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**Psychosocial benefits of substitution
therapy in opioid addicts. Buprenorphines
versus Methadone**

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague, June 2010

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Summary

Substitution therapy has shown to be a very effective treatment strategy to reduce overdose related deaths and reducing the spread of HIV and Hepatitis C. It would be fair to say that substitution treatment is necessary and the most important part in the treatment process in opioid addiction also illustrated by the fact that it has become widely used. It is proven to be more effective than medication assisted detoxification and abrupt withdrawal treatment in reducing heroin use. The psychosocial benefits regarding employment, family relations and crime are evident. Methadone and buprenorphine are of different pharmacological natures and have different effects on the patient. It is generally claimed that buprenorphine has less of a euphoric effect, even though an increase in abuse has been reported in several countries. Buprenorphine is a safer drug than methadone due to its dosing ceiling effect, which virtually eliminates the danger over overdose. Both drugs show similar effect in terms of retention rates when given in high doses. Overall very little evidence so far exists that sustaining long-term abstinence after buprenorphine maintenance is any more likely than after methadone maintenance. It is likely to see substitution therapy programs being implemented on larger scale world wide as the foremost treatment alternative to opioid addiction whether it be with methadone, buprenorphine or other alternative medicaments.

Introduction

In this dissertation different aspects of addiction therapy in opioid addicts will be discussed with a more detailed discussion on substitution therapy with methadone and buprenorphin and its advantages. It is based on relevant articles identified by PubMed search. Search terms included 'opiate', 'heroin', 'dependence', 'substance abuse', 'community maintenance', 'methadone', 'buprenorphine', 'clinical trial', and 'substitution therapy'. In addition the Norwegian Journal Of Medicine (Tidskriftet for den Norske Legeforening) and Internet websites were also used.

I chose the theme of my diploma thesis, psychosocial benefits in opioid addicts – buprenorphine vs. methadone based on my long-term interest in this subject and after having worked as a junior doctor at the department of Detoxification Narcotics at Oslo University Hospital in Norway.

Opioid addicts account for a considerable amount of resources spent in social and health institutions in Europe and the world in general (1). It has been shown in several studies that the most effective treatment for people addicted to opioids - which include illegal drugs such as heroin and opioid based prescription medication - is "substitution therapy". In substitution therapy the patient is given an alternative opioid medication with a safer profile and often in higher doses than necessary to

prevent withdrawal symptoms. By doing so the patient may find it harder to achieve the euphoric effect of the illegal opioid substance and thereby prevent relapse to drug abuse (2). Opioid substitution therapy is usually combined with counseling services and other addiction recovery programs. This combination has been shown to decrease drug related deaths (3). The results of research studies and practical experiences from many different studies and experiences from clinics and institutions clearly indicate that patients benefit substantially from substitution therapy (ST) when it comes to drug related mortality and drug related morbidity (blood born infections like HIV and Hepatitis C or infectious endocarditis) (5,11,14,44,45,46). Furthermore ST has an impact on social circumstances like employment and family relations (3). From a community point of view it has a positive effect on crime rates and criminal recidivism (3,4).

Methadone maintenance therapy has long been viewed as the gold standard for substitution therapy. However, due to concerns about abuse and overdose, methadone treatment for opioid addiction is limited to specially licensed programs that usually require daily visits from patients. This restrictive environment is a key reason why methadone reaches less than 15% of patients needing treatment for opioid addiction. (5)

Buprenorphine is a relatively newly approved medication that is an effective alternative to methadone. Because it is safer and less susceptible to abuse, many countries have permitted buprenorphine treatment to be delivered by qualified physicians in their offices in addition to specialty treatment programs. This change in the way treatment is provided has allowed substitution therapy to be offered to more patients, in more locations, and at earlier stages of disease (5, 6).

