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EXECUTIVE SUMMARY
During the past thirty years, methadone has been the most widely used medication in the treatment of opioid dependence. A large body of scientific evidence shows that methadone, when prescribed appropriately, helps significantly to improve the health and social situation of people with an opioid dependence. Buprenorphine was introduced a decade ago and has rapidly gained popularity in the treatment of opioid dependence.

While the evidence base and clinical experience of buprenorphine is much smaller than that of methadone, the research available to date points to the conclusion that buprenorphine is an effective medication in the treatment of opioid dependence, albeit not more effective than methadone at adequate dosages.

To date, many myths and beliefs still exist about the various medications used in the treatment of opioid dependence. This is also the case for buprenorphine. Some of these myths are based on a lack of available evidence, but other myths find their roots in a lack of information or inappropriate use of the medication by patient and/or treatment provider. Besides myths and beliefs there are also critical issues based on facts, which need to be addressed.

Euro-Methwork believes it is important to provide accurate information, based on the latest scientific evidence and clinical experience, in order to facilitate informed decisions regarding which medication to use for which patient.

The aim of this special publication is to discuss critical remarks regarding buprenorphine, its adoption, its effectiveness, its safety and in particular its costs.

This booklet can be considered as a combination of a short review of the scientific evidence and the experience in clinical practice with regard to buprenorphine substitute treatment. We collected prevailing ideas and opinions regarding buprenorphine through an informal electronic audit with a number of experts in the field and addressed them by reviewing the available evidence.

How to read this booklet

This booklet can be considered as a combination of a short review of the scientific evidence and the experience in clinical practice with regard to buprenorphine substitute treatment. The booklet is divided into two main parts. After a brief introduction, Part 1 summarises the state of the art of buprenorphine and substitution treatment in general. Part 2 discusses the various critical issues with regard to buprenorphine which were mentioned by experts in the field.

In the introduction, Euro-Methwork’s mission is briefly explained and reasons are given as to why it was important to write a booklet about buprenorphine. To ensure that all the important aspects of buprenorphine would be addressed, experts of the Euro-Methwork network were asked to provide their major ideas and opinions with regard to buprenorphine. Their comments provided the structure for this booklet.

In Part 1, opioid dependence is discussed and questions are addressed such as: What is addiction? What is substitution treatment? How many people are addicted world-wide and what sort of treatment do they get?

Buprenorphine is a partial agonist with a high affinity for μ opiate receptors and is an antagonist at κ opiate receptors. It was developed in the 1970s and first registered under the analgesic brand name Temgesic® (a low dose medication). The sublingual tablet Subutex® (also available at higher dosage) was developed in the 1990s and first registered for the treatment of opiate dependence in France in
1995. Recently, a tablet combining buprenorphine and the antagonist naloxone has been introduced first in the USA and also in Australia in July 2005 under the brand name Suboxone®. A summary of the scientific evidence regarding buprenorphine is provided: there is a growing body of evidence about the effectiveness of buprenorphine as a useful medication in the treatment of opioid dependence, although further research is still required to fill some gaps in the knowledge base.

In Part 2, the critical questions are examined, which were raised in the audit amongst experts in the field. This part is divided into three chapters: part 2.1 addresses clinical issues, part 2.2 non-clinical issues and in part 2.3 some patient perspectives are discussed.

Although it is not our intention to provide clinical guidelines, we nevertheless discuss issues related to good clinical practice in part 2.1. For example, the question was raised whether the induction onto buprenorphine is more demanding than inducing onto methadone. This will be the case in settings where buprenorphine is introduced and treatment staff have little or no experience. The fact that induction is started when the first withdrawal symptoms set in (this can be 6-12 hours after last heroin use and 24-48 hours after last methadone use) could create some tension in the treatment process. If buprenorphine is administered too early, so-called precipitated withdrawal could occur. Treatment providers may need training to handle the induction phase effectively. If physicians and patients are both well informed about what to expect, problems can be minimised.

Buprenorphine is a medication, which should be taken sublingually. It needs time to dissolve and thus calls for more staff time when supervised consumption is required. An important feature of buprenorphine is that it can be administered on alternating days or even thrice weekly. This has the advantage that patients can attend less frequently and still take their medication under supervision.

The question whether to shift patients from methadone to buprenorphine is examined. When this is done too abruptly, it could cause problems. It works best when patients are reduced to 40 mg methadone per day and subsequently wait 24-48 hours for withdrawal symptoms to start. However, it should be clear there is no clinical reason to shift patients who are stable and well functioning on methadone onto buprenorphine. It can only be done on a voluntary basis and patients should have the choice to return to their old medication.

When buprenorphine was first introduced it was believed to be a medication for detoxification. Both research data and clinical experience have shown that buprenorphine can indeed be used in a detoxification process, but that it can very well play a significant role in maintenance treatment as well. Sometimes, the reason to use buprenorphine only for short-term treatment is based on the cost of the medication rather than on its pharmacological properties.

Because of its partial agonist properties, buprenorphine seems to cause less respiratory depression than full agonists such as heroin and methadone. Although this safety profile is a major advantage, this only holds as long as buprenorphine is not used in combination with alcohol and/or benzodiazepines, since this could -as with any opioid agonist- lead to an overdose situation.

The final paragraphs of the clinical issues are dedicated to possible misuse of buprenorphine. There is evidence that buprenorphine, which is taken home or bought on the black market, is sometimes injected, which can produce euphoria. It could be dangerous especially when injected with used needles and syringes and/or taken in combination with other drugs, in particular alcohol and/or benzodiazepines. In Germany, some patients seem to sniff crushed tablets. More research is needed on the potential negative consequences of using buprenorphine inappropriately.

Part 2.2 describes non-clinical issues. Here the optimal setting for treating opiate dependence is discussed: patients should feel welcome, accepted for whom they are, informed about the advantages and disadvantages of the treatment and feel engaged in the treatment. Staff should be professional, well
trained and do their work with a non-judgemental attitude. These are general principles of any treatment setting and consequently also apply to buprenorphine treatment. Since buprenorphine is a relatively new medication, extra staff training may be needed.

A special paragraph is dedicated to the question whether buprenorphine can be used in harm reduction oriented settings. Although treatment with buprenorphine as an opioid substitute medication helps to reduce drug related harm, and is thus an important tool in the harm reduction approach, it may not be the kind of medication preferred by those patients who are not committed to give up their heroin use totally. Such patients may be better off with methadone.

The role of primary care and general practitioners in treating people with an opioid dependence is very important. Whether they can be involved differs from country to country and depends on the organisation of the health care system. There are numerous reasons why they should be involved which range from therapeutic reasons (more flexibility, holistic approach, social context, less stigmatising etc.) to logistics reasons (normalisation of drug dependency treatment, more people can be treated). However, for a successful engagement of general practitioners in the treatment of opioid dependent patients with buprenorphine, it is important to give general practitioners sufficient support in order to prevent potential problems (leakage to black market, stress, too high workload, et cetera).

As mentioned earlier, sometimes the price of buprenorphine is a crucial factor in deciding whether to use it and for how long. Cost-benefit studies all indicate that providing treatment for heroin dependence is much more cost effective than not providing treatment or than criminal justice interventions. So, it pays off to use buprenorphine. However, in most countries methadone is much cheaper than buprenorphine. In Western countries, personnel costs make up the largest part of the budget, which means that using methadone or buprenorphine only have a minimal impact on the total budget. In resource-poor settings in transitional and developing countries, the cost of staff is relatively low and the cost of medication takes up a relatively large part of the budget. In such settings, the difference in price between methadone and buprenorphine becomes is a very important factor. It is important that service providers and patients have a free choice in deciding which medication would be best and Euro-Methwork argues that the price of buprenorphine should be brought down in resource-poor settings.

The last paragraphs of part II are dedicated to the role of the pharmaceutical industry. In the case of buprenorphine, they are an important player in the field: they have paid for research, contributed towards costs of training and sponsored conferences. This booklet was also written with financial support of the pharmaceutical industry, namely Schering-Plough International. It is argued that there is a certain risk that sponsors influence the policy of organisations. An example is given on how the USA, as the single largest donor, recently put pressure on the UNODC to remove references to harm reduction from all official documents. We think it is possible to work with the industry as long as clear agreements are made which secure no interference with the contents other than expecting good quality of the final product.

Part 2.3 looks at buprenorphine from the perspective of the patient. It is extremely important that drug users are involved in the development, implementation and evaluation of drug policies and practices. In the end, it is their lives, which are at stake and they have experiences from ‘within’, which may be different from the experiences of service providers and policymakers.

Obviously, people with opioid dependence are both curious and frightened when a new medication is introduced. They are curious, because it might be a medication, which serves them better than what they have experienced so far. But they are also frightened, that they will be forced to give up something they know well and are familiar with (in this case methadone) for the unknown. An important factor for patients is the fact that buprenorphine is reported by many to give them a ‘clear head’. Some patients are pleasantly surprised with this effect, while for other patients this is a very unwelcome effect, when old conflicts and emotions suddenly appear more in the forefront.
Patients, who are in substitution treatment for a while and who have managed to structure their lives, could benefit from a **more flexible medication delivery system**. Sometimes (local) regulations do not allow for take home dosages. In that case, the fact that buprenorphine can be taken on alternating days, could provide more flexibility for the patients.

In the last chapter, the **conclusions** are drawn: buprenorphine is an important medication in the treatment of opioid dependence. A large number of studies have been conducted over the last decade and the overall conclusion is that there is solid scientific evidence and increasing clinical experience showing the effectiveness of buprenorphine as a useful additional medication in the treatment of opioid dependence. It has proven to be a safe medication, effective in keeping patients in treatment and preventing the use of illegal opiates, yet not more effective than methadone. Although not supported by objective evidence, both patients and doctors have reported that withdrawal symptoms may resolve more quickly from buprenorphine than from methadone.

