10 Maintenance treatment

Guidelines for treatment improvement
Moretreat-project
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1 Introduction

1.1 Definitions

What is maintenance treatment?

Treatment of drug dependence by prescription of a substitute drug (agonists and antagonists) for which cross-dependence and cross-tolerance exists, with the goal to reduce or eliminate the use of a particular substance, especially if it is illegal, or to reduce harm from a particular method of administration, the attendant dangers for health (e.g. from needle sharing), and the social consequences (Demand Reduction – A Glossary of terms, UNDCP).

Aspects of opioid dependence

Opioid dependence develops after a period of regular use of the drug and it is characterized by a triad of cognitive, behavioral and physiological symptoms which ultimately result in an individual continuing to use the drug despite the significant harm associated with the drug. In conjunction with this, the individual no longer is choosing to use the drug for it's apparent benefits, but the use has become habitual and cravings to reuse mean the user feels the habit...
is no longer under control. Opioid dependence is a health problem worldwide with enormous economic, personal and public health consequences. At present, there are approximately 15.6 million opioid users in the world of which 11 million are heroin users with an estimated 2-4 million or more in Western Europe and North America alone (UNODC 2007). Based on information from UNODC 2006, the trends for the usage of opioid class of drugs shows increased consumption over the past 14 years, from 13.5 million people in 1990 to 16.1 million at 2006. Opioid dependence affects approximately 10 million people worldwide each year in excess of 200 000 people die as a consequence of their opioid dependence, predominantly through overdose or HIV infection (UNODC 2007). Many million people will attempt to cease their opioid use, although only a minority will be successful in the long term (Hser et al. 2001). The social costs by opioid dependence accrue from the combination of health care costs, crime and lost productivity (Mark et al. 2001). The global epidemic of HIV/AIDS, which is in many cases fuelled and maintained by unsafe injection practices necessitates the widespread implementation of effective interventions against opioid dependence (Monteiro 2001). Opioid dependence has similarities with other medical conditions in which biological changes occur as a result of the behaviour of the individual and the progress to conditions only partly under individual’s control (such as diet and diabetes, smoking and respiratory disease, diet and heart disease).

Also, like many other chronic conditions, opioid dependence tends to follow a relapsing and remitting course.

Is opioid dependence a medical condition?

Historically opioid dependence was often seen as a dysfunction in the individual will power, reflecting also the character of an individual. However with recent advances in the understanding of the biological mechanism behind dependence and its implications, it has now been widely accepted that opioid dependence is as much a prominent disorder of the brain like many other disorders of the brain. Therefore opioid dependence can be considered as a medical condition characterized by a series of symptoms, and a predictable natural history, for which treatment options now exist.

1.2 Aims and objectives

Aims of treatment
Treatment of opioid dependence consists of pharmacological and psychosocial interventions with the intention of reduction or cessation of opioid use and reduction of harms associated with opioid use. Agonist maintenance treatment consists of usually daily consumption of an opioid agonist, such as methadone or buprenorphine. The resulting stable levels of opioids are experienced by the dependent user neither as intoxication nor withdrawal, more as “normal”. The aims of agonist maintenance treatment include: reduction or cessation in illicit opioids; reduction or cessation of injecting and other blood borne virus risks, reduction of overdose risk, reducing criminal activity and improving psychological and physical health. In practice most patients will cease heroin or use it infrequently, with 20-30% reporting ongoing heroin use (Hser et al. 1998; Teesson et al. 2006). Treatment of drug dependence serves multiple purposes. It assists the drug users to see his or her problems from a different perspective, enhances self-reliance and empowers the individual to make choices and work for changes, confers self esteem and gives hope At the same time it must ensure access to physical and psychiatric care and social assistance, and be oriented towards the family as well as the individual. Client groups served Agonist maintenance treatment is indicated for all patients who are opioid dependent and are able to give informed consent and for whom specific contra-indications do not exist.

The choice of treatment

In recent years it has become clear that a handful of medicines are powerful in assisting people suffering from dependence on opioids. Providing treatment for those dependent on opioids reduces the burden of addiction by reducing health and social costs. Opioid agonist maintenance treatment (especially with oral methadone and sublingual buprenorphine) is increasingly recognized to be the most effective management strategy (Kleber et al. 2006). Oral methadone and sublingual buprenorphine are the most effective opioid agonist maintenance pharmacotherapies. Opioid agonist maintenance therapy is defined as a long-term treatment by use of opioid agonists, without limiting the duration of treatment. In the context of high quality, supervised and well organized treatment services, these medications substitute for the effects of heroin and other illicit opioids, interrupting the cycle of intoxication and withdrawal and greatly reducing heroin use, crime and the risk of death through overdose. In recent years, the value of psychosocial treatment has also been demonstrated, particularly when used in combination with pharmacotherapy, be it in the context of opioid agonist maintenance therapy, opioid withdrawal or relapse prevention.

2 Evidence base
2.1 Non-comparative design

Methadone

Methadone maintenance treatment is known to reduce drug-craving as well as morbidity associated with opioid dependence. Furthermore treatment outcome in methadone maintenance seems to be improved with increased dosages and the provision of adequate psychosocial support. Naturalistic studies assessing the polish methadone maintenance program found an increase of the general health state of the study group as well as positive effects on the most common physical illnesses including disorders of the superficial venous system, skin infections, internal organs mycoses, lowered body mass index and lack of menstruation (Habrat et al. 2001; Habrat et al. 2002). Further work showed that methadone treatment significantly improved quality of life in seven of eight subscales of SF-36 after six months of treatment, while a moderate decrease was observed after another six months of treatment (Habrat et al. 2002). Interdisciplinary methods of rehabilitation and regular pharmacological treatment with methadone resulted in a lower rate of depression (Karakiewicz et al. 2006). An evaluation of the lithuanian outpatient methadone treatment program showed a significant reduction of morbidity and an improvement of the quality of life of patients (Žilvinas et al. 2007). In a further naturalistic study methadone significantly reduced opioid, benzodiazepine and multiple-drug use and was effective in reducing criminal behavior (Subata et al. 2007). Large-scale quality-of-life examinations in Spain showed a strong relation between methadone treatment and reduced mortality from natural causes as well as overdoses (Brugal et al. 2005). Brugal et al. included 5049 patients in Barcelona which provided 23,048 person-years for follow-up. The main factor for overdose mortality was not being in maintenance treatment at the time of death. Other factors were being a current injector at baseline and being HIV positive. For AIDS mortality, the main factor was the calendar year, the next major factor was more than 10 years of heroin consumption, followed by not being in MT, being unemployed, then having a prison record.