1. Substitution therapy and its background

Heroin found its way to the European illicit market in the late sixties and early seventies, and a rapid increase in the number of heroin users and addicts followed. The European Monitoring Center for Drug and Drug Addiction (EMCDDA) estimates that there are between 1.2 and 1.5 million problem opioid users in the European Union (EU)(7). In the beginning most drug policies focused on the so-called „abstinence paradigm” or „cold turkey“. It was not until the increase in HIV infections and AIDS among injection drug users started to spread in the mid 1980s that the attitude changed towards a more pragmatic approach (8). This meant that a more harm-reduction strategy was starting to take form. Some of the first methadone – projects took place already in the 1970s, but substitution therapy for heroin abusers remained a controversial topic for a long period of time. This happened in spite of the fact that there was a significant reduction in criminal activity and an increase in social reintegration and employment rates among users. The main reason for the controversy and that the trials were looked upon as a failure was because the patients failed to achieve and maintain complete abstinence (9).

It took several years before ST was introduced on a larger scale. Again it was the increase of HIV and AIDS among IV users that forced through a new approach on the increasing problem. At the same time the rapid increase in crime rates related to drug abuse combined with increasing mortality, a general lack of treatment services, and pressure from families affected by drug abuse, contributed to more harm reduction oriented services emerging throughout the 1980s (5).

Until the early 1990s methadone could only be administered to drug users when highly specific indication criteria were met (e.g. emergency cases, such as life-threatening conditions of withdrawal, severe pain, pregnancy or HIV infection). During this period many GPs ignored the guidelines and prescribed methadone to opioid addicts. Several of these doctors were later prosecuted for their way of

dealing with addicts. In reaction to this GPs started to prescribe codeine or dihydrocodeine to heroin addicts, thereby avoiding general narcotic regulations. A large number of addicts were treated in this way during this period (10).

Only after several pilot programs showed MMT to be effective, did the German Social Health Insurers (SHI) approved this treatment modality and introduced, in 1991, methadone treatment guidelines for financing this kind of treatment. Soon several other European countries followed (11).

1.1 Provision of treatment, criteria and treatment goals

Provision of treatment varies greatly though from country to country. For example, in Scandinavia methadone is traditionally prescribed to opioid addicts in highly regulated methadone clinics. These clinics are usually connected with an out-patient clinic in a hospital. On the contrary, in Australia ST is provided by community pharmacies and the patient has to pay a small fee to cover practical expenses associated with the service (the methadone itself is free, subsidized by federal government and prescribed by physicians in specialized clinics or by GPs to more stable patients) (11). Also the UK and France, to a large extent, rely on pharmacies for provision of methadone. (12). In many countries like Australia, Scandinavia, and Germany, new patients are required to visit the clinic daily so the nurse can observe that the patient actually takes the medication on the spot and does not sell it later on and to buy illegal opioids (e.g. heroin). It also prevents the user to save up doses and later on to take many at the same time risking an overdose. Only after several months (NICE guidelines recommend 3 months) (13) of being treated at the clinic, is the patient allowed to receive “take-home doses” and only after having delivered clean urine samples. These settings vary from clinic to clinic though. Some clinics don’t allow for take-home doses at all, and some places will discharge the patient if he or she misses medication in 3 consecutive days. The way ST is delivered may be a reason for low compliance and is related to the inconvenience of daily visits to the clinics and the stigmatization of the visits to a local pharmacy. Yet another policy is for the patient to receive maintenance

treatment with methadone or with buprenorphine in a primary care setting. This is becoming popular in the US, Canada, and several EU countries including the Czech Republic.

One US trial compared methadone maintenance treatment provided by primary care physicians in their office with methadone maintenance delivered in an outpatient clinic. In this trial it was shown that 77% of office-based subjects were very satisfied with the care that they received and 55% of clinicians expressed their satisfaction with treating office-based patients. It also showed that treatment in primary care and in an outpatient clinic had same effectiveness as no differences were observed in illicit drug use and functional status (14). Another trial showed that primary care-based buprenorphine maintenance treatment was more effective than treatment in an outpatient clinic in terms of the rate of treatment retention (78% versus 52%), the proportion of opiate-positive urine samples (85% versus 63%) and the proportion of subjects who are abstinent from opiates for more than 3 weeks (43% versus 13%) (15).