If the price of buprenorphine could be brought down particularly in resource-poor settings, it would be a great step forward into the direction of creating a situation where patients and treatment providers can freely choose between medications. This is a prerequisite for tackling drug related harm effectively.

We hope that this booklet will assist our network, which includes service providers, service users and their families and friends, researchers and policy makers, in making informed decisions regarding which medication would serve a patient best in a particular time and setting.
INTRODUCTION
Why this booklet about buprenorphine?

Euro-Methwork is a forum for those who are active in the field of medical treatment of opioid dependence in the European Region. The network includes practitioners, researchers, policy makers, but also heroin users, their friends and families. During the last decade or so Euro-Methwork has focused its efforts on improving the availability and quality of opioid substitution treatment in Europe.

Since the start of our network and related activities the focus has very much been on methadone as a substitute medication, largely because until recently this was the main medication used for this purpose. In recent years other medications, such as buprenorphine, morphine sulphate and codeine compounds, have been adopted for the treatment of opiate dependence with more or less positive results. Although methadone is still the medication most used in the treatment of opioid dependence across the world, there is an increasing body of experience and evidence of the successful use of buprenorphine.

There are several reasons why we wanted to make this booklet about buprenorphine. The first is that we felt that given the increasing prevalence of buprenorphine substitution treatment our former publications may lack specific information about this form of treatment. Second, we decided that after a great deal of work on methadone we needed to expand our own knowledge on the issue. In a way this booklet can therefore be considered as an addendum to the European Methadone Guidelines (Verster, 2000) and the Training Manual (Verster, 2003). A third and main reason for this special publication is that we have heard and read about critical remarks regarding buprenorphine, its adoption, its effectiveness, its safety and in particular its costs. We decided we wanted to look at these critical issues in order to examine and discuss them.

Method

We have adopted a combination of methods. After the collection of the relevant international literature we reviewed the scientific evidence and clinical practice.

At the same time we organised an informal electronic audit with a number of experts in the field and asked them about their ideas and opinions regarding buprenorphine. The question was formulated as follows: "What sort of objections do you have against buprenorphine and/or which objections do you hear from your colleagues, clients and policy makers?"

This audit was conducted in two phases. First, we contacted 33 people from different professional backgrounds (medical professionals, researchers, policy makers as well as consumers) and from different countries, including Western and Eastern Europe, Australia and the US. People were selected on a convenience basis as experts from the network of Euro-Methwork, who had been involved in the development of former publications (Verster, 2000, 2003a, 2003b). Professionals contacted were both from countries where buprenorphine has been registered and adopted as well as from countries where it is not available. The rationale behind this was to collect a range of critical issues related to clinical practice as well as to the potential resistance to the adoption of the medication. Overall, 23 out of 33

1 In the nineties, Euro-Methwork developed a network of people and centres involved in methadone treatment for opiate dependence and built its website with the Methadone Assistance Point (MAP). The MAP contains addresses and details of people and centres prescribing methadone for opiate dependence in Western Europe. In 2000, the MAP was updated and extended to include Central and Eastern European countries. During this same year, the European Methadone Guidelines were published; initially in English, French, German and Spanish. To date, they have also been translated into Russian, Greek, Italian, Slovenian, and Slovakian. In 2003 two documents were published with a slightly broader outlook on substitution treatment in general, the Training Manual Key Aspects of Substitution Treatment for Opiate Dependence and a special publication Information for Policy Makers on the Effectiveness of Substitution Treatment on the same issue addressing policy makers. These two publications were also published in the four official European languages and subsequently translated into Polish, Russian and Czech. In addition to these publications a virtual clinic was built and added to our website www.euromethwork.org.
people responded to this first phase audit by email or over the telephone. People with no or limited experience in prescribing buprenorphine were over-represented in this sample. Their comments and feedback were collected and analysed and grouped into a number of themes. The outcome of this first audit was presented at an international conference and on the bases of feedback received from this occasion, it was decided to organise a second audit. A small group of practitioners with extensive expertise in prescribing buprenorphine were contacted to provide us with critical issues from the clinical perspective. The themes collected on both occasions were then looked at separately and discussed according to the state of the art of the scientific evidence. In addition, we attended two training seminars for clinicians, where the latest scientific evidence was presented on buprenorphine by a wide range of international experts. A draft was prepared and sent to a number of experts, whose comments were included in the second draft.

**Perspective**

The work of Euro-Meth work is based on a number of principles. From the perspective of public health substitution treatment is considered a vital part in addressing the drug problem. Good quality medical treatment should be available and accessible to drug users and provided according to the latest evidence base. Substitution treatment should be easily accessible, and the staff should act in a non-judgemental way towards drug users. Although the ultimate goal could be to stop the use of drugs all together, drug treatment should first focus on improving the physical, mental and social well being of drug users and their families.

In order to provide good quality treatment it is considered important to include the consumer perspective in the various phases of planning and evaluating treatment.

**Bias?**

There are two ways in which a bias may have occurred with regard to the contents of this booklet. First, the critical issues discussed in Part 2 have been provided by a selection of experts from our network. It cannot be excluded that if we had contacted other people, different issues would have been addressed. As described above, we repeated the audit because it was felt that more feedback was needed from people with more experience with buprenorphine.

A second bias could occur because of the fact that this project was funded by Schering-Plough International, New Jersey, the pharmaceutical company marketing buprenorphine in Europe and Asia. Working with the industry and accepting their financial support poses some interesting dilemmas. On the one hand, one could argue that it is impossible to remain objective once receiving funds from the industry, referring to the proverb 'cuius panem edo, illius carmina edo', which means 'whose bread I eat, his songs I spread'. On the other hand, one could say that - as long as clear and transparent agreements are made - it is possible to remain objective.

Although we accept there could be a risk of an unacceptable influence by the pharmaceutical industry, we support the idea to work with them, provided that clear agreements are made. If it were just up to governments, universities and NGOs, there would be few funds available for research into any medication in general and in particular into buprenorphine, since the target group, i.e. drug users, do not have a powerful lobby. With the financial support from companies such as Schering-Plough, a lot of research has been conducted, which now enables us to examine whether it works, with which dosages, for whom, in what situations et cetera. We feel that if such research is not done independently and does not follow scientific scrutiny, the scientific community will never accept the results and thus the money would be wasted.

Our former publications have been developed with the financial support from the European Commission but also to some extent from smaller local pharmaceutical companies. We have always made sure that the content of our work would remain independent and based on the available scientific evidence and
clinical practice. In the case of the current project and the development of this booklet, we can say that Schering-Plough gave us ample space to develop the booklet the way we thought was best. The booklet was presented to them in its final phase and at no stage has there been any control or influence on its contents from their side.

Outline booklet

This booklet can be considered a combination of a short review of the scientific evidence and experience in clinical practice with regard to buprenorphine substitute treatment and a discussion of the various pros and cons or critical questions examined. The book is therefore divided into two parts:

- Part 1 contains a short summary describing the ins and outs of buprenorphine treatment as maintenance or detoxification treatment for opiate dependence. After an introduction on opioid consumption and the epidemiology of opioid dependence, a short description is given on substitution treatment in general, its aims and objectives as well as the evidence base for its effectiveness. The third paragraph focuses specifically on buprenorphine. A general description is followed by its pharmacological profile, clinical practice, evidence base and some comparison with methadone.

- Part 2 discusses the various critical issues that have come across during the audit amongst experts in the field. These themes include a variety of clinical issues (induction, precipitated withdrawal, dosage, dispensing, diversion, etc) as well as non-clinical issues (costs, politics, the role of the industry and safety). This part is concluded with some subjective issues from the consumer perspective.

- The appendices include information with regard to relevant and recommended literature, including guidelines for clinical practice, and websites as well as a list of the experts involved.

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In particular, we would like to thank several of our key informants, who have also provided us with papers and documents, which weren't published at the time and which have helped us to review the scientific evidence and clinical practice with regard to buprenorphine treatment.

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Finally, we would like to express our gratitude to Schering-Plough International for providing funding which enabled us to write this booklet.
PART 1

GENERAL OVERVIEW OF THE MEDICAL TREATMENT FOR OPIOID DEPENDENCE
In this part we will provide a general overview of substitution treatment for opioid dependence. The first chapter gives an introduction on opioid consumption and the epidemiology of opioid dependence. The second chapter describes medical treatment for opioid dependence in general and its aims and objectives. The third chapter focuses specifically on buprenorphine and a general description is followed by its pharmacological profile, clinical practice and the scientific evidence, with particular focus on comparison with methadone.

### 1.1. OPIOID DEPENDENCE

Opioid dependence is a medical condition, which is difficult to control due to compulsive drug use and craving, leading to drug seeking and repetitive use even in the face of severe negative health and social consequences. Opioid dependence (mostly heroin) is a complicated condition that has both metabolic and psychological components and, partly due to its illegality, is currently associated with severe morbidity and a high risk of death.

Opioid dependence is a problem that exists in most countries today. Heroin use has become increasingly common in North America since the 1960s and in Europe since the 1970s. In Europe, the epidemic first occurred in the sixties in the West, followed by the South in the eighties and, today, most countries in the Central and Eastern European Region, Newly independent States (NIS) and Russia have growing populations with opiate dependence. Furthermore, opiate use and dependence seems to be increasing in other regions, where traditionally it was less prevalent, including (Southeast) Asia, China, South and Central America and even in Africa. Reports by the United Nations Office on Drugs and Crime (UNODC) and the World Health Organisation (WHO) have shown, that there has been a global increase in the production, transportation and consumption of opioids, mainly heroin. The worldwide production of heroin has more than doubled or even tripled since 1985. Evidence from national surveys and other data sources suggests that the prevalence of heroin use in general populations is relatively low. Globally, it is estimated that 13.5 million people take opioids, including 9.2 million who use heroin. In 2002, UNODC estimated a total of 185 million users of illegal drugs and 1.3 billion smokers and 2 billion alcohol users (UNODC, 2003). However, in many countries (notably those in Europe), the majority of people seeking treatment are primarily addicted to opiates.

