Finland. In the last four countries, there seems to be an inverse relation between the legal availability of the drug, which depends on the nature of national regulations, and diversion to the illegal market.

A tightening of national regulations in the Czech Republic and national importing regulations of pharmaceuticals in Finland resulted in a decrease in the availability of buprenorphine on the legal market; as demand for buprenorphine remained stable or even increased (e.g. Finland), this appears to have contributed to an increase in availability of the substance on the black market.

In contrast, in Estonia and France, ease of access to buprenorphine through doctors' prescriptions or pharmacies has contributed to a generally increased availability on the legal and illegal market. In France, clients can obtain several prescriptions by going from one doctor to another (so-called 'doctor shopping'), while Estonian users supply the Finnish illegal market. In Estonia, specific measures have now been adopted, and political agreements with Finland negotiated, to prevent the diversion of buprenorphine.

In addition, in Finland, a decrease in the availability of heroin, resulting from a reduction in heroin production in Afghanistan, is reported to be a crucial factor in the increase in buprenorphine availability in the illegal market (Nordic studies on alcohol and drugs, 2004).

Another element which has contributed to the increase in buprenorphine demand and availability is the low cost of the drug in the illegal market. In Finland, an 8 mg tablet of buprenorphine costs EUR 30–35, whereas the price of heroin is around EUR 60–350 per gram; in France, the price of an 8 mg buprenorphine tablet varies from EUR 1 to 4. Indications of a current decrease in the price of buprenorphine on the illegal market are also reported.

Conclusions

Buprenorphine appears to represent a valuable additional prescribing option for clinicians treating opiate dependence. The pharmacology of this drug may also help in making medically assisted treatment more widely available and more easily accessible, if it results in more flexibility in prescribing options. In particular, this could be the case if buprenorphine were to be considered as a particularly suitable treatment option for prescribing by non-specialist general practitioners. Largely, any increased flexibility in prescribing options will be dependent on existing national guidelines and practice on methadone distribution. And to some extent, those countries where buprenorphine provision is currently most common, historically have tended to have a fairly restrictive approach to methadone provision. This may be changing as several countries appear to be developing a flexible approach in this area, where buprenorphine

(4) The 112 (119) cases in France occurred between 1996 and 2001 (there were only eight deaths in 2003), and the two cases in Luxembourg between 1992 and 2003, whereas the 40 cases in Finland occurred in a single year. The relative risk is very different.

is available alongside methadone as a possible treatment option. In this respect, buprenorphine can be seen as a valuable additional element to the options available to clinicians and may provide some useful benefits in treating some groups of patients or prescribing in some settings. On the other hand, drawing conclusions about the relative costs and benefits of this drug in comparison to other treatment options is not a simple question. Certainly, it would be a concern if the use of buprenorphine meant that overall access to treatment became more limited due to cost constraints. Additionally, there are still questions about which groups of clients are likely to benefit most from which prescribing option and this remains an important area for future research.

That said, with some notable exceptions, most Member States report that the use of buprenorphine treatment appears to be low to modest and it would appear that there is considerable scope to improve availability to this

treatment option. Compared with methadone, buprenorphine has advantages and disadvantages, but it can be viewed as an alternative and relatively safe drug that has proved efficient in both withdrawal and maintenance treatment. Although there are reasons why buprenorphine may be not a particularly attractive drug to illicit opiate users, a risk of diversion to the illicit market still exists and therefore measures to diminish diversion and misuse are necessary. It may be that the introduction of new formulations of the drug may reduce this risk further but, again, questions of cost and benefits will need to be carefully elaborated. Finally, information and data on use of buprenorphine in the treatment of opiate dependence and buprenorphine misuse in the EU Member States are still insufficient, and more research and investigation are needed although the current evidence base does suggest that the drug may represent a valuable addition to the clinical arsenal for treating opiate dependence.

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