These findings suggest that there are GPs that are interested in providing treatment for opioid addicts and that substitution therapy in this setting is acceptable to clients. However, the need to train and supervise primary care physicians, and how to choose what patients are trustworthy enough (meet the right criteria) to enroll into such treatment may restrict the potential for office-based treatment by GPs (14).

1.2 The significance of occupational reintegration

Unemployment is associated with isolation and feelings of uselessness and depression. In drug addicts, such a situation may have a reinforcing effect on drug use. The significance of social and occupational reintegration has been widely emphasized in different publications(11, 16). One of the reasons is due to a generally high unemployment rate in general (according to Wikipedia, unemployment rate in Germany was 8.5 % in March 2010, in Spain 18.8 % in December 2009 and in Czech Republic it was 7.0 % in September 2009). Another important reason is the negative attitudes against patients in substitution therapy among employers. Opioid addiction is often associated with a low education level, decreased social and verbal communication skills, and criminal records, which reduce their chances of getting employed. The fact that many patients have never had a traditional job or is no longer familiar with the demands of work life makes this part of social reintegration difficult (11). One way of obtaining work experience is to work a number of hours in a charitable organization or government supported businesses (11). Overall, social and occupational reintegration is a crucial part of substitution therapy and more options should be offered.

1.3 Self-help activities

Self-help groups and family support groups are important parts of remaining drug-free and should be easily accessible to patients in substitution therapy. Narcotic Anonymous (NA) is one of the largest self-help groups, operating in over one hundred countries all over the world. It is a non-profit organization mainly focusing on group activities. The only requirement for membership is "a desire to stop using," and people currently receiving prescribed replacement drugs are allowed to sit in on meetings. Even though some groups do not allow such patients to talk at meetings, many find it useful and supportive (17). NA's primary focus is in providing a recovery environment whereby drug addicts can share their recovery experiences with one another." Since there are no attendance records kept, it is difficult to estimate what percentage of those who come to Narcotic Anonymous remain active in the groups over time. Based on surveys performed by the organization, in 2008 NA members had a mean average of 9.1 years of

abstinence(18). This can be compared to a survey done in 2003 where the mean average was 7.4 years of abstinence (19).

Another example is the “Junkies, Ex-users, Substitutionists” (JES) group in Germany. This group operates in nearly 25 cities in Germany and is completely organized by the people affected by opioid addiction themselves. The idea is that members are working for their own interest. In their founding statement this philosophy is expressed as a federation based on solidarity among junkies, ex-junkies and substitute drug users. Those directly affected know best, and that JES should be a voice for recognition and dignity; that opioid addicts should have a right to humane, healthy, and social living conditions. (20)

1.4 Psychosocial support

In substitution therapy, participation in psychosocial activities is often mandatory. Even though empirical evidence is lacking when it comes to the necessity of such support, it is generally looked upon as beneficial for most patients. Psychosocial care is a collecting name for a number of different services. This can be everything from legal advice, administration of financial problems (debts etc.), recreational activities (the need to replace drug use with some other activity), psychotherapy and group-therapy to help finding a place to sleep, work training, and education. There are great variations regarding what services are provided in addition to the ST between nations and treatment centers. Worldwide there is a lack of research on the views of the patient on what psychosocial treatment works the best. By listening more to the patients, one should believe that it would be easier to find out what philosophies and policies work better and what outcomes that can be expected from different psychosocial treatment strategies (21); there is one example reported by patients: "The doctors, they only know about the effects and side effects from book, but we are the experts. For instance, the doctor says that everyone who gets methadone feels the same thing but that's not true." (11)