Some stipulate that opioid dependence is a condition in which the neurochemistry and receptor sites of the brain change, causing the need for drugs to become as biologically driven as the need to eat or breathe. Although not everybody agrees with these views, it is generally accepted that opiate addiction is a chronic relapsing condition, which is difficult to control due to compulsive drug use and craving, leading to drug seeking and repetitive use, even in the face of severe negative health and social consequences. It is true that not all cases of addiction are chronic and some who meet diagnostic criteria for substance dependence recover completely without treatment. However, many of those who develop addiction disorders suffer multiple relapses following treatments and are thought to retain a continuing vulnerability to relapse for years or perhaps a lifetime (WHO, 2004; UNODC, 2003).

The use of heroin in particular is causing widespread health and social problems in many countries. In Europe, heroin injectors who regularly consume large amounts of different drugs, face a risk of death, which may be 20 to 30 times higher than non-drug users in the same age group. Since heroin is commonly injected, the health risks including that of the transmission of HIV and hepatitis are substantial (WHO, 2002).

At this moment there is a variety of treatment options available, ranging from drug-free residential to outpatient pharmacologically assisted treatment, including maintenance and detoxification regimes. Scientific evidence has shown that opioid addiction is best treated by a combination of continuing outpatient therapy, medication and monitoring, with the goal of retaining patients in treatment to maximise and maintain the full benefits of treatment (UNODC, 2003). Substitution treatment has proven the most effective form of treatment for the largest proportion of people with an opioid dependence (WHO, 2004).
1.2. WHAT IS SUBSTITUTION TREATMENT?

Substitution treatment is a form of medical care for opioid dependence using prescribed opioid agonists, which have similar or identical properties to heroin and morphine on the brain and which alleviate withdrawal symptoms and reduce the craving for illicit opiates. Examples of opiate agonists are methadone, diamorphine and morphine.

Antagonists on the other hand, are also used in treating opiate dependence. They occupy the same receptor sites in the brain as opiates and therefore block the effects of other opiates. Antagonists reduce but do not eliminate craving. Due to the fact that antagonists have a higher affinity to the receptor than the agonist, antagonists displace the opiates from the binding site. This results in an immediate onset of opiate withdrawal. If someone has undergone detoxification and has started a medication of an opiate-antagonist, additional intake of opiates results in no effect as the antagonist already occupies the receptors. Naltrexone is the most commonly used opioid antagonist. Buprenorphine is a partial agonist but has some antagonist properties.

While the medication most commonly used for opiate dependence is the agonist methadone, the partial agonist buprenorphine is increasingly being used for this purpose.

Figure 1: Opiate effects of full agonists, partial agonists and antagonist

Source: Induction into buprenorphine treatment. Dr Nicholas Lintzeris. Presentation at Conference Safer options, Hamburg 19-21 April 2005

Substitution maintenance therapy is one of the most effective types of pharmacological therapy of opioid dependence. There is consistent evidence from numerous controlled trials, large longitudinal studies and programme evaluations, that substitution maintenance treatment for opioid dependence is associated with generally substantial reductions in illicit opioid use, criminal activity, deaths due to overdose, and behaviours with a high risk of HIV transmission (WHO, 2004).
Substitution treatment is generally considered for people who find it difficult to stop their drug use and to complete withdrawal. The value of substitution treatment lies in the opportunity it provides for dependent drug users to reduce their exposure to risk behaviours and to stabilise in health and social terms before the problem of opioid dependence is addressed. It is desirable for substitution drugs to have a longer duration of action, or half-life, than the drug they are replacing in order to delay the emergence of withdrawal and reduce the frequency of administration. This allows the person to focus on normal life activities without the need to obtain and administer drugs. Scientific evidence suggests that substitution treatment can help improve the physical, social and psychological well-being of the patients as well as reduce infectious diseases, drug-related deaths and criminality (WHO, 2004; UNODC, 2003; Ward, 1999; Marsch, 1998).

What are the objectives of substitution treatment?

Although the long-term goal of treatment may be to help people to stop using drugs altogether, the short-term aims of substitution treatment are based on the concepts of public health and harm reduction, to improve the physical, mental and social wellbeing of the patient.

The aims of substitution treatment can be summarised as to:

- Assist the patient to remain healthy, until, with the appropriate care and support, they can achieve a drug-free life
- Reduce the use of illicit or non-prescribed drugs by the individual
- Deal with problems related to drug misuse
- Reduce the dangers associated with drug misuse, particularly the risk of HIV, hepatitis B & C, and other blood-borne infections from injecting and sharing injecting paraphernalia
- Reduce the duration of episodes of drug misuse
- Reduce the chances of future relapse to drug misuse
- Reduce the need for criminal activity to finance drug misuse
- Stabilise the patient where appropriate on a substitute medication to alleviate withdrawal symptoms
- Improve physical and mental health and overall personal, social and family functioning.

Types of treatment

Apart from the different medications that can be prescribed, treatment programmes also vary in duration, dosage and scheme. Although there is much evidence that substitution treatment, in particular methadone is more effective when higher dosages are prescribed on a long-term maintenance basis (WHO, 2004; Ward, 1999), many programmes still focus on short-term detoxification with decreasing dosages.

Historically, methadone maintenance therapy (MMT) was the earliest form and continues to be the most widely used form of opiate substitution (or replacement) therapy in the United States, Australia and Europe. In various countries, buprenorphine is now also prescribed on a maintenance basis. Both methadone and buprenorphine are also used in detoxification. Detoxification programmes provide supervised withdrawal from opiate dependence with a substitute medication (i.e. methadone or buprenorphine and often combined with other medications in the process) in order to minimise the severity of withdrawal symptoms. After being totally switched to the substitute medication, the dose is gradually reduced.

Relapse following detoxification alone is extremely common, and therefore detoxification rarely constitutes an adequate treatment of substance dependence on its own. Simple detoxification or stopping opioid use is often insufficient: a therapeutic process is required. Detoxification, however, is a first step
for many forms of longer-term abstinence-based treatment. Both detoxification with subsequent abstinence-oriented treatment as well as substitution maintenance treatment are essential components of an effective treatment system for people with opioid dependence (WHO, 2004).

Because of the high relapse rate in opioid dependence, detoxification is generally seen as a stage in the process and not as a stand-alone treatment modality. Recent research has shown high mortality rates amongst those detoxified (Ford, 2005, Strang et al, 2003). The majority of patients has a poor prognosis for withdrawal and should not be encouraged or be imposed to cease treatment. Therefore, patients who do not meet key clinical criteria for detoxification are likely to have poor outcomes regardless of how withdrawal is attempted (Lenne et al, 2001, WHO, 2004).

In some countries substitution treatment is provided by specialist centres for drug dependence, in others by the general system of primary care and general practitioners and in other countries again by a combination of the two. Pharmacological treatment in fact should always be part of a wider comprehensive treatment plan, addressing both somatic and psychosocial issues.

**Epidemiology of treatment**

It is difficult to estimate the numbers of people with opiate dependence across the world and the percentage of those who are in treatment. In some countries, in particular in Western Europe and the US and Australia, monitoring systems provide us with estimates and these figures are not always comparable and have to be interpreted with caution.

Across the world, substitution treatment has a long and varied history in different countries and continents, where changes in medical opinion and legislation have led to developments and changes in prescribing practices. In 1999, it was estimated that over half a million people worldwide were in maintenance treatment, predominantly with methadone (approximately 300,000 in Europe, 200,000 in the United States and 20,000 in Australia) (Farrell, et al, 1999, Parrino, 1999). There are no exact numbers of persons in buprenorphine treatment worldwide, but based on the available information, it is estimated that at least 200,000 people receive buprenorphine under the trade name Subutex. Buprenorphine is also manufactured by other companies, e.g. by Rusan in India, but estimates of the use of their products in this indication are not available. There are many countries in the world where different forms of drug treatment are provided. Although the bulk of substitution treatment to date is still administered in Europe, North America and Australia, there is also a trend towards the provision of substitution treatment in Central and Eastern Europe and in Southeast Asia and other parts of Asia.

**Substitute medications**

The majority of opioid substitution in the world is still delivered in the form of oral methadone, but buprenorphine is being increasingly prescribed in various countries with success, and is the second most widely prescribed opioid substitute for the management of opioid dependence. The evidence base for methadone is still much larger than the one for other substitute medications. Methadone has proven to be effective in maintenance treatment in retaining people in treatment, in preventing the use of illegal opioids, in preventing the spread of HIV/AIDS and other infectious diseases, in improving the mental, physical and social well-being of the patient and his family. Detailed information on methadone is described in former publications of Euro-Methwork (the European Methadone Guidelines, the Training Manual Key Aspects of Substitution Treatment for Opiate Dependence) and other recommended publications listed in appendix 1.

In the last few years clinical practice and the results of research have demonstrated that buprenorphine is an effective substitute medication in both maintenance and detoxification treatment for opiate dependence.
In Europe, out of the 30 countries where substitution treatment is available, all have methadone and 17 countries also provide buprenorphine. Since its registration in the US and Australia, buprenorphine is quickly becoming popular. In several countries buprenorphine is not bound to such strict regulations as methadone. Reasons for this are partly historical and due to the general fear of opiates as prescribed medication. The main reason why buprenorphine has been introduced without these strict regulations is due to its more favourable safety profile with reduced risk of overdose. In the US, like in France, methadone maintenance is provided in specialized centres and as a consequence can not meet the general demand (in 2000 an estimated 800-1000.000 individuals were addicted to heroin in the US, while only around 200.000 were in treatment). Buprenorphine, on the other hand, can be prescribed in office-based settings or in primary care facilities, lowering the threshold for many practitioners and patients in these countries. In Southeast Asia, substitution treatment is much less available. China has several small-scale pilot programmes with both medications (and planning to scale up at a very large scale in the next few years), Thailand provides methadone maintenance, and Hong Kong has both. India has buprenorphine and so do Malaysia, Indonesia and Singapore. Worldwide, methadone is used in 89 countries and in the year 2003 approximately 18 tons were consumed (INCB, 2004). Buprenorphine under the brand name Subutex® has been registered and approved as medication for the treatment of opioid dependence in 38 countries and actually launched in 30 countries (Chris Chapleo, personal communication).