Buprenorphine

A german naturalistic trial assessing buprenorphine treatment found a highly significant decrease of the prevalence of heroin, black market methadone and cocaine use (Verthein et al. 2004). Changes in alcohol abuse were non-significant. 74 adverse events and one severe adverse event (admission to psychiatric treatment) were noted. Two small scale (Fiellin et al. 2002; O'Connor et al. 1996) and a larger (Fudala et al. 2003) study associated buprenorphine prescription in primary care with good retention (70-80%) and reasonable rates of opiate free urines (43-64% achieving three or more consecutive weeks of opiate free urines). Similar
results were obtained in France some years ago (Duburcq et al. 2000). An Italian group found significant improvements with respect to withdrawal symptoms, psychic conditions (obsessive traits, hostility and depression), and social roles (particularly job performance, substance abuse and legal problems) in a cross-sectional study evaluating buprenorphine treatment (De Rosa et al. 2002). A control group undergoing methadone maintenance treatment (on average daily doses of 20.19 mg) showed similar rates for retention in therapy to those of the buprenorphine-treated sample, but a much higher frequency of heroin abuse. An observational cohort study from France described an overall 24-week buprenorphine treatment retention rate of 37% (Lapeyre-Mestre et al. 2003). Misuse of buprenorphine and benzodiazepines was significantly more frequent in patients with three or more prescribers or pharmacists. Another naturalistic report from Czech Republic (Hampl et al. 2003) recalls positive experiences with buprenorphine treatment while daily doses of 2-8 mg proved sufficient for long-term treatment of patients addicted to heroin.

Buprenorphine/Naloxone

The buprenorphine/naloxone combination compound with the tradename Suboxone® contains buprenorphine, a partial agonist at the µ-opioid receptor, as well as naloxone, an antagonist at the µ-opioid receptor (Matzenauer et al. 2008). Administered sublingually, naloxone is not resorbed and is later on eliminated due to a pronounced first-pass effect in the liver. Sublingual naloxone does not influence the effect of buprenorphine (Chiang et al. 2003; Harris et al. 2004; Elkader et al. 2005). On the contrary, after nasal or parenteral application naloxone unfolds its full effect as a µopioid receptor antagonist and leads to unpleasant withdrawal symptoms. 68.3% of the participants of a Finish study reported intravenous application of buprenorphine/naloxone, but only 8.3% reported a regular consumption. 80.4% of the participants, who have administered buprenorphine/naloxone intravenously, recalled it as a “bad” experience (Alho et al. 2007). Buprenorphine/naloxone showed to be effective in a 13 day detoxification study of 243 opioid dependent patients -partly consuming street-heroin and partly being in a maintenance treatment program. 90% of the patients finish the induction phase and 68% completed the program (Amass et al. 2004). Another study compared the use of buprenorphine/naloxone and buprenorphine alone for the maintenance treatment of opioid dependent patients. The number of opioid-negative urine tests was in both the buprenorphine/naloxone and the buprenorphine group significantly higher than in the placebo group. No difference in the efficacy of buprenorphine/naloxone and buprenorphine alone was found (Fudala et al. 2003). An analysis of a maintenance program with buprenorphine/naloxone found that 54% (51% at a general practitioner, 58% at an addiction clinic) of the patients were relapse-free after 6 months of treatment (Mintzer et al. 2007).

Slow-release morphine
Slow-release morphine might prove as an alternative to methadone and buprenorphine substitution treatment. An Austrian group assessed the use of slow-release morphine for the treatment of opioid dependence in a non-comparative study (Kraigher et al. 2005). A mean daily dose of 665 mg was administered, which led to a significant decrease of craving for heroin and cocaine and a significant reduction of somatic complaints. Withdrawal symptoms were decreased from a mean Wang scale 12.1 on day 1 to 1.7 on day 7. The consumption of benzodiazepines remained almost unchanged. A Bulgarian naturalistic report evaluating the use of slow-release morphine found a significant drop of signs and symptoms of opioid withdrawal as well as craving for heroin in the first eight weeks and then a stabilization at low levels (Vasilev et al. 2006).

Heroin

A rather new development is the prescription of heroin to chronic, treatment-resistance, heroin-dependent patients in some countries of Europe. Heroin-assisted substitution treatment might be an effective option for chronically addicted patients for whom other treatments have failed. However, it requires considerable resources as patients usually inject three times per day under supervised conditions at treatment centers, which need to have long operating hours as well as high demands on personnel and security. Two non-comparative studies report on the Swiss experiences with a heroin-assisted treatment program. Heroin-assisted treatment has been available in Switzerland since January 1994 in 21 community outpatient treatment centers. Rehm et al. 2001 assessed 1969 opioid-dependent drug users who began heroin-assisted substitution treatment between January 1994 and December 2000. The mean daily dose of intravenous heroin administered was 474.0 mg (SD 206.1) with administration of an average 2.6 (SD 1.0) applications a day. More than 70% (1378) of patients remained in treatment for more than a year. The treatment showed positive effects with respect to health and social outcomes. A longer stay in treatment was related to a higher chance of starting abstinence-oriented therapy than a short stay. A more recent six-year follow-up report from 8 treatment centers substituting heroin in Switzerland was conducted by Güttinger et al. in 2003. Compared to the situation of the opioid-dependent patients at entry, the results of the follow-up showed a significant decrease in the use of illegal substances, illegal income and most other variables concerning social conditions, but they also showed an increase in unemployment and reliance on social benefits. The Swiss results suggest that heroin-assisted treatment is efficient in the long-term course of treatment and also after termination of treatment with respect to living conditions and use of illicit substances.