Psychosocial counseling can support patients with structuring their life again, based on changed values, because the pressure to find drugs is reduced when receiving substitution medication. It is not easy though for the patients. Often relatively small problems can lead to major crisis and fall-backs. For example, injuries and illnesses

or negative experiences with the past can be very painful. Loss of the daily routine of all-consuming drug seeking behavior together with the loss of the euphoric effect of heroin and consequences of co-existing illness (psychiatric double diagnosis, viral illness) may easily lead to depression and loss of prosperity. A lot of patients become apathetic and are not able to structure their everyday life. For example, patients end up spending their time hanging around and watching TV all day. The social networks they used to have are often no longer there, and keeping away from the drug scene can be difficult (self help groups play an important role in this aspect). Some patients develop extra use of alcohol and benzodiazepines to handle such a void or to deal with depression, usually with the opposite effect (22).

To improve family relations can be hard as family issues are often a part of the problem. Family support is, however, often essential to a successful outcome and should be encouraged (11).

1.5 Opiate use and substitution therapy around the world

According to the United Nations World Drug Report 2009, the number of people who used opiates at least once in 2007 is estimated at between 15 and 21 million people at the global level. More than half of the world's opiate- using population is thought to live in Asia. The highest levels of use are found along the main drug trafficking routes close to Afghanistan. Opiates remain the world's main problem drug when it comes to treatment (23). Europe has the largest opiates market in economic terms, and even though the prevalence seems to be relatively stable in many Western European countries, there seems to be an increase in Eastern Europe. In the EU the EMCDDA estimates that there around 1.2 to 1.5 million users. It is estimated that nearly 600.000, more than half of the estimated one million opioid users in Europe, have access to substitution treatment (7).

The countries that report lowest documented prevalence of opioids use is the Czech Republic, Latvia, Poland and Finland. The highest numbers are found in Malta, Italy and Spain. (Fig 1.)

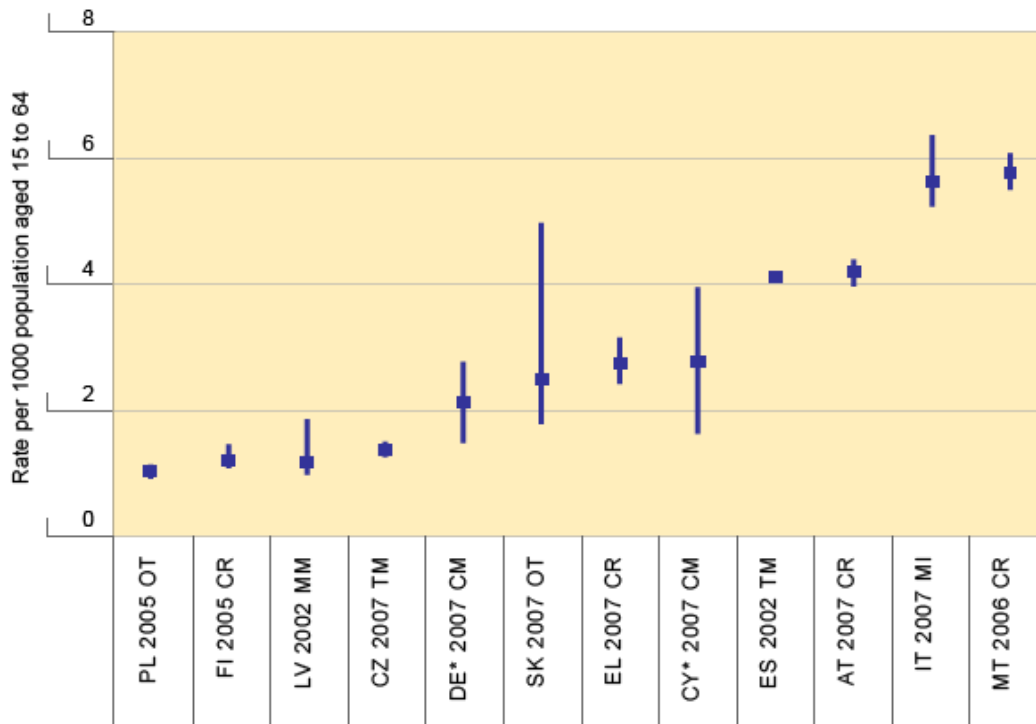


Figure 1. Rate per 1000 population aged 15 to 64 using opioid drugs. Adapted from the 2008 EMCCDDA annual report.