1.3. BUPRENORPHINE

Introduction

Buprenorphine is a partial agonist (low intrinsic opiate activity) with high affinity to µ opiate receptors, and antagonist at κ opiate receptors. Buprenorphine produces opiate-like effects, prevents withdrawal, reduces craving and reduces effects of other opiates, without producing a strong euphoria. It has a long duration of action and has a mild withdrawal profile. Side effects of buprenorphine are similar to other opioids, but with less sedation and less respiratory depression.

Buprenorphine comes in sublingual tablet preparations, which is soluble in saliva and water, hence also injectable. Subutex® is the registered medication, produced by Reckitt Benckiser Pharmaceuticals Inc., which has licensed Schering-Plough to market the product in Europe and other regions.

History

Buprenorphine was developed in the 1970s in an attempt to find a 'non addictive' analgesic and was first registered and made available in the UK under the brand name Temgesic® in 1978. In the 1980's it was first reported that buprenorphine was being injected and 'abused' by heroin users. Phase II clinical research was conducted by the mid 1980s with heroin users and Phase III randomised trials in the late 1980s and early 1990s. The sublingual tablet Subutex® was developed in the mid 1990s and first registered for the treatment of opiate dependence in France in 1995, followed by the UK in 1999, Germany and Australia in 2000.

Pharmacologically, buprenorphine is a partial agonist but has some antagonist properties. As a partial opiate agonist it blocks withdrawal and craving without producing a strong euphoria. Partial agonists exhibit ceiling effects, which means that increasing the dose only has effects to a certain level. The chemical name of buprenorphine is 17-(Cyclopropylmethyl)-alpha-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-alpha-methyl-6,14-ethenomorphinan-7-methanol.

Subutex® (buprenorphine hydrochloride) is a sublingual tablet and is available in 0.4 mg, 2 mg and 8 mg strengths. Suboxone® (buprenorphine hydrochloride and naloxone hydrochloride) is also a sublingual
Summary of the characteristics of buprenorphine:

- A partial opiate agonist with high affinity for opiate receptors
- Opiate-like effects & side-effects
- Prevents withdrawal
- Reduces craving
- Reduces effects of other opiates
- A safer medication (e.g. in overdose) than full opiate agonists
- Long duration of action
- Mild withdrawal profile
- Sublingual tablet preparations, because not orally active

Scientific evidence

The bulk of the scientific evidence supporting the effectiveness of substitution treatment as a treatment for opioid dependence is based on studies on methadone treatment. The evidence base for buprenorphine is much smaller as a result of its much shorter history. While methadone has been used in the medical treatment of opioid dependence since the 1960s, buprenorphine was only first registered and adopted for the same purpose in 1995. However, in the last few years the evidence base of buprenorphine as a medication for the medical treatment of opioid dependence has increased considerably. Both individual studies, including Randomised Clinical Trials (RCTs) and Controlled Clinical Trials (CCTs) and naturalistic uncontrolled studies have been carried out as well as reviews and statistical meta-analyses. In addition, guidelines or guidance documents on buprenorphine have been published in various countries, including the US, Australia and the UK.

When reviewing the available evidence, generally most weight is given to systematic reviews such as the meta-analyses of the Cochrane Collaboration. The Cochrane Collaboration has conducted five systematic reviews and meta-analyses with regard to substitution treatment, two of which are specific to buprenorphine, one on maintenance and the other on detoxification with buprenorphine, compared to other medications. Most studies and reviews have looked at retention in treatment and heroin consumption as outcome indicators. Some studies have made a comparison with methadone and or naltrexone (Cochrane Library, Issue 1, 2005).

Mattick et al (2005) reviewed the relative effectiveness of buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. The authors concluded that buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses and very high doses. However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo. When compared with methadone, buprenorphine given in flexible doses appeared statistically significantly less effective in retaining patient in treatment. Low dose...
buprenorphine is not superior to low dose methadone. High dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for high dose buprenorphine over high dose methadone in retention and high dose buprenorphine was inferior in suppression of heroin use. The authors concluded that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages.

However, the review is based on studies, which adopted slow and/or low-dose induction protocols based on methadone treatment, which may not have been recommended for buprenorphine and may therefore have influenced these outcomes (Mattick et al, 2003; Gerra, 2004). Furthermore, the effectiveness of high dose methadone (80-120mg) compared with high dose buprenorphine (16-32mg) was not examined (RCGP, 2004). Various studies come to a similar conclusion and call for further research to determine if buprenorphine is more effective than methadone in particular settings or in particular subgroups of patients (Barnett et al, 2001; Giacomuzzi et al, 2003).

Gowing et al (2005) looked at buprenorphine for the management of opioid withdrawal, or detoxification and concluded ....

For groups treated with buprenorphine, withdrawal severity was less than that in groups treated with clonidine; peak severity was similar to those treated with methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. The authors conclude on the basis of the meta-analysis that buprenorphine is more effective than clonidine for the management of opioid withdrawal. There appears to be no significant difference between buprenorphine and methadone in terms of completion of treatment, but withdrawal symptoms may resolve more quickly with buprenorphine.

Other Cochrane reviews looked at pharmacological treatment in general and in relation to psychosocial treatment. Amato et al (2005) reviewed psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. The conclusion is that ...

psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, results at follow-up and compliance. Although a treatment, like detoxification, that exclusively attenuates the severity of opiate withdrawal symptoms can be at best partially effective for a chronic relapsing disorder like opiate dependence, this type of treatment is an essential step prior to longer-term drug-free treatment and it is desirable to develop adjunct psychosocial approaches that might make detoxification more effective. Limitations to this review are imposed by the heterogeneity of the assessment of outcomes. Because of lack of detailed information no meta-analysis could be performed to analyse the results related to several outcomes.

A large number of studies have been conducted over the last decade and the overall conclusion is that there is a growing evidence base in combination with a growing experience in clinical practice showing the effectiveness of buprenorphine as a useful additional medication in the treatment of opioid dependence. It has proven to be a safe medication, effective in keeping patients in treatment and preventing the use of illegal opiates, but not more effective than methadone (Mattick et al 2004, Lintzeris & Ford, 2005, WHO, 2004, Barnett et al, 2001, RCGP, 2004). There seems to be a stronger evidence base for withdrawal treatment than for maintenance treatment, in particular for motivated patients who want to stop their opiate use (Gowing et al, 2005; WHO, 2004, Lintzeris et al, 2005, RCGP, 2004, Ford, 2005).
PART 2:
CRITICAL QUESTIONS EXAMINED
In this part, critical issues that were collected through our audit amongst experts in the field of substitution treatment will be discussed in three chapters: all questions and issues related to clinical practice in the first chapter and issues of a non-clinical nature in the second chapter. The last chapter includes some consumer perspectives.

2.1. CLINICAL ISSUES

How to decide which medication to use?

Today, both methadone and buprenorphine are proven effective medications for the substitution maintenance treatment of opioid dependence. Research is not conclusive in terms of whether methadone or buprenorphine is more effective or safer in special populations. Initially, it seemed that patients with certain characteristics (e.g. younger, those with concurrent pain, psychiatric co-morbidity) were more or less likely to benefit from one medication over the other, but recent research and broader experience has proven these assumptions to be unfounded. The conclusion to date is that there is insufficient evidence base to prioritise the use of either methadone or buprenorphine according to patient characteristics and further research is required.

Hence, the decision of which medication to use is made based on other factors, i.e. client and service provider preferences, previous positive or negative experiences, costs, risks of abuse, availability, pharmacological profiles, etc.

The choice between methadone and buprenorphine depends upon:

- Logistics
- Response to treatment
- Individual variation in absorption, metabolism, clearance of medication
- Side effects
- Consideration of concomitant medications
- Ease of withdrawal from medication
- Client (and clinician) expectancy and preference
- Ability to transfer from methadone
- Concern about greater stigma of methadone

Some patients will do well on methadone and others on buprenorphine. There is no reason to swap a patient who does well on methadone on to buprenorphine and vice versa.

Is induction more demanding?

An issue mentioned by various experts was the fact that induction does seem more demanding both for the patient and for the staff. However, this assumption seems to come especially from people with no or limited experience with prescribing buprenorphine. When a group of experts with experience in prescribing was asked about this, this assumption was proven unfounded.

Of course, buprenorphine is a new medication with different characteristics, which means that practitioners need to undergo training before starting to prescribe it. Whether this training is readily available to all practitioners remains to be seen and will differ from country to country. Because there is little if any risk of respiratory depression, buprenorphine does not need titration and a patient can be induced quickly, usually within a few days. Guidelines for clinical practice recommend the following:
An initial test dose to exclude significant precipitated withdrawal (2-4mg, if patient is not in opiate withdrawal, 8mg if patient is in moderate to severe opiate withdrawal), and then titration up to at least 8mg as the first day dose. Doses can be increased by as much as 8mg per day on subsequent days until stabilisation is achieved (Lintzeris, 2005). In some centres (in Germany in particular), loading doses up to 24mg (3 times 8mg) are given on the first day of treatment and reduced to 16mg (2 times 8mg) on the second day and 8mg on the third day. At this point, the correct dose needed to prevent withdrawal is derived and the individual dose is calculated (between 2-24mg). (Haemmig, 2005; Pollak, 2005).