2.2 Comparative design
Buprenorphine vs. Methadone

Kleber et al. (2006) found the efficacy of buprenorphine in the maintenance treatment of opioid dependents to be comparable to that of methadone, when using equipotent doses. The maximum therapeutic effect of sublingual buprenorphine tablets occurred in the range of moderate (8 mg) to higher doses (16 mg), comparable to moderate methadone doses of 40-60mg, whereas moderate doses of buprenorphine are superior to low doses of methadone. From a clinical point of view, dosing of buprenorphine on every fourth day seemed possible and was found to lead to similar effects on the measures of adverse effects and efficacy than daily doses. Mattick et al. (2007) have found no significant differences between low dose buprenorphine and low dose methadone with regard to treatment retention, opiate free urine samples and self-reported heroin use. In flexible dosage, methadone is significantly more effective than buprenorphine in retaining patients in treatment, perhaps because of the higher potential of methadone to suppress heroin use, especially if high doses of methadone are used. Schottenfeld et al. (2005) compared the efficacy of buprenorphine and methadone in treatment opioid dependents with co-occurring cocaine dependence. The administration of an average maximum dose of 80 mg methadone leads to higher treatment durations, longer periods of sustained abstinence and a greater proportion of cocaine-and opioid-free urine samples than liquid buprenorphine in an average maximum dose of 15 mg. However, Montoya et al. (2004) showed in their double-blind, controlled clinical trial with strict eligibility criteria that daily doses of 8 and 16 mg of buprenorphine solution in combination with drug abuse counselling are feasible and effective in maintenance treatment of outpatients with co-occurring opioid and cocaine dependence. Lofwall et al. (2005) examined the safety and side effect profiles in 164 opioid dependents in buprenorphine and methadone outpatient treatment. After randomisation to buprenorphine \( (n = 84) \) or to methadone \( (n = 80) \) all patients were maintained for 16 weeks. Besides very few clinical gender differences, common profiles of safety and side effects were found for both groups. Connock et al. (2007) found in their recent health technology assessment no generalisable results in the comparison of methadone and buprenorphine with regard to mortality. An italian non-randomized comparative trial assessed the use of buprenorphine and methadone for the treatment of opioid dependence (Gerra et al. 2004). A mean dose of buprenorphine \( 9.2 \pm 3.4 \) mg and methadone \( 81.5 \pm 36.4 \) mg was administered. Methadone-treated patients had a higher retention rate after week 4, but buprenorphine and methadone were equally effective in sustaining retention in treatment and compliance with medication at week 12. Retention rate was influenced by dose, psychosocial functioning and not by psychiatric comorbidity in methadone patients. No relationship between retention and dose, or retention and psychosocial functioning was evidenced for buprenorphine patients. The risk of positive urine testing was similar between methadone and buprenorphine, as expression of illicit drug use in general. At week 12 however, the patients treated with methadone showed more risk of illicit opioid use than those treated with buprenorphine. Negative urines were associated with higher doses in both methadone and buprenorphine patients. High doses appear to predict a better outcome, in terms of negative urines, for both methadone and buprenorphine, but not in terms of retention for buprenorphine patients. Buprenorphine seems to be equivalently efficient
compared to methadone during a clinical procedure, however buprenorphine seems to be more effective than methadone in patients affected by depressive traits and dysphoria. Another Italian non-randomized comparative study discussed the role of buprenorphine and methadone maintenance and found that both therapies resulted in better treatment retention in higher dosage subgroups than in lower dosage subgroups (Guglielmino et al. 2005). An Austrian report assessed the quality of life with a three year follow-up period of buprenorphine and methadone maintained patients (Giacomuzzi et al. 2005). At the end of study period mean methadone dose was 55.4 mg and mean buprenorphine dose was 8.4 mg. Buprenorphine had significantly better outcomes in quality of life concerning partnership, overall satisfaction, leisure time, housing as well as law and security. Buprenorphine had also significantly less physical symptoms including stomach cramps, fatigue, aggressions, poor appetite, feelings of coldness and yawning. Less additional consumption of illicit substances was observed in the buprenorphine group. Mattick et al. (2007) found the efficacy of buprenorphine maintenance treatment to be comparable to methadone maintenance with advantages in some treatment settings, in alternate day dosing, better safety profile, and milder withdrawal syndrome.

Slow-release morphine vs methadone

An Austrian group evaluated the use of slow-release morphine compared to methadone in a randomized double-blind double-dummy cross-over trial (Eder et al. 2005). The retention rate of the entire study group was 86% with a mean methadone dose of 85 mg and a mean slow-release morphine dose of 680 mg. No significant differences in retention or use of illicit substances (opioids, benzodiazepines, cocaine) were observed, irrespective of treatment group or medication. However, patients receiving slow-release morphine had significantly lower depression and anxiety scores and fewer physical complaints. Craving was reduced with both methadone and slow-release morphine, but more during slow-release morphine treatment. Furthermore withdrawal scores were only slightly lower for slow-release morphine.

Comparison of methadone, buprenorphine and slow-release morphine

A randomized analysis of the quality of life at admission versus therapy with methadone, buprenorphine and slow-release morphine was conducted by an Austrian research group (Giacomuzzi et al. 2006). The comparison of illicit drug use showed more favorable results for all three substances compared to patients at admission, while the buprenorphine and the methadone groups showed less physical symptoms (less stomach cramps, fatigue or tiredness, yawning and insomnia) than the slow-release morphine group. Methadone caused less problems with insomnia and buprenorphine less depressions than slow-release morphine. Buprenorphine and methadone had nearly the same outcomes in quality of life while
slow-release morphine showed generally less favorable outcomes.

Codeine vs methadone

Codeine (Dihydrocodeine = DHC) is an analgesic agent, which is available for maintenance treatment in a few European countries. Due to a shorter bioavailability compared to other opioid agonists, codeine treatment might require closer monitoring as it has to be administered more than daily (Hall & Mattick 2007). Robertson et al. (2006) enrolled 235 patients in an open-label randomized controlled study comparing the efficacy of methadone (1 mg/ml) and dihydrocodeine (lower dose = 30 mg and higher dose = 60 mg). Over a period of 42 months, participants treated with dihydrocodeine were more likely to switch treatments; however, no group differences were found at follow-up and over the observation time. A recent open-label randomized controlled trial compared buprenorphine with dihydrocodeine for detoxification from illicit opiates in primary care (Wright et al. 2007). Sixty illicit opiate users were randomly treated either with daily sublingual buprenorphine or daily oral dihydrocodeine, both under a standard regimen including reduction of not more than 15 days. Abstinence was indicated by a urine sample, and the secondary outcomes were recorded during the detoxification period and three and six months after detoxification. The attrition rate was high: Only 23% of the participants stayed in the prescribed course of detoxification medication and provided a urine sample at the final prescription. Risk of non-completion of detoxification was higher in the administration of dihydrocodeine, and a lower proportion of people allocated to dihydrocodeine provided a clean urine sample compared with those who received buprenorphine (3% vs. 21%). Furthermore, the participants allocated to dihydrocodeine were more likely to call on professional carers during detoxification, and more participants allocated to buprenorphine were abstinent at three months and six months post detoxification.