In the Czech Republic in 2007, it was estimated that there were 5 750 heroin users and 4 250 Subutex users. Among the 8 122 drug users that entered treatment 23.2% were opioid users (Czech Republic has a very high proportion of problem methamphetamine users and as much as 60.9 % of those entering treatment in 2007 were methamphetamine users). However, since 2007 any medical doctor, regardless of specialization, may prescribe high dose Suboxone (buprenorphine and naloxone, see below) as substitution treatment for opioid addiction and an estimated 4 300 patients received such treatment in 2007 (24).

It is difficult to find any good estimates on the prevalence of opioid users the United States (US). Data from the 1996 National Household Survey on Drug Abuse (NHSDA) showed that there were approximately 2.4 million persons who used heroin at least once in their lifetime and approximately 455 thousand people who

used heroin at least once in the past year. Methadone remains the most prescribed substitution drug in the US, even though buprenorphine is gaining popularity after it was approved for ST in 2002 (25).

Whatever the situation is in EU and US, it is a fact that more than half of the world's opiate users are living in Asia. Even if the number of drug users is lower in Europe compared to the population as a whole, the absolute numbers of opioid addicts has been rising steadily over the past 10 years. It is now estimated that there are more than 3 million heroin users in China (1.4 million are officially registered), 2 to 4 million opioid users in the Islamic Republic of Iran, several hundred thousands in India and Pakistan, more than 170 thousands in Vietnam, several hundred thousand in the Central Asian region, 3 million in the Russian Federation, and 380 thousands in Ukraine (26). In many of these countries, apart from Russia, which is still rejecting substitution treatment, new substitution treatment programs have been started or are on the way. Most of these provide methadone. The World Health Organization has initiated collaborative studies on ST with focus on prevention of the spread of HIV in developing countries in Asia and so-called transition countries in Europe. So far they have showed convincing results both concerning the health status and quality of life of the patients participating, on the severity of dependence and it was shown that HIV and hepatitis C rates did not increase(22).

2. Substances prescribed

2.1 Opioid receptors and their function

The opioid receptors have important regulating functions in the body and are stimulated and tuned by endorphins and enkephalins. Opioids are a general term used to describe both morphine substances that originate from the opium poppy and those that are synthetically produced. These opioids can stimulate the receptors in excess of the normal regulation. The term ‘morphine effect’ is often used about the stimulation of the receptors and ‘withdrawal symptoms’ about the hypostimulation following abstinence. The receptors have many functions throughout the body and not all are associated with the morphine effect. In addition, there are long term effects associated with hyperstimulation, partially due to changes in gene transcription. Therefore it can be more useful to separate between the direct effects shown when the receptors are stimulated and the indirect effect when the stimulation is stopped as in ‘cold turkey’ or tapered as in detoxification. In the dopaminergic motivation pathways in the brain, the direct effects given to the user are a sense of wellbeing and purpose. The indirect effect is dominated by depressed mood, dysphoria and apathy. In noradrenergic pathways the direct effect is depressing, leading to hypotonus in the entire sympathetic nervous system. The indirect effect is opposite. The opioid has in addition effects on the hypothalamic-pituitary-adrenal pathway and can lead to hypocortisolism and reduced adrenaline secretion. The indirect effect here can be a hyperstimulation of the adrenals (27).