One of the main issues that need attention during the induction phase is the risk that the patient may experience precipitated withdrawal. In the next paragraph this will be discussed further.

Induction onto buprenorphine may seem more demanding for the patient, as it requires them to experience the first withdrawal symptoms before starting the medication. We will discuss this more in detail in the next paragraph as well as in chapter 2.3. Consumer Perspectives.

**What about 'precipitated withdrawal'?**

A key challenge in the induction to buprenorphine is the so-called precipitated withdrawal, which may occur when the patient has recently used heroin, methadone or any other opioid. It is caused by the high affinity of buprenorphine displacing other opioids (e.g. heroin, methadone) from opioid receptors, but having less opioid activity (partial agonist). This rapid reduction in opiate effects can be experienced as precipitated withdrawal, typically occurring within 1 to 3 hours after the first buprenorphine dose, peaking in severity over the first 3 to 6 hours and then generally subsiding.

When sufficient time has passed between last consumption of opioid and induction of buprenorphine the risk of precipitated withdrawal is minimized. There are several indications mentioned in the literature, but in general this means that the patient must have some withdrawal and the longer one waits the easier the induction. This would be at least between 6 -12 hours after last heroin use and 24 - 48 after last methadone dose. Other factors influencing the occurrence of precipitated withdrawal include the amount of full agonists in the system, the size of the first buprenorphine dose (higher doses are more likely to displace full agonists), patient expectancy and concomitant drug use or medical conditions. Also, patients transferring from high methadone doses tend to be at greater risk of precipitated withdrawal (Lintzeris et al, 2005).

If it occurs, it is very important to reassure the patient and carer and explain that it is time limited. Symptomatic treatment can also be offered, such as lofexidine, or clonidine as appropriate, if withdrawal symptoms are severe. It is not recommended to prescribe more buprenorphine until the opiate withdrawal symptoms have settled (see: Ford and Lintzeris Guidance for the use of buprenorphine for the treatment of opioid dependence in primary care, appendix 1).

**Is there a 'most effective dose'?**

Several of our respondents have mentioned the limited evidence for clear dosage regimes. Partly because of the limited experience of both patients and prescribers, more research is needed to provide clear dose regime suggestions.

Obviously, an effective dose is individually defined, depending on patient characteristics and choice of treatment. In general, the literature suggests that although some people respond well to low doses such as 4-8mg of buprenorphine, doses between 12-24mg per day are associated with significantly less heroin
use, withdrawal, craving and greater blockade effects. Doses higher than 32mg do not seem to be effective (Lintzeris, 2005).

**Is dispensing more complicated?**

Buprenorphine has to be taken sublingually. The tablets can take 3-8 minutes to dissolve, which means an increased time of dispensing as compared to other forms of substitute medication. In practice it may be difficult for busy pharmacists or clinical staff to supervise patients until the tablets have completely dissolved. If the tablets are swallowed before they are dissolved, it will reduce the effect. In some countries (UK, France, Australia) tablets are crushed in order to facilitate and speed up dissolving. It is not clear what the effect of this practice is.

It is important for the patients to be informed about this and for the staff to ensure supervision of the intake of medication. In general, clinical practice includes supervised dispensing at the onset of treatment. If the patient seems to comply well and perform well on the medication, less stringent dispensing can be considered.

**What about dispensing less than daily?**

One of the major advantages of buprenorphine is that - because of its stronger and longer binding to the \æ-receptor - it has a long pharmacological half-life, hence the potential for less frequent dispensing. The maximum duration of action of buprenorphine is less than five days when five times the daily maintenance dose is provided (Petry et al, 2001). But more common is alternate daily and less frequent dispensing of once every three days, which has advantages for both the patient and the treatment provider, for example to manage the weekend. It can reduce the costs of treatment by reducing dispensing time and cost of staff as well as reduce the time lost to treatment compliance for the patient. In a study under naturalistic conditions in which patients and doctors could select the frequency of dispensing, approximately one third of patients required daily buprenorphine dispensing, one third chose alternate day dispensing and one third used regimens in which at least 3-day dose was administered each week (Lintzeris et al, 2005). Patients who prefer to come every day should be accommodated.

**Why should one shift a patient from methadone to buprenorphine?**

It goes without saying that a patient stable and happy on methadone should remain on it and should not be transferred onto another medication. However, there can be reasons to shift a patient from methadone to buprenorphine, which include:

- If the patient experiences difficulties with methadone (e.g. side effects, rapid metabolizers, other drug interactions)
- In case regulations do not allow take home dosages
- To facilitate detoxification, as it has been proven that withdrawal from buprenorphine is less severe than from pure agonists, such as methadone and heroin
- Socio-cultural motivation in countries where methadone is severely stigmatised
- If the patient requests it.

If there are reasons to change a patient from methadone to buprenorphine, it can be done without major problems or side effects for the patients. It is advised to bring the patient down to a methadone dose of around 40mg before commencing with buprenorphine in order to minimise the risk of severe precipitated withdrawal (Breen et al, 2003; Lintzeris, 2005).

Some problems can occur during this process. First, because the methadone dose needs to be brought down to approximately 40mg, this implies that a stable methadone patient may become destabilised.
Hence, under such circumstances it may be appropriate to conduct the transfer at a higher dose (e.g. between 40 to 80mg). This involves stopping methadone and delaying the initiation of buprenorphine until the patient experiences moderate features of withdrawal from methadone - usually between 24 to 72 hours (often 36 to 48 hrs).

Clinical experience indicates that it often takes several days (and up to 2 weeks) for a patient to feel comfortable on buprenorphine. If motivation is limited, a patient may relapse to heroin and/or drop out of treatment. A second problem may arise because patients on buprenorphine report that they feel 'clear- headed' again. Some clients do not like the effects of buprenorphine - or more specifically, the lack of methadone effects. Emotions, which may have been blocked by an agonist such as heroin or methadone, may return. Whilst for many patients this can be a welcome experience, for others it may be something that they are not prepared for and the suppression of emotions could even have been one of the reasons for continued opioid use. It is important that treatment providers address this.

It is important that clients who attempt transferring to another medication should have the possibility to transfer back to their first medication should they encounter difficulties with the new regime. This assurance may be important in minimising treatment drop out.

Patients who use other substances with their methadone and shift to buprenorphine may be at risk of overdose. Although buprenorphine on its own is associated with a smaller risk of overdose compared to methadone because of the limited respiratory depression and is better tolerated by non-dependent people, patients who use benzodiazepines and/or other depressant drugs (either prescribed or from the black-market) are at risk of overdose.

**Is it true that buprenorphine is more effective for detoxification than for maintenance?**

Buprenorphine can both be used to detoxify patients as well as to maintain them. In the detoxification process, an appropriate reduction of the dose will help the patient to experience minimal withdrawal. Because of its strong and long binding to the opiate receptors, it can in principle even be reduced quite abruptly. Several studies have demonstrated that withdrawal from buprenorphine is effective and, although there is little objective evidence, patients seem to experience less severe withdrawal symptoms than from methadone (Gowing et al, 2005; Lintzeris, 2005; Ford, 2005). However, many aspects of treatment protocol and relative effectiveness need to be investigated further in order to determine the most effective way of using buprenorphine to manage opioid withdrawal (Gowing et al, 2005).

One needs to consider however in general that relapse following detoxification is extremely common, and therefore detoxification rarely constitutes an adequate treatment of substance dependence on its own. Detoxification is generally seen as a stage in the process and not as a stand-alone treatment modality and should in any case be supported by psychosocial interventions. Furthermore, recent research has shown high mortality rates amongst those detoxified (Ford, 2005; Strang et al, 2003). The majority of patients has a poor prognosis for withdrawal and should not be encouraged or coerced to cease treatment. Therefore, patients who do not meet key clinical criteria for detoxification are likely to have poor outcomes regardless of how withdrawal is attempted (Lenne et al, 2001; WHO, 2004).

In practice, some clinicians prefer to use buprenorphine only for detoxification, since they find it too expensive to use on a maintenance base. The costs will be further discussed in 2.2. Although the evidence base for detoxification compared to longer treatment approaches such as maintenance is not encouraging, it is nevertheless a popular treatment approach for many individuals who do not, for whatever reasons, want to enter longer-term programmes. As such, the popularity of buprenorphine for detoxification is not surprising. One of the advantages of the use of buprenorphine as a detoxification agent is that programmes can more easily be transferred into longer-term maintenance programmes.
than is possible with other detoxification approaches utilising symptomatic medications, methadone or other opioids (e.g. codeine, dihydrocodeine) (Lintzeris et al 2002). Here we should note, that if a patient is forced into short detoxification, the chances of success are limited (see Part 1 ‘types of treatment’).

**Indications and contra-indications?**

Although this is not the context to provide clinical guidelines some issues regarding indications and contra-indications that have been mentioned in the literature and by experts will nevertheless be addressed.

When buprenorphine was first introduced, it was believed that it was especially useful for young patients and for detoxification. With a longer clinical experience available today, this no longer stands. When properly dosed, buprenorphine can be very useful in maintenance treatment and long-term heroin users can benefit from it as well. In fact, as stated earlier, more evidence is needed to determine the relative effectiveness of buprenorphine as compared to other medications for specific settings and sub-populations.

One of the major benefits of substitution maintenance treatment in general is the prevention of infection with blood borne viruses, particularly HIV, as well as enabling patients with opioid dependence to receive and adhere to anti-retroviral treatment (ART) and HAART (highly effective ART). As far as is known from the literature there are no interactions between buprenorphine and medications for HIV or HCV, whilst there is some evidence that methadone may result in Zidovudine toxicity or may suppress T cells (CD4), needed to fight HIV-infection (Forum for Collaborative HIV Research, 2005).