Comparative trials of heroin-assisted treatment

In some countries of Europe, heroin-assisted treatment is available as an option for treatment-resistant opioid-dependent patients. A growing body of controlled trials assesses the benefits of different heroin-assisted treatment combinations and application methods in comparison to standard opioid-substitution treatment. Although heroin seems to be effective for maintenance of chronic treatment-resistant patients, the administration requires considerable resources in treatment centers. A report of two multicenter open-label randomized controlled trials from the Netherlands (van den Brink et al. BMJ 2003) compared inhalable or injectable heroin (maximum 1000 mg per day) combined with methadone (maximum 150 mg per day) to methadone (maximum 150 mg per day) alone over twelve months of treatment. The target population consisted of 549 heroin addicts, who did not sufficiently benefit from methadone
maintenance treatment, while regularly attending maintenance programs during the previous six months and suffered from poor physical or mental health or poor social functioning. With intention to treat analysis, 12 month combination treatment with heroin plus methadone was significantly more effective than treatment with methadone alone in both trials. The incidence of severe adverse events was similar across treatment conditions. In a subsequent trial, pooled data from two randomized trials was assessed to investigate which baseline patient characteristics of treatment-resistant heroin addicts differentially predicted treatment response to medical heroin prescription compared to standard methadone maintenance treatment. Multivariate logistic regression analyses showed that only one of all baseline characteristics was predictive of a differential treatment effect: patients who had previously participated in abstinence-orientated treatment responded signiﬁcantly better to heroin-assisted treatment than to methadone treatment (61% versus 24%), while patients without experience in abstinence-orientated treatment did equally well in heroin-assisted or methadone maintenance treatment (39% and 38%, respectively). One RCT from the Netherlands on cue exposure therapy in an inpatient setting for opiate dependence even found signiﬁcantly higher dropout and relapse rates for the treatment group (Marissen et al. 2007), so it does not seem to be an intervention that can be advisable presently.

Blanken et al. (2005) pooled the data of two open label randomised trials including four hundred and thirty heroin dependents to investigate predictors for the treatment response to medical heroin prescription compared to standard methadone maintenance treatment (Blanken et al. 2005). The participants were randomly allocated to methadone plus injectable heroin or methadone plus inhalable heroin administration or to methadone alone prescribed over 12 months. The outcome measures were recorded according to a response index, including indicators of physical health, mental status and social functioning. An intention-to-treat analysis resulted in a signiﬁcantly better treatment response for the participants in heroin-assisted treatment. Heroin dependent patients with a history of several abstinence oriented treatments beneﬁted more from heroin prescription and showed a higher treatment response compared to patients in methadone maintenance treatment. Patients without a history of abstinence-orientated treatment do not beneﬁt more from heroin-assisted treatment than from methadone maintenance treatment and show equal treatment response rates (Blanken et al. 2005). In another open-label multicenter randomized controlled trial from Germany (Haasen et al., 2007) 1015 heroin-dependent patients received a variable dose of injectable heroin (n=515) or oral methadone (n=500) for 12 months. Inclusion criteria represented methadone-treatment failure or a termination of treatment as well as poor physical or mental health. Retention was higher in the heroin (67.2%) than in the methadone group (40.0%). The heroin group showed a signiﬁcantly greater response in improvement of physical or mental health as well as in decrease of illicit drug use. As administration of injectable heroin might be problematic a group from Switzerland compared heroin tablets only with heroin tablets combined with injected heroin and/or other opioids in an open-label prospective cohort study with two non-randomly assigned treatment arms and historical controls (Frick et al. Addiction 2006). In the intention to treat analysis, 1-year retention rates after 1 year in the heroin tablets-only group as well as in the subgroup combining oral application of heroin with intravenous application or other opioids were higher compared to historical controls (Swiss cohort of patients who had been substituted intravenously with heroin). Rates of serious adverse events under study medication were comparable to the historical rate of the Swiss heroin-assisted treatment. One german randomized controlled trial assessed the effects of racemic D,L-methadone and L-methadone in
substitute patients (Verthein et al. 2005). No differences were found in observed outcome variables (craving, anxiety, depression). Both substances were interchangeable in a ratio of 2:1 (D,L-methadone : L-methadone) while withdrawal symptoms were of transient nature only.

3 Recommendations

Strength of evidence:
**** Strong evidence: High quality meta-analyses, systematic reviews including one or more RCT with a very low risk of bias, more than one RCT a very low risk of bias *** Moderate evidence: Limited systematic reviews, one RCT with a low risk of bias or more RCTs with a high risk of bias ** Some evidence: one RCT limited by research factors or more case-control or cohort studies with a high risk of confounding *
Expert opinion ? insufficient evidence/unclear/unable to assess

3.1 Treatment

Treatment environment

Can programs of pharmacotherapy for opioid dependence operate in isolation from other treatment modalities? Rec: Pharmacological treatment programs and interventions should be integrated or linked with other medical and social services and interventions to ensure possibility of transition of patients to another treatment modalities as their treatment needs change. No single treatment option can match the needs of all patients. Multiple medical, social and legal problems as well as changing needs influence the choice of treatment with time. What considerations should be taken into account in decision making process regarding planning and development of pharmacological treatment for opioid dependence? Rec: The scope of present and potential public health problems associated with opioid dependence and current treatment coverage should form the basis of planning and development of pharmacological treatment for people with opioid dependence. Inclusion of opioid dependence in epidemiological surveys, rapid assessment of a scope of the problems and formal assessment of current treatment systems can provide important information on treatment needs and treatment coverage. Also monitoring essential patient information and trends in target population that comes in specialized treatment services can be useful for treatment planning. Should men and women be treated in same facility? Rec: Men and women can be treated in the same facility, providing that culturally appropriate and gender specific needs Support for recommendation
Women have been found to differ in their drug use patterns than men, using less quantity but advancing more quickly to dependence and using more prescription sedatives than men. They are more likely to have less education, fewer financial resources and have higher rates of sexual and physical abuse (Nelson-Zlupko et al., 1996). Often the needs of women in substance abuse treatment settings are also different. They are more likely to have child care responsibilities which may limit access to treatment, and may be reluctant to participate in activities with men. They also report surprisingly high rates of sexual harassment by male treatment staff (Nelson-Zlupko et al., 1996). There has been little research on the relative efficacy of gender specific services for women. One non randomized study found that lesbian women and women with a history of sexual abuse in childhood and those with dependent children were less likely to drop out from women only treatment services compared to standard care (Copeland et al., 1992). For services to retain women, it seems important for them to provide either individual or female only group counselling, be able to provide care to people with small children, and have measures to guard against sexual harassment of female patients by male staff. Support of recommendation: expert opinion* Effectiveness and choice of treatment, methadone or buprenorphine? In patients to be treated with agonist medications, should preference be given to methadone or buprenorphine?