These effects are both short term and long term. In heroin which has a short half life, the short term effects can be present already after 4-6 hours and are dominated by hypofunction of motivation pathways in addition to gastrointestinal, muscle and

skeletal symptoms. The more long term indirect effects of withdrawal is believed to be due to changes in gene transcription and can give the patient disturbances in motivation aspects and stress management and therefore a tendency to relapse a long time after withdrawal(52).

2.2 Treatment strategies

When it comes to treatment of opioid addicts there are in principle five treatment options: abrupt withdrawal (cold turkey), symptom-oriented palliative treatment, tapering with declining doses of an opioid drug, withdrawal under deep sedation and substitution therapy. Users with temporary or fluctuating consumption can be treated successfully without medication provided strong motivational support. The main symptom relief drugs have been pre-synaptic adrenergic agonists that suppress hyperadrenergic conditions. Several controlled randomized trials show that this gives about as good symptom relief as the use of an opioid agonist, but the desire for opioid substances is still strong and the majority interrupt the treatment. The most common recommendation is therefore now decline or maintenance treatment. The ones that are best explored are methadone and buprenorphine (5).

2.3 Methadone

Methadone is, like heroin, a full μ -opioid agonist. The slow half-life and a very high fat solubility makes the effect last longer than other morphine based medications, including heroin. Methadone typically has a half-life ranging from 15 to 60 hours, with an average of 22 hours. This half-life has great individual variability though and in some patients as long as 160 hours and in others only around 4 hours (28). The advantage of a long half-life in substitution therapy is that methadone can be prescribed once daily. Some patients with a high metabolic rate may need to get methadone prescribed two times daily to get sufficient symptomatic relief and to avoid too many variations in blood concentration (28).It is also interesting to note that apart from being a full μ -opioid agonist, methadone

also binds to the N-methyl-D-aspartate (NMDA) receptors and functions as glutamate antagonist. Glutamate is the most important excitatory neurotransmitter in the central nervous system which plays an important role of memory formation (29). This may explain why methadone has such a negative effect on memory and other cognitive skills. It may also explain its good effect in treatment of neuropathic pain (30).

Routes of administration

Methadone is available in the form of pills, sublingual tablets and different solutions designed for the patient to drink. Drinkable solution comes in different doses directly from the producer. This type of administration is most common. Injection of methadone does not give the same “rush” as heroin does. This is because a very large volume of distribution will make the injection spread to other body tissues, especially fat. Therefore, the maximum blood-concentration will be achieved more or less at the same time (27).

Dosage

Most randomized clinical trials of methadone maintenance therapy have found that high doses are more effective for reducing heroin use(31,32). Clinical guidelines recommend 60 mg/day as a minimum dose and most patients receive between 60-100 mg/day. Review articles that collected data from 8 different methadone clinics in the US reports that the average effective dose was 69 mg (11). Authors concluded that effective and ineffective doses of methadone overlap substantially and to optimize therapy, methadone dosages must be titrated in the individual patient until heroin abstinence is reached. The degree of methadone tolerance varies greatly and it was found that patients with post traumatic stress syndrome (PTSD), depression, numerous prior opioid detoxification treatments or withdrawal episodes, and those who use low-purity heroin are likely to require higher dosages of methadone to achieve abstinence.

Duration

The length of treatment varies greatly. Some patients may receive substitution therapy on an indefinite basis. Methadone maintenance therapy is generally seen as ongoing symptom management and in this aspect can be viewed upon as a prescription drug taken for a long-term chronic illness (53).

Dosage reduction

When the patient is ready to start tapering doses depends on many factors. The duration of therapy seems to be the most important one. An ideal patient should also have proper counseling services around him and be offered a medically assisted tapering. In general, to minimize or prevent patient discomfort, the methadone dose must be decreased slowly. Typical reduction rates vary and should be adjusted based on patient response (33).