There is some evidence that buprenorphine has a potential utility in depression and pain management (Gerra, 2004; Ling 2005), but further research is needed.

In general, mixing opiates with benzodiazepines, alcohol, and/or anti-depressants is risky and may lead to overdose. In France, 80% of the buprenorphine-related deaths are related to benzodiazepines (Kintz et al, 2002). However, adequate dosing of buprenorphine can reduce this risk as was shown in France, where adequate dosing had the effect of a 10-60% reduction of benzodiazepine use (De Ducla et al, 2000).

Patients, who are motivated to give up the use of illicit substances, might benefit more from buprenorphine, because it blocks the effect of ‘on top’ heroin and has little risk for overdose (see Part 1 and 2.1.).

**Pregnancy and buprenorphine?**

Heroin dependence can lead to pregnant women neglecting their medical, nutritional and social well-being. This may in part lead to preterm birth and low birth weight of neonates. Substitution maintenance therapies are well established for use in pregnancy and result in general improvements in physical and psychosocial well-being of the mothers and better outcomes for their babies. Both methadone and buprenorphine are safe medications for the foetus, although buprenorphine appears to be associated with a similar or lower incidence of neonatal withdrawal syndrome compared to methadone (Fischer et al, 2000; Johnson et al, 2003; WHO, 2004). Further research is needed on the long-term effects for the child whose mother used buprenorphine during pregnancy.

In general, pregnancies in opioid-dependent women are associated with high risk both for mother and for the child. Substitution maintenance treatment is recommended. If the woman is already on methadone treatment, the advice is that she should be kept on this; if she is using street heroin, she should be commenced on buprenorphine or methadone, based upon preferences of the patient and clinician and prior experiences with these medications (Fischer et al, 2000).
The fact is that a large number of pregnancies among opioid dependent women are not planned and it is therefore recommended that providing medical treatment to opioid dependent women should always include the assessment and provision of other psychosocial and medical interventions, including the possibility of prescribing contraception. Other issues often prevalent amongst pregnant opioid dependent women, which need to be addressed include:

- Housing, financial problems
- Nicotine addiction (perhaps the main factor for reduced birth weight)
- Anxiety disorder (with concomitant benzodiazepines misuse)
- An addicted partner.

**Is it safer in overdose?**

Partial agonists, such as buprenorphine, usually have greater safety profiles than full agonists (such as heroin or morphine). Because of the ceiling effects they are less likely to cause respiratory depression, the major toxic effect of opiate drugs, in comparison to full agonists. This will translate into a reduced chance of accidental or intentional overdose (NIDA, www.nida.nih.gov/Bupupdate.html)

This improved safety profile has been the major motive for countries such as France and the USA to register buprenorphine as a medication not bound to strict prescribing regulations as is the case for other opioids, including methadone. Even in the case of diversion, the risk for opioid naive people and for opioid users not in treatment is much reduced, and this is discussed further in the next paragraph.

However, the presumed safety profile for buprenorphine only holds when not taken with other drugs. When buprenorphine is used in combination with alcohol and/or benzodiazepines there is a major risk for an overdose situation.

**Is it true that there is a high prevalence of misuse of buprenorphine?**

Because of its opioid agonist properties, injecting of buprenorphine is reported to produce euphoria, i.e. typical opioid-like effects. There is evidence that some patients who receive take-home dosages administer their medication intravenously. Several studies from France, where buprenorphine has the longest treatment history and is most widely available, report the practice of buprenorphine injecting, both by people in treatment and by people not in treatment (Auriacombe, 2004). Sniffing crushed tablets with peak effect concentration is reported by patients in Germany (personal communication HG Meyer-Thompson, 2005)

There are several risks involved with injecting buprenorphine:

- Injecting with used needles and syringes, is associated with infectious diseases, in particular HIV and hepatitis, and systemic bacterial and fungal infections
- Buprenorphine comes in the form of sublingual tablets. Apart from the general risk of injection of crushed tablets with insoluble ingredients, it is not clear what the pharmacodynamic effects of this practice are besides the association with opiate rush effects
- When buprenorphine is misused in combination with other psychotropic substances, in particular alcohol and benzodiazepines, there is an increased risk of overdose.

Means to prevent the practice of diversion or injecting of own dose of buprenorphine include:

- Supervised dispensing of the medication
- Suboxone®.
What about Suboxone?

Suboxone® is a combination of naloxone and buprenorphine and was developed in order to prevent patients from taking the medication intravenously. As yet, Suboxone® is only available in Australia and the USA. In the USA, it has been approved by the FDA as a schedule III narcotic for the treatment of opioid dependence (like Subutex®). Methadone is a schedule II drug. This allows for Suboxone® to be used in office-based settings (primary care) with a maximum of 30 patients per prescribing physician. It is expected that the addition of naloxone should reduce Suboxone® tablets from being misused by injecting. Because of its recent history, there is not enough clinical experience to say anything conclusive about the effectiveness of this medication, except that the combination tablet appears to decrease but not eliminate abuse potential.
2.2. NON-CLINICAL ISSUES

What is an optimal treatment setting?

Seeking treatment is a major step for most drug dependent patients. It is important that the first contact with a patient who seeks help is encouraging, motivating and stimulating. The attitude of the treatment staff and the general atmosphere in the clinic play a crucial role in this respect; the patient should feel accepted and welcomed. It is of the utmost importance that the staff are well-trained and professional. It is vital that the induction phase is done properly according to the latest standards (4mg as first dose, followed by another 4mg on that same day and completed within three days with a daily dose. The most usual range is between 12-24mg daily. See: Guidelines RCGP, 2004).

At intake, patients should be informed about precipitated withdrawal and action should be taken to both avoid it and limit the effect (see part 2.1.). In terms of classical conditioning, the precipitated withdrawal could create the opposite of what one would wish in a first contact with a drug dependent patient: a nervous, anxious patient is told to wait until withdrawal symptoms occur. This is perhaps not an ideal way to start treatment, since some patients might be reminded of punitive measures in the past or hear the echo of moralistic voices 'you have to suffer for this!!' In practice, however, precipitated withdrawal can usually be avoided for the vast majority of patients and is manageable. It is important to provide information to the patient about what to expect, and to engage the patient in the induction process, i.e. that a possible precipitated withdrawal is only temporarily and that he will benefit from this medication in the longer term. Other information to the patients could include:

- You need to take your first dose of buprenorphine approximately 6-12 hours after last heroin use and 24-48 hours after last methadone dose
- Let your buprenorphine tablet dissolve under the tongue. If you swallow it, it doesn't work as well
- If you want to continue using heroin then buprenorphine is not the drug for you.

Can buprenorphine play a role in harm reduction oriented settings?

When looking at the concept of harm reduction, it should be made clear that substitution treatment in general assists opioid dependent patients in reducing the harm they cause to themselves and others. This is also the case with treatment using buprenorphine. Research clearly indicates that patients on buprenorphine no longer need to use illicit substances and thus can refrain from injecting with contaminated needles; they no longer need to use contaminated street drugs; they no longer need to be involved in criminal activities to obtain money to support their drug habit, et cetera. So, when the question is posed 'Does buprenorphine reduce drug related harm' the answer is positive.

However, when the question is more focused on the use of buprenorphine in harm reduction settings, the answer is more complicated. Many drug addicts have developed a system of 'self-management' of their addiction. This means that they have a range of possibilities and options to obtain drugs and prevent withdrawal. Getting a prescription is one of the options. Such patients would not comply with treatment and alternate the use of prescribed pharmaceutical drugs with the use of illicit drugs. Such patients would attend user-friendly treatment programmes, user rooms and needle exchange schemes. Although staff of these facilities may wish to see their patients/clients abstaining from the use of illicit substances, they accept the fact that opioid dependence can be a chronic relapsing condition and that patients/clients continue to use illicit substances. Discharge from the programme can have negative consequences, including harmful behaviour, HIV-infection/transmission through needle sharing, criminal behaviour, overdose etc. As patients in these particular Harm Reduction programmes continue the use of illicit substances, staff and patient would probably choose an agonist like methadone rather than a
substance with a partial agonist effect. For this group of patients the 'clear-headed' effect on buprenorphine might be another reason for not choosing this medication.
An important component of the harm reduction paradigm is the respect for individual choices. This also implies that patients should have an optimal choice in treatment modalities, which they think are best for them. It goes without saying, that a heroin dependent person should also have a choice between methadone and buprenorphine. This means that both substances should be available and that proper treatment facilities should be available to deliver such treatment in a professional manner.

**Is there sufficient training?**

Many myths about buprenorphine (and also about methadone) are rooted in inappropriate use of the medication. Often the medication is inappropriately used because staff are insufficiently trained. For example, if induction is not properly carried out, a patient will drop out and decide 'buprenorphine does nothing for me'. If precipitated withdrawal is not handled properly, patients will say 'buprenorphine makes me sick'. If inappropriate doses are given, patients will say 'with buprenorphine I still have withdrawal symptoms'. When high doses of buprenorphine are prescribed and patients are allowed to take the medication without any supervision, it is possible that buprenorphine is injected and/or ends up on the black market, which would lead to the myth that 'all buprenorphine is injected, just another drug...'.

To guarantee optimal quality treatment and to prevent further myths, it is very important to provide independent training for all those who are working in drug treatment. It concerns both practitioners who are just beginning as well as those with more experience. For those who are just beginning to prescribe buprenorphine, the following items should be addressed:
- Induction
- Precipitated withdrawal
- Indications and contra-indications
- Dosing
- Diversion to the black market
- Patient information

For those with experience in prescribing buprenorphine, regular peer supervision/support groups should be available to share experience and discuss specific clinical issues, such as the use of buprenorphine in special patient groups and flexibility in dosing regime.