Summary of evidence

Methadone results in lower rates of drop out than buprenorphine (RR=0.82; 95% CI: 0.69-0.96). Data on heroin use is equivocal, including the possibility of less heroin use with buprenorphine (SMD=-0.12; 95% CI: -0.26-0.02). A systematic review and metaanalysis was conducted on this topic by the Cochrane collaboration in 2003 (Mattick, 2003). Ten studies compared methadone and buprenorphine either using flexible dosing or at doses greater than 6mg buprenorphine or 50mg methadone.

Discussion

It seems clear that methadone retains patients in opioid agonist maintenance treatment longer than in substitution treatment with buprenorphine. This is a consistent finding of the clinical trials and fits with the pharmacology of methadone and buprenorphine, in that methadone patients are more likely to experience severe withdrawal symptoms if they miss doses. It seems that there is also less heroin use with methadone than buprenorphine at the doses compared. Higher doses of buprenorphine may result in greater reduction in heroin use as the capacity to block the effects of heroin appears to be dose dependent. Methadone is, however, significantly cheaper than buprenorphine when both are administered under supervision. Some patients will prefer the effects of buprenorphine and making both treatments available will
probably increase the number in treatment although the degree to which this occurs is difficult to determine.

Conclusion

In studies to date, methadone was shown to be more effective in retaining people in treatment and reducing illicit opioid use, however uses of higher doses of buprenorphine may produce different results. On this basis methadone should be considered the optimal treatment with buprenorphine reserved for patients in whom methadone is not wanted, inappropriate or ineffective, of for whom it is anticipated that buprenorphine will improve the quality of life in other ways. Buprenorphine might be a safer option but the evidence is not yet sufficient to advocate its value over methadone on this basis. This conclusion places a high value on treatment outcomes over possible safety differences, because of the high mortality due to untreated opioid dependence. Rec: In patients to be treated with opioid agonists, clinicians should use methadone maintenance treatment in preference to buprenorphine. 

*Support of recommendation: Strong evidence****

It should be encouraged that methadone maintenance treatment to be provided in conjunction with psychosocial interventions such as regular counseling. Despite this general recommendation, individual reasons may lead to a preference for one medication. Reasons for use of buprenorphine include: previous response to buprenorphine or lack of response to methadone; short duration of action of methadone in the past; interaction between methadone and other medications taken; specific adverse effects of methadone; treatment availability; and patient preference. A stepped treatment of heroin dependence (Kakko et al 2007) appears equally efficient compared to optimally delivered methadone maintenance therapy. Together with prior data on the advantageous safety of buprenorphine, this suggests that broad implementation of strategies using buprenorphine as alternative treatment should be considered. Rec: Buprenorphine is effective for the treatment of opioid dependence and where available should be offered as alternative to methadone for opioid dependent patients. 

*Support of recommendation: Strong evidence****

Remarks: Buprenorphine maintenance should be supported as a maintenance treatment, only where higher doses of methadone cannot be administered. The reasons for not applying the best available treatment should be investigated rather than promoting less effective treatment approaches. Given buprenorphine’s different pharmacological properties, it may have advantages in some settings and under some policies where its relative safety and alternate-day administration are useful clinically compared to methadone.

What doses of methadone should be used?
High dose versus low dose. There is good evidence that high doses of methadone (above 60mg) result in better retention in treatment and less heroin use than lower doses (Faggiano et al. 2003). Methadone doses above 60mg have higher rates of retention in treatment (RR 1.36; 95%CI 1.13 to 1.63) and higher rates of opioid abstinence in treatment (RR 1.59; 95%CI 1.16 to 2.18) and higher rates of cocaine abstinence (RR 1.81; 95%CI 1.15 to 2.85) than lower doses (1-39mg) of methadone. Doctors should prescribe effective doses of methadone and be prepared to increase the dose if patients are still using illicit opioids. In studies in which patients were given fixed doses of methadone, higher doses (above 60mg) were more effective than low doses (1-39mg) in treatment retention and had higher rates of opioid abstinence (RR 1.59; 95%CI 1.16 to 2.18) and higher rates of cocaine abstinence. Higher doses also had better retention in treatment in the long term (RR 1.23; 95%CI 1.05 to 1.45), compared to middle doses (40-59mg).

Conclusions

These findings are consistent with observational studies in which patients on higher doses of methadone have less heroin use than patients on middle or low doses.

Clinical recommendation

Rec: In patients being treated with agonist maintenance pharmacotherapy, clinicians should be encouraged to use adequate methadone doses, 60-120mg.
Support of recommendation: Strong evidence****
Remarks: Clinicians should be encouraged to use high methadone doses and not to reduce their dose, particularly when they are still using illicit opioids. Strong recommendation, high quality evidence. What maintenance doses of buprenorphine should be used?

Summary of findings

Higher doses result in less heroin use than lower doses. In clinical trials, 12mg per day is more
effective than 4mg per day, and two studies comparing 16mg/day to 8mg/day are equivocal including less heroin use in the 16mg group and no difference in the 95% confidence interval. Brain imaging and blockade studies, suggest that high rates of receptor occupancy and capacity to block heroin are obtained with 32mg than 16 mg and 24 mg, particularly when considering the effect over the 24 hours dosing interval, but there are no RCTs comparing these doses in clinical practice. Rec: In patients being treated with agonist pharmacotherapy, clinicians should be encouraged to use buprenorphine doses in the range of 8-24 mg.