Adverse effects and toxicity

Methadone side effects are the same as other opiates and are mostly seen in the beginning of treatment. The most dreaded side effect is respiratory insufficiency, which is largely dependent on dose and tolerance. Doses taken by an opioid-tolerant person may be fatal to a non-tolerant person. The combination of methadone with alcohol and sedatives like benzodiazepines may however lead to respiratory failure and also hepatic failure in a tolerant person. Previous reports has expressed concerns about the effect on QT intervals which can be prolonged in patients receiving methadone. A prolonged QT interval can lead to Torsade de Points and ventricular fibrillations (34). One report concluded though that methadone maintenance is generally safe; however, the possible toxicity of high dose (> 120 mg/day) should be monitored for QTc (35).

2.4 Buprenorphine

Buprenorphine is a partial μ -opioid receptor with antagonist actions at the kappa opioid receptor. Its two main indications is management of moderate to severe pain and substitution therapy (36). It has also shown to have a positive effect in treating major depressions (37).

Subutex and Suboxone

Two formulations of buprenorphine (Subutex and Suboxone) are approved for opioid addiction treatment throughout most of the world (plus a generic version since October 2009). Both are available in 2 mg and 8 mg preparations. Suboxone contains, in addition to buprenorphine, the opioid antagonist naloxone in a ratio of 4:1. The naloxone is meant to prevent intravenous misuse by creating withdrawal symptoms. It does not have this effect when taken sublingually. It has however been reported that Suboxone is being misused. It is claimed by users themselves that it gives the same effect as Subutex when taken intravenously when outwaiting the relatively short effect of the naloxone. (38)

Routes of administration and duration

Buprenorphine is most commonly administered in sublingual tablets (Suboxone and Subutex for opioid addiction). Due to their long duration of action buprenorphine can be administered every 2 or 3 days even though most patients receive their doses daily. The sublingual tablets are suitable for resolution. Therefore one problem with buprenorphine is that they can be misused by injections.

Dosing

Buprenorphine has an upper dose-response limit. This is called a ceiling effect and is at 32 mg. This makes the drugs less dangerous with regards to overdosing compared to methadone. This ceiling effect also makes the drug no more effective in higher doses than 24 mg and most patients receive between 12 and 24 mg

depending on the individual's tolerance to opioids. When starting a dosing regimen it is normal to give the patient a dose of 8 mg the first day and then increase by 4 mg and then 2 mg until the desired dose is achieved. Care should be taken by prescribing doctors, pharmacists and nursing staff, not to administer the first dose to a patient within 6 hours of heroin use, and especially not to patients intoxicated on opioids. If they do, the patient may experience opioid withdrawal, as the buprenorphine displaces heroin from the opioid receptors. Buprenorphine-precipitated withdrawal typically begins 1- 4 hours after the first dose, is generally mild to moderate in severity, and lasts for up to 12 hours.

Adverse effects and toxicity

Common adverse drug reactions associated with the use of buprenorphine are similar to those of other opioids and include: nausea and vomiting, drowsiness, dizziness, headache, itch, dry mouth, miosis, orthostatic hypotension, decreased libido, and urinary retention. Constipation and CNS effects are seen less frequently than with morphine. (39)

2.5 Methadone vs. Buprenorphine

The effect of buprenorphine and methadone on the patient is somewhat different because of the different nature of the drugs. Since buprenorphine is a partial μ -opioid receptor agonist and methadone is a full agonist, buprenorphine is generally viewed as having less euphoric effect than methadone. When buprenorphine was introduced it was therefore predicted that it would be less likely to cause dependence and be less likely to find its way to the black market. However it is worth noting that none of the two drugs will cause any significant euphoric effect when taken over a long time and given in the appropriate doses. One trial tested the abuse potential for buprenorphine and found that it can actually cause significant euphoria and was identified as heroin by the subjects participating in the trial (40). Another important difference between the two drugs is that, while buprenorphine is only a partial agonist on μ opioid receptors it has higher affinity to them than other