It is important as in any other field of medicine that training, which could be financed by the industry, is carried out by independent organisations and experts in the field.

**What could be the role of primary care and general practitioners?**

A number of countries have experience with general practitioners (GPs) providing drug treatment and in particular prescribing methadone and/or buprenorphine for opioid dependence. Although some may argue that primary care is not the best setting for this particular type of treatment, there are a number of advantages of including GPs in the treatment of drug dependence:
- GPs are crucial in the treatment of chronic conditions, such as hypertension and diabetes. In the management of another chronic condition, i.e. opioid dependence, GPs can play an important role as well.
- Receiving buprenorphine from a GP is less stigmatising than having to go to a specialised clinic. The patient is treated like other patients by his own family doctor. Often this is a very good start for taking distance from the drug scene.
- **It solves logistic problems** since specialised drug treatment centres often have limited capacity and thus work with a waiting list. Whilst on a waiting list, patients might (a) continue harmful practices (including risks for HIV infection/transmission and overdose) and (b) lose motivation. From a public health point of view it is important to have as many drug addicts as possible receive medical treatment.
- Receiving a script from one's GP and collecting buprenorphine at the local pharmacy can create a **more flexible situation** for the patient then when he goes to a specialised clinic. Especially for patients who have (irregular) work, this will be a major advantage.
- Including GPs in the overall system to treat drug-dependent patients is **cost effective**. Generally, treating a drug dependent patient in a primary care setting is cheaper than treating him in a specialised centre.
- The GP sees the patient in his own **social context** and can address other psychosocial and **medical issues**, such as prescribing contraception.

However, there are also possible disadvantages, such as:
- A GP may not be as well equipped to manage complicated situations such as poly-drug use, psychiatric co-morbidity and manipulating behaviour as sometimes displayed by drug addicts.
- In situations without supervised dispensing some patients may use take home doses inappropriately (either swallow it too quickly, inject or divert it); in specialised services with supervised dispensing of the medication this risk will be smaller.
- GPs tend to have a high workload and with limited training they are frightened by the prospect of getting involved in this area of work.
- Some drug dependent patients may prefer not to go to their own GP because of the myth that the GP will give this information to members of their families.

In general, we believe that GPs/Primary Care centres have an important role in drug treatment. Collaboration between specialised centres and GPs/primary care centres is important, where drug treatment clinics focus on the more complicated and 'difficult' patients and GPs take care of the more stable patients.

**Why are regulations stricter for methadone than for buprenorphine?**

In most countries, methadone prescription is surrounded by complex administrative procedures, which means that only specialised centres or doctors with a special profile can prescribe methadone. In particular, in France and the USA, buprenorphine is more available because doctors in primary care can prescribe it.

Differences in strictness of the regulation are primarily due to the safety profile of buprenorphine. Buprenorphine alone produces less respiratory depression than methadone and therefore the risk of overdose is reduced. Only when buprenorphine is used in combination with alcohol or benzodiazepines, this can lead to an overdose. In the USA, buprenorphine has been classified as a Schedule III medication, while methadone is a Schedule II medication.

Medical doctors should decide which medication is best for which patients. However, in the field of addiction, this is not always the case. Decisions about medication, treatment regime and even the dosage are often influenced by interference of managers, policy makers and politicians (Dutch Medical Inspection, 2005). In many countries, methadone has received the image of 'another opiate', where prescribing doctors are almost equal to 'drug dealers in a white coat'. Accepting maintenance treatment also means that one accepts that drug addiction is a chronic condition. Many politicians and policy makers do not like this idea, especially because of the financial implications. These are some of the reasons why buprenorphine has a much more positive image among politicians and policy makers. Buprenorphine can be used in a detoxification process, patients are clear-headed and if abuse takes
place, it is less dangerous than the abuse of methadone. In general, one can say that it is good that there is now a less stigmatising medication for the treatment of opioid dependence. However, this should not be the main reason to prescribe it. It is still up to the doctor and his patient to see which medication serves a particular patient best, independent of political reasons.

Inappropriate prescribing, for example as reported in the Czech Republic (Jiri Richter, personal communication), where some GPs are said to give out buprenorphine scripts for up to two months, can result in large quantities of buprenorphine on the black market. This could be a reason for policymakers to develop more strict regulations for prescribing. The industry has anticipated this by developing Suboxone®, which works as buprenorphine when used sublingual, but results in acute withdrawal symptoms when injected by opioid dependent individuals/subjects (because of the addition of naloxone, see chapter 2.1.).

Regulations regarding driving vary from country to country. Research indicates that patients who are on a stable dose of buprenorphine (or methadone) and comply with their treatment are fit to drive a car. If countries have strict laws regarding the use of methadone and driving (as is the case in Italy) patients may prefer to use buprenorphine in order to be able to continue driving.

Is Buprenorphine too expensive?

Probably the comment most often reported by our respondents is the fact that buprenorphine is too expensive. Before considering this question, it is important to remember that treatment is always much more cost-effective than no treatment or than criminal justice interventions. Data from the UK indicate that with each pound invested in treatment, three pounds are saved on costs to the criminal justice system (Gossop et al., 1998).

Furthermore, at the beginning of buprenorphine prescription, staff need to give more attention to the patients compared to methadone. During treatment supervised dispensing of buprenorphine (because of the slower process of dissolving sublingual tablets) requires more staff time than supervised methadone. However, buprenorphine can be taken twice or thrice a week, while methadone should be taken once a day. So, in the long term, patients receiving buprenorphine might need less attention in terms of supervised consumption.

There are several ways, albeit difficult to actually carry out, to calculate treatment costs and several studies have looked at these aspects in the past few years. The review of Lintzeris and Ford (2005) summarises this as follows. In the UK, the costs of the medication and dispensing of buprenorphine is calculated between 1.5 and 3.4 times more expensive than for methadone, depending on the doses used and dispensing arrangements. As already mentioned above, buprenorphine can be dispensed on a less than daily basis, which has a great impact on the costs of treatment. Another way of calculating treatment costs is to consider the fact that medication is only one component of total costs of maintenance treatment. When overall comprehensive treatment costs are calculated, including staff, overhead and other services, the total cost difference between buprenorphine treatment and methadone treatment are less impressive (Lintzeris, 2005).

We would argue that this way of calculating costs may be suitable in countries like Australia, the USA and most of Western Europe. However, from a public health perspective, in particular in resource-poor settings where treatment costs will be of a different nature, it is important to treat as many people as possible within a given budget. In order to create a situation where doctors and patients can make a proper decision on whether to use methadone or buprenorphine, the price of the substance should not be a barrier. It is yet unclear what will happen when buprenorphine becomes available as a generic medication. Will this bring the price down as we have seen with anti-retroviral medication for HIV treatment?
Can one work with the industry and remain independent?

One of the comments we received during the audit was the question whether we should work with the industry and whether we would be able to keep our neutrality. In the introduction we already briefly discussed this issue. In the following paragraph we further elaborate on this.

First, we would like to give an example of how an international organisation, i.e. the UNODC (United Nations Office on Drugs and Crime), has been put under pressure by its single largest donor, the United States of America. In 2003 and 2004, Mr. Costa, director of the UNODC, expressed support for positive changes in the Russian criminal code, expansion of syringe exchange in countries facing injection driven HIV epidemics and other measures to reduce drug-related harm. In March 2004, the UN (including UNODC) published a number of policy briefing documents. One was on the provision of sterile injecting equipment, which clearly recommended the implementation of needle and syringe exchange programmes to curb the spread of HIV among drug injectors. On November 10, 2004, Mr. Costa, director of the UNODC met with Mr. Robert Charles, Assistant Secretary for International Narcotics and Law Enforcement Affairs U.S. After this meeting, Mr. Costa wrote a letter to Mr. Charles in which he pledged to review all UNODC electronic and printed documents for references to "harm reduction", remove those references and to be "even more vigilant in the future". The change of Mr. Costa's position seems an illustration on how a donor puts pressure on an (large international) organisation and succeeds in bringing about changes in policy.

Further to our statements in the introduction with regard to the role of the pharmaceutical industry we can see the following: it goes without saying that it is their business to sell medications and make profit. At the same time, it is in their interest that a medication has a good 'image' and that it is prescribed properly. Research and training are therefore important tools. These days, many countries have regulations and a code of conduct for pharmaceutical companies. Such measures restrict gifts and other rewards that pharmaceutical manufacturers can give to doctors and insurance companies to encourage prescribing particular drugs. In our case, we can state that we have had no specific pressure regarding the contents of this booklet other than a clear agreement that we would provide a good quality product.

Why such an aggressive campaign?

Some experts have suggested that the industry is campaigning too aggressively for the adoption of buprenorphine, while this was never done for methadone. This can be explained by the fact that methadone is not a brand, but a generic product and therefore methadone has always been produced by smaller companies or by in-house pharmacists, who made only low levels of financial gain from this medication.

When Subutex® was marketed in France, many experts in the drug field were surprised with the actions of the pharmaceutical companies, such as subsidising conferences and paying for research projects, because this was a new experience for most in the addictions field, despite being commonplace in other areas of medicine. This may in fact explain why in the beginning, many experts have been sceptical about buprenorphine.
2.3. CONSUMER PERSPECTIVES

This part looks at buprenorphine from the patient's perspective. Consumers from the UK based Alliance2 have provided us with some of their ideas, fears and experiences.

Although buprenorphine is still relatively unknown in some parts of the European Union, it has certainly attracted interest amongst patients where it has been introduced. The nature of buprenorphine (the fact that it is a partial agonist) has both excited and frightened prospective patients seeking treatment for opiate dependence. For those who have not found methadone helpful, buprenorphine represents a hope. But for those who are doing well on methadone, or who want to return to it, buprenorphine could be seen as a possible threat. Such negative feelings are minimised in a treatment setting where information is easily available, and treatment decisions are made with the active consent of the patient. There may be situations in which the clinical decision is taken to use buprenorphine but the patient is not happy. It helps a lot to give such patients reassurance that they can return to full agonist alternatives if buprenorphine does not help them.