Support of recommendation: Strong evidence****

Remarks: The effectiveness of higher doses (16–32 mg) buprenorphine maintenance treatment has not been examined in clinical trials. In practice, the dose should be titrated to effect with the assumption that higher doses are likely to be more effective.

Strength of recommendation: Strong, high quality evidence.*** Should fixed or flexible dosing of agonist be used? Summary of findings There are no studies identified comparing fixed and flexible doses for methadone or buprenorphine maintenance treatment. Opinion is that flexible dosing schedules are preferable as the dose of methadone and buprenorphine should be increased until illicit opioid use ceases. Thereafter there should be frequent review of the dose without encouraging patients from becoming obsessed with minor changes in their dose. The methadone dose should be reviewed more frequently during induction and dose increases, after missed doses and on reduction. In general the patient should be reviewed at least monthly. Rec.: To maximize recruitment into, and retention in agonist maintenance treatment programs, policies and regulations should allow flexible dosing structures, without restriction on dose levels and the duration of treatment.

Support of recommendation: expert opinion*

Remarks: This recommendation takes place a high value on ethical and legal principles aim to prescribe controlled substances.

Supervision of therapy, take away doses

Treatment should be initiated with supervised dosing, assessing response to treatment, and subsequently allowing unsupervised doses to patients who demonstrate stability. The key elements of “stability” appear to include housing, employment, not being dependent on multiple drugs, and ceasing injecting after entering treatment. Rec.: Take away dosing can be recommended when stabilization of dose and social situation are achieved, and when there is a low risk of diversion.

Prescriptions

Legal requirements for prescriptions vary by jurisdiction, however in general a prescription for
opioid agonist maintenance therapy should specify:
• The name, address and telephone number of the doctor.
• The name of the pharmacy.
• The name and address of the patient.
• The date of the prescription.
• The preparation to be dispensed (i.e. methadone or buprenorphine).
• The dose to be dispensed in milligrams (words and numbers).
• The frequency of dispensing (daily, twice daily, alternate daily, three times a week).
• The start and end dates of the prescription.
• Whether all doses are to be supervised or taken home. Because of the potential seriousness of dosing errors, some jurisdictions ensure that the medical practitioner endorses a photograph of the patient which is given to the pharmacy or dispensing point. Also to reduce dosing errors, it is a requirement in some jurisdictions for doses of opioids to be written in both words and figures. To reduce prescription fraud, it is useful to send a copy of the prescription to the pharmacy by facsimile or secure email.

Dispensing

Dispensing of methadone and buprenorphine may take place in a variety of settings. In specialist clinic settings, it is most useful to have a pharmacy or dispensary on site. This enables patients can be observed at each time of dosing. In this way, clinic staff is able to more thoroughly assess the patient, whom they would otherwise observe less frequently. In community settings, dispensing can occur at community pharmacies, although regulations in some countries allow buprenorphine to be dispensed in the physician's office. Dispensing staff can have a valuable contribution to multidisciplinary care planning. In the clinic setting this is more easily accommodated. In the community setting, medical staff should be encouraged to regularly discuss patients with the dispensing pharmacist to determine the number of missed doses and the level of intoxication on presentation for dosing. Methadone and buprenorphine should be kept in a secure safe, according to the national requirements, and the amounts checked and witnessed by a second party daily to ensure the amount used is reconciled with amount dispensed. Dispensing staff are generally pharmacists, although in most jurisdictions, medical and nursing staff can also dispense medication. Training for pharmacists in the issues involved in dispensing methadone and buprenorphine should be available, if not mandatory. Prior to dosing of methadone and buprenorphine, the pharmacists should:
• establish the identity of the patient and confirm with the name on the prescription.
• confirm that the patient is not intoxicated.
• check that the prescription is valid and that the current day is a dosing day (i.e. for alternate or three times a week patients).
• confirm the dose of the prescription. To further reduce dosing errors and assist with record keeping, computerized systems are available which confirm the identity of the patient with retinal or iris scanning and automatically dispense the dose on the prescription (after it has been entered by the pharmacist). It is vital not to dispense methadone or buprenorphine to people
who are sedated or intoxicated as it may lead to oversedation. Dispensing staff must be skilled in the assessment of the degree of sedation and confident in refusing doses to intoxicated patients. It can be helpful to test breath alcohol levels if patients have been drinking. Patients who present intoxicated or sedated should be asked to return when the intoxication or sedation has worn off. The dose dispensed should be recorded in accordance with jurisdictional requirements.

Administration of buprenorphine

Buprenorphine tablets should be dispensed in a dry dosing cup. The number and dosage of tablets should be verified. Prior to administration, patient should be advised to place the tablets under the tongue and not to swallow (tablets or saliva) until the tablets have dissolved (5 minutes on average) and the pharmacist should check the patients mouth cavity for absence of food or receptacles to divert buprenorphine. After administration, the pharmacist should check the patient's mouth cavity again to determine that the buprenorphine has dissolved and the patient should be offered a drink to rinse the mouth cavity. To avoid disputes over dose, patients should witness that they have received a dose in some way. If the patient attempts to spit their dose out, or to leave the dispensary before the dose has dissolved, the doctor should be informed. Crushing buprenorphine tablets into course granules has been tried in some places to limit diversion of buprenorphine although the efficacy of this approach has not been evaluated.

Contra-indications and precautions to the use of opioid agonist maintenance therapy

Methadone and buprenorphine are not suitable for people with decompensate liver disease (for example cirrhosis with jaundice and ascites) as they may precipitate hepatic encephalopathy. They may also worsen acute asthma and other causes of respiratory insufficiency. Other contra-indications listed by the manufacturers are: severe respiratory depression, acute alcoholism, head injury, raised intracranial pressure, ulcerative colitis, biliary colic, renal colic. Precautions for both include: high risk polydrug use, mental illness, low levels of neuroadaptation to opioids (i.e. recent incarceration), and significant concomitant medical problems.