full agonists have. That means that it will block the effect of other opioids, for example any additional self-administration of heroin. When it comes to what drug is more effective in substitution therapy, this is often measured by treatment retention and mostly negative urine samples. It has been shown that high-dose buprenorphine (meaning 8-16 mg) is more effective than low dose methadone (20-40 mg) and shows same effectiveness in moderate doses (between 50–70 mg). Also in high doses of methadone (to up to 100 mg) buprenorphine can show comparable effect. In all cases, high-dose buprenorphine has been found to be far superior to placebo and an effective treatment for opioid addiction, with retention rates of 50% as a minimum. Again, it is worth noting that while methadone's effectiveness is generally thought to increase with dose, buprenorphine has a ceiling effect at 32 mg. That means, where a methadone dose of 80 mg most probably will be more effective than a methadone dose of 60 mg, a buprenorphine dose of 40 mg will not be more effective than a buprenorphine dose of 32 mg. Therefore, buprenorphine may be better regarded than methadone since the risk of overdose is practically non-existing and thereby patients may be prescribed doses meant to last for weeks and even month in some practices. This is opposed to methadone prescription where the patient is required to make daily office, pharmacies or specialized center visits (14). Another advantage with buprenorphine is that it is less likely for the patient to become dependent on the drug compared with methadone. This also means that tapering and eventually going off buprenorphine may be easier for the patient compared with methadone. The *choice* by the patient of buprenorphine over methadone is usually due to the to the benefits of the less-restrictive outpatient treatment; prescriptions for take-home doses for up to a month early versus the possibility of heavy restrictions in some clinics, and frequent visits to the clinic and the possibility of the "stigma" of going to a methadone clinic as compared to making trips to a doctor's office (11). On the other hand buprenorphine is significantly more expensive than methadone and thus the cost-benefit aspect should be considered. Nevertheless, this seems to add to its better reputation among users. Overall very little evidence exists that sustaining long term abstinence after buprenorphine maintenance is any more likely than after methadone maintenance (41).

Trials have been set out to measure cognitive performance among methadone users and buprenorphine users (42). It was proven that methadone-treated patients, as a group, had significantly slower simple reaction time compared to buprenorphine/saloon-treated patients. Furthermore, it was shown that only methadone patients were inferior to controls in story recall. However, both patient groups were significantly debilitated compared to controls in working memory and verbal list learning.

2.6 Substitution and pregnancy

Opioid maintenance therapy is the recommended treatment approach during pregnancy. The aim is both to reduce the peaks and troughs of short acting heroin and its possible effect on the fetus and to as much as possible avoid neonatal abstinence syndrome (NAS) (47). NAS is suffered by infants withdrawing from substances (opioids in this case) on which they have become physically dependent after in utero exposure. Aside from the withdrawal symptoms, common findings in infants exposed to opiates include low birth weight, prematurity, and intrauterine growth retardation(48). When comparing methadone and buprenorphine in the treatment of pregnant woman, some evidence show that buprenorphine has advantages when it comes to higher birth weight due to longer gestation. Also the incidence of NAS of any intensity, as well as its incidence that required pharmacological treatment was lower, while length of hospital stay was shorter (49). Other studies are inconclusive (50, 51).

2.7 Diamorphine (heroin)

Since the first Swiss heroin-assisted treatment (HAT) study was conducted in the mid-1990s, several other countries in Europe and North America have started HAT trials. In a review article (43) it was concluded that HAT trials have been as safe and effective as traditional substitution therapy. Even though problems related to the practical aspect of administering the drug (usually heroin is administered IV) and the politico-social controversy, HAT may play a role as a last resort alternative when traditional treatment options has failed.

Conclusion

Substitution therapy remains the most effective treatment alternative in the management of opioid addicts. Both methadone and buprenorphine shows similar effects when given in appropriate dosages. While methadone still is a cheaper and more available alternative, buprenorphine is a less dangerous drug due to its ceiling effect and therefore a virtually non-existing danger of over dosing. Overall substitution therapy should be made more readily available for opioid addicts and a shift from methadone to buprenorphine as the gold standard should be considered.

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