To people outside the treatment field, there may appear to be little difference between the two medications as both are licensed for the treatment of opiate dependence. Whilst there are certainly similarities between methadone and buprenorphine, there are also some differences. It is therefore important that patients get accurate information about all the different treatments so that they can take an active role in determining the treatment that is best for them.

Subjective effects

The differences between the two medications that patients seem to experience have to do with the subjective effect of the drugs and the way in which they are taken. These subjective differences are summarised as follows.

Buprenorphine appears:
- To provide less of a perception of having taken a medication stimulating the opiate receptors in comparison to methadone (clear headedness)
- To be less unpleasant when withdrawing than other opiates
- To block heroin use much more effectively than methadone, which some patients seeking abstinence may value.
- To have less stigma associated with it compared to methadone

And these are reflected in the three specific issues that tend to interest patients particularly about buprenorphine:
- Its reputation as a faster and less uncomfortable way of withdrawing from heroin
- Its ability to precipitate an acute withdrawal syndrome in people physically dependent on opiates
- The fact that it blocks the effect of heroin more successfully than methadone.

An alternative to methadone?

For some patients, the fact that buprenorphine is not methadone, but something different, is an important factor. Some patients on methadone and compliant with its use, have not felt “satisfied” by methadone. This may be a good indication for seeing if buprenorphine might make a more satisfactory medication. However, it is important to bear in mind that sometimes patients are unhappy because of poor matching of methadone dose to patients, as well as the often daily monitoring that is still compulsory in some methadone programmes.
In situations where the dissatisfaction with methadone relates to excessive sedation, then buprenorphine with its much lower number of reports of such side effects may be helpful. Conversely, some patients value that sensation in particular and these patients may do better on methadone.

**A more demanding induction?**

Buprenorphine treatment requires a slightly more demanding induction for patients because of the need to be in withdrawal at the time of the first dose. There can also be a short period of discomfort as the body gets used to the drug.

**Clear head?**

Some patients on buprenorphine report that they have a 'clearer-head' when taking buprenorphine compared to methadone, although there is no objective evidence for this. Emotions and unpleasant feelings, which might have been blocked by full agonists such as heroin or methadone, may be more apparent to the patient. For some, this may be a welcome experience. For others however, it can be something for which they are unprepared. The blunting of painful feelings might have been one of the reasons for continued opioid use. If patients are not prepared for this possibility, they may be disappointed. This could ultimately lead to the patient dropping out of treatment with potentially harmful consequences.

**Less than daily dispensing**

One of the objectives of treatment is to make a patient more independent, not only of illicit substances such as heroin, but also to make the person more independent of helping agencies. This is a slow process, which needs to be done with care. When a patient is 'left on his own' too quickly, he may relapse. However, when a patient is treated with too many strings attached and having to obey too many rules, there is a risk of a patient becoming hostile. When everything is decided for the patient, they lose the ability to take initiatives for themselves and can become semi-institutionalised. It may be important at the onset of treatment for a patient to come every day to pick up his medication at the onset of treatment, but it is also a burden after a while that prevents patients from integrating into 'normal' society. In methadone programmes, the medication needs to be taken each 24 hours, so there are two options: the patient has to come each day for supervised intake or the patient gets a take-home dose. With buprenorphine, there are more options: the patient can come three times a week and take a two or even three day dose supply under supervision. This has advantages for both the patient as well as the treatment staff: there is much less risk that buprenorphine will be diverted to the black market and the patient has more freedom to do things which they feel are important to their process of recovery.

**Each patient is unique**

Each patient is unique in his response to the different medications. It is therefore difficult to generalise. It has also taken time for substantial numbers of people who are opiate-dependent to experience treatment with buprenorphine, so that people can start to share their experiences and sort out the exaggerations from the facts. However, now that buprenorphine has been in use for a few years in Europe, more and more insight is being gained into some of the reasons why some patients prefer it to methadone.

**Decision making process**

Once it has been decided that the patient is suitable for pharmacotherapy, some treatment services allow the patient to make the final decision about the medication that is used, having first provided the patient
with information about both medications. Other services, particularly when presented with users with less-entrenched dependencies, ask the patient to start with buprenorphine. Ideally, the patient and the medical team should make the decision jointly by working together, and agreeing a plan of action should the patient experience problems in settling on the medication.

The most effective treatment programmes are those that provide optimal doses of medication (usually between 60-120mg daily of methadone and 12-24mg of buprenorphine) as part of a comprehensive treatment programme. This should include regular reviews, general medical care and psychosocial support as required. They also validate maintenance as much as abstinence as a desirable treatment goal and ensure that their patients feel they play a meaningful role in determining their optimum dose.

Given the high morbidity and mortality seen in opioid dependence, the public health challenge is to deliver safe and effective medical treatment to as many patients as can benefit from it, whilst minimising the risk of diversion of prescribed medication.
A large number of studies have been conducted over the last decade and the overall conclusion is that there is a growing evidence base in combination with a growing experience in clinical practice showing the effectiveness of buprenorphine as a useful additional medication in the treatment of opioid dependence. It has proven to be a safe medication, effective in keeping patients in treatment and preventing the use of illegal opiates, but not more effective than methadone. There seems to be a stronger evidence base for withdrawal treatment than for maintenance treatment, in particular for motivated patients who want to stop their opiate use (Gowing et al, 2005; WHO, 2004, Lintzeris et al, 2005, RCGP, 2004, Ford, 2005).

Because buprenorphine is a partial agonist, the safety profile is better than that of full agonists such as methadone and heroin. Buprenorphine produces less respiratory depression than methadone and therefore the risk of overdose is reduced. However, when buprenorphine is used in combination with alcohol and/or benzodiazepines, one should be alert that an overdose may occur as for all opioids.

There are differences both of an objective and subjective nature between the two medications. The choice between one or the other is a decision which involves a number of factors and should ideally be taken after a thorough discussion of the pros and cons between doctor and patient. Other non-clinical factors, such as the availability and costs of the different medications, also influence the decision.

Buprenorphine can be abused. Data confirm that buprenorphine is sometimes injected when given as a take home dosage or bought on the black market. Injecting buprenorphine gives a light euphoric effect and is risky if it is injected with used equipment and/or injected in combination with the use of alcohol and/or benzodiazepines.

Myths about buprenorphine do exist and are often based on a lack of evidence, lack of information, poor clinical practice and/or abuse by patients. It is very important that these myths are addressed properly. Although much research has been conducted in the last decade, the evidence base for some issues is still missing or poor, such as for example for the adequate dose regimen for certain groups of patients. Where the evidence does exist, clinical practice will improve with the provision of information and training, by the prevention of inappropriate use and by working according to clinical guidelines. Many countries have such guidelines and mechanisms to ensure that these guidelines are implemented. Although not a clinical guideline, this booklet nevertheless addresses some examples of good clinical practice, such as the need for proper patient information, appropriate induction, proper dosing and the provision of additional psychological and social care.

An important issue is the price of medications: buprenorphine is significantly more expensive than methadone. Although one should keep in mind that treating a heroin dependent patient is always much more cost effective than no treatment or criminal justice interventions, the issue of the cost of medication is notably a serious issue in resource-poor settings. Therefore, Euro-Methwork strongly recommends that the price of buprenorphine in developing and transitional countries should be reduced. This would greatly contribute to a situation where doctors and patients can freely decide which medication would serve a particular patient best.

We sincerely hope that this booklet is helpful for treatment providers, services users and their friends and family, researchers and policy makers, who are interested in learning more about buprenorphine. We anticipate that it will contribute to tackling some of the myths about buprenorphine and will further add to ameliorating the quality of treatment of heroin dependence.
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• Verster A, Buning E. European Methadone Guidelines. Euro-Methwork, Amsterdam, 2000
• Verster A, Buning E. Information for Policy makers on the Effectiveness of Substitution Treatment. Euro-Methwork, Amsterdam, 2003..
APPENDIX 1:
RECOMMENDED LITERATURE
& WEBSITES

Recommended literature


USEFUL Websites

http://www.jointogether.org/sa/issues/hot_issues/bupe/
http://opioids.com/buprenorphine
http://www.update-software.com/Abstracts/AB002025.htm
http://www.cochrane.org/cochrane/revabstr/AB00002207.htm
http://www.patient.co.uk/showdoc/27000288/
http://buprenorphine.samhsa.gov/about.html
http://www.fda.gov/cder/drug/infopage/subutex_suboxone/default.htm
http://www.euromethwork.org
http://www.ihra.net
APPENDIX 2:

LIST OF EXPERTS CONSULTED

The following experts provided us with their comments and feedback:

- Andrew Bennett, United Kingdom
- Wim van den Brink, the Netherlands
- Barbara Broers, Switzerland
- Andrew Byrne, Australia
- Holly Catania, USA
- Anindya Chatterjee, UNAIDS
- Maurizio Coletti, Italy
- Marina Davoli, Italy
- Michael Farrell, United Kingdom
- Gabriella Fischer, Austria *
- Chris Ford, United Kingdom *
- Robert Haemmig, Switzerland *
- Sue Henry-Edwards, Australia
- Andrej Kastelic, Slovenia
- Hans-Guenter Meyer-Thompson, Germany *
- Bill Nelles, Canada *
- Nicolas Lintzeris, United Kingdom *
- Bob Newman, USA
- Eduardo Polidori, Italy*
- Vladimir Poznyak, World Health Organization
- Gerrit van Santen, the Netherlands
- Emilis Subata, Lithuania
- Marta Torrens, Spain
- Adam Winstock, Australia
- Alex Wodak, Australia *

* experts who reviewed the draft version of this booklet