3.2 Access

Rec: A national treatment strategy document should be developed, aiming for adequate coverage, quality and safety of treatment. When a treatment system is developed in any
country, it should be planned as part of that communities overall resources to deal with health and social problems (WHO expert committee 30th report). Responses to substance use problems should be disseminated throughout the whole community and be population based, with an orientation towards "Health for All". Estimating the need is important for planning treatment services, and for reviewing the accessibility of services to different population groups. Estimating the number of opioid dependent people is difficult due to their under representation in large scale epidemiological surveys. Alternative techniques are capture recapture, back projection and multiplier from overdose rates, needle and syringe distribution numbers, numbers in opioid agonist maintenance treatment presentations to treatment centres (Hall, Ross, Lynskey, Law, & Degenhardt, 2000). Other methods of estimating treatment need are based on systems of treatment monitoring, especially measuring the demand for first time treatment. It is important to distinguish between demand and treatment need, keeping in mind that populations that have difficulty gaining access to treatment are women, the young, street children, refugees, the poor and minority ethnic and religious groups. It is also important to have data on the number of patients treated with each modality. Data on numbers in opioid agonist maintenance treatment can be gathered from treatment centers and/or pharmacies dispensing methadone and buprenorphine in real time or intermittent basis. Data on numbers of people treated for detoxification is more difficult and requires a co-ordination of data from residential facilities, outpatient specialist services and primary care. Needs assessment is a formal systematic attempt to determine important gaps between what services are provided and what should be provided. It involves documenting important gaps between current and desired outcomes and then placing the gaps in order of priority for closure. In planning treatment systems, resources should be distributed in a way that delivers effective treatment to the most number of people. Available evidence suggests that opioid agonist maintenance treatment is the most cost effective treatment and should form the backbone of the treatment system for opioid dependence. Countries with established opioid agonist maintenance programs usually attract 40-40% of dependent opioid users into opioid agonist maintenance treatment, with higher rates in some urban environments. Given the difference in cost between inpatient and outpatient withdrawal, inpatient facilities should be reserved for those with specific needs, the majority being encouraged to attempt opioid withdrawal as outpatients. Psychosocial services should be made available, particularly for people in opioid maintenance treatment, and those attempting to remain abstinent from opioids, although they need not be mandatory. In considering the balance of treatments types, funding should be evidence based. In general, opioid agonist maintenance is likely to be the most cost effective treatment, and treatment systems should aim to have no waiting list for opioid agonist maintenance treatment. Moderate levels of psychosocial support are generally more cost effective than intensive psychosocial support and priority should be on broad access to standard psychosocial support rather than intensive access for a reduced number. Health regions will need to examine their own needs and costs of services to determine the optimal balance of funding for treatment types. The different components of opioid dependence treatment programs have differing requirements for training and infrastructure. Outpatient psychosocially assisted pharmacotherapy (including opioid agonist maintenance therapy, outpatient opioid withdrawal, outpatient relapse prevention) requires as a minimum medical staff, dispensing staff and psychosocial support staff.
3.3 Diagnosis and assessment

Patient history and self report of drug use can be relied upon in most circumstances for making a diagnosis of dependence but they should be correlated with other methods of assessment, including the clinical examination and history from family and friends. Urinanalysis should not be used to diagnose presence or absence of dependence. Clinicians should differentiate between dependence and harmful use as it has implications for the appropriate treatment strategy. Previous history of opioid dependence and treatment should not exclude patients from further entry to treatment programs.

Diagnosis of opioid dependence

One important role of the assessment process is to confirm the diagnosis of opioid dependence. In particular the degree of neuroadaptation must be determined before the administration of methadone or buprenorphine. The international classification of diseases (10th edition) defines opioid dependence a cluster of physiological, behavioural, and cognitive phenomena in which the use of opioid takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take opioid (which may or may not have been medically prescribed). There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals. How should the diagnosis of opioid dependence be made? Rec: The diagnosis of opioid dependence and other medical conditions should be made by trained health care personnel. If the diagnosis justifies an agonist maintenance treatment it should be accomplished by a trained physician. Social conditions should be determined by social workers or staff trained in social conditions. Support of recommendation: expert opinion* Rec: Patient history and self reported drug use are generally reliable, but for making a diagnosis of drug dependence other methods of assessment including and history from family and friends, the clinical examination and relevant investigations should take into account.

The ICD-10 diagnostic criteria for opioid dependence: A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:
- a strong desire or sense of compulsion to take opioid.
- difficulties in controlling opioid-taking behaviour in terms of its onset, termination, or levels of use.
- a physiological withdrawal state when opioid use has ceased or been reduced, as evidenced
by: the characteristic withdrawal syndrome for opioid; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms.

- evidence of tolerance, such that increased doses of opioid are required in order to achieve effects originally produced by lower doses (clear examples of this are found in opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users).
- progressive neglect of alternative pleasures or interests because of opioid use, increased amount of time necessary to obtain or take the substance or to recover from its effects
- persisting with opioid use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.
- Narrowing of the personal repertoire of patterns of opioid use has also been described as a characteristic feature. It is an essential characteristic of the dependence syndrome that either opioid taking or a desire to take opioid should be present; the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use. This diagnostic requirement would exclude, for instance, surgical patients given opioid drugs for the relief of pain, who may show signs of an opioid withdrawal state when drugs are not given but who have no desire to continue taking drugs. Rec: Clinicians should differentiate between dependence and harmful use of all substances used as it has implications for the appropriate treatment strategy. Strength of evidence: expert opinion*

Assessment

Other important functions of the assessment are to determine physical, psychological and social health care needs. Included in the assessment should be past treatment experiences, living conditions, legal issues, occupational situation, social and cultural factors, that may influence drug use.

Recommendations

Rec: A detailed individual assessment of treatment needs includes: past treatment experiences; medical and psychiatric history; living conditions; legal issues; occupational situation; and social and cultural factors, that may influence drug use. Rec: Patients should have proof of identity before commencing treatment with controlled medicines. The patient must be able to give informed consent before treatment. Rec: Voluntary testing should be offered as part of an individual assessment, accompanied by pre-and post-test counselling. In places in which the prevalence if HIV is high in injecting drug users, HIV testing should be offered on an "opt out", rather than an "opt in" basis, because of risk to others. Serology testing for Hep B and Hep C
testing should be considered, given the availability of treatment for both viruses and a vaccine for hepatitis B.

Rec: All patients who have not been exposed to hepatitis B should be vaccinated against it, with consideration given to accelerated vaccination schedule to improve completion rates. Rec: Voluntary pregnancy testing should be offered as part of an individual assessment. Pregnancy testing should be offered to all women as it may influence the choice of treatment. Urinalysis alone should not be used to diagnose presence or absence of dependence but can offer additional information which should be interpreted in the light of other aspects of the assessment. A negative urine drug screen, in the absence of withdrawal features on examination would indicate a low level of neuroadaptation and should prompt caution in the use of sedative medication. Urine testing is also useful to identify other unknown substances that have been ingested. On the other hand, waiting on results of urinalysis to confirm dependence can delay entry or be a barrier to appropriate treatment programs and can be expensive. Where they are affordable, it is suggested that urine drug screens be routinely collected as part of the assessment although treatment should not be delayed unless the remainder of the assessment raises doubts about the diagnosis. Naloxone challenge testing should not be routinely used to confirm the current neuroadaptation as it can induce significant withdrawal effects and the same information can be gathered from urine drug screening. Sometimes it is not possible to make a complete assessment on one day. The patient may be intoxicated, or in withdrawal or in crisis and have limited time. It may be necessary to make an initial plan based on the initial assessment which will then evolve over time with more comprehensive assessment and the response to initial treatment.

3.4 Management

Provision of care Pharmacotherapy of opioid dependence should be developed as a part of an overall treatment system that includes other treatment modalities to ensure that available treatment options match diverse, multiple and changing needs of people with opioid dependence. Pharmacological treatment of opioid dependence can be provided in primary health care, expanding treatment coverage. To achieve better coverage and treatment outcomes, pharmacological treatment of opioid dependence should be provided free of charge, or covered by health insurance. The choice of treatment for an individual should be based on a detailed assessment of the treatment needs, evidence-based appropriateness of treatment to meet those needs, patient acceptability, and treatment availability. Voluntary testing of blood born diseases should be offered as part of an individual assessment, accompanied by pre-and post-test counselling. Health care providers involved in the treatment of an individual, and patients themselves, should have access to patient data according to national regulations. Central registration of patients receiving agonist treatment is acceptable and is recommended, if feasible, and if access to the register is restricted to health authorities. Involuntary discharge from treatment is justified only if there is repeated violence, or there is evidence of diversion or dealing on the treatment premises. Noncompliance with program rules should not be a reason for involuntary discharge.
Programme duration

In some cases, a simple and short-term intervention such as assistance with opioid withdrawal will result in an immediate and lasting improvement. However, in many others, treatment will have to be regarded as a long-term, or even a life-time process, with the occasional relapse. The aim of treatment services in such instances is not only to reduce or cease opioid use, but also to improve their health or social functioning gradually, to encourage them to try again, or to avoid some of the more serious consequences of drug use. This does not imply that practitioners should assume that treatment is unsuccessful in such patients. On the contrary, treatment should be viewed as supporting the natural and long-term process of change and recovery. In this context, the start of the treatment process is a time for the clinician and the patient to consider the current circumstances and, in the light of previous experiences, make plans towards mutual treatment goals.

Staffing/ Competencies

• Medical staff

Medical staff are required for prescription of pharmacotherapy. They should also play a leading role in the assessment and discussions around treatment matching. In specialist clinics, medical staff should be supervised by a medical or psychiatric specialist in the treatment of substance dependence. In generalist settings, general practitioners and other medical staff should have a minimal level of training in the diagnosis and treatment of opioid dependence. This will vary depending on the undergraduate training in the field of substance abuse in that setting, the specific requirements for training can be to be determined in consultation with the specialist group caring for opioid dependent patients in that health area. Because of the potential for methadone and buprenorphine to do harm if prescribed inappropriately, many countries have a system of licensing medical staff to prescribe opioid agonist maintenance treatment. Ideally, all medical staff working in the field of substance abuse should have some avenue for clinical supervision, be it from peers, senior colleagues or professional supervision. This helps to avoid inappropriate prescribing and maintain professionalism between medical staff and patients. To increase efficiency, medical staff may delegate some of their responsibilities to nursing and other health care staff, in accordance with local regulations. Because of the cost and availability of medical staff, in many occasions nursing and other health care staff may have more experience than medical staff and this should be reflected in a multidisciplinary approach to decision making.
• Psychosocial support staff

Traditionally psychosocial support staff have come from a variety of professional and non professional backgrounds. Many staff have been substance dependent themselves. To ensure professionalism and consistency of service delivery, a certain minimal training in professionalism and substance dependence is advisable. Further training requirements depend on the nature of the psychosocial intervention being offered. Rec: National health authorities should ensure that treatment providers have sufficient skills and qualifications to use controlled substances appropriately. These requirements may include compulsory post graduate training and certification, continuing education and licensing.

3.5 Ethical principles of care

Ethical principles should be considered with clinical trial evidence when making clinical decision for the treatment of dependent opioid users, respecting the human rights of opioid dependent individuals at all times. Treatment decisions should be based on standard principles of medical care ethics, with equitable access provided to treatment and psychosocial support that best meet the needs of the individual patient. Treatment should respect and validate the autonomy of the individual, with patients being fully informed about the risks and benefits of treatment choices. The use of legal coercion into treatment for opioid dependence should respect basic ethical and legal principles. Furthermore, programs should create supportive environments and treatment relationships to facilitate treatment, providing co-ordinated treatment of co-morbid mental and physical disorders and addressing relevant psychosocial factors. Substance dependence should be treated as a health and not a legal problem. Also taking into account multiple medical problems associated with opioid dependence and nature of pharmacological treatment, health care sector should be given a priority for provision of pharmacological treatment for opioid dependence.

Involuntary discharge and other forms of limit setting

Outcomes after involuntary discharge from treatment are poor, with relapse to heroin use occurring in 75% of patients (Kornor & Waal, 2005). Are there reasons for involuntary discharge from treatment? Rec: Involuntary discharge from treatment is justified only if there is repeated violence, or there is evidence of diversion or dealing on the treatment premises. Noncompliant
with program rules should not be a reason for involuntary discharge. One of the primary responsibilities of a treatment service is to protect its staff and patients from harm. If a situation arises in which the past behaviour of a patient would indicate that there is a significant risk of harm to other patients or staff then the treatment service must act to reduce that risk, discharging the patient if necessary. Such situations are potentially avoidable if the patient's behaviour is identified and managed at an earlier stage. Sometimes called "limit setting", the effective treatment service will have clear boundaries on what is and what is not acceptable behaviour and will apply the limits consistently and transparently to all patients. To avoid replicating the rejection that patients experience from other parts of society, limit setting must have a graded response including positive feedback for "good behaviour", minimal responses such as being refused a dose while intoxicated, and final responses such as treatment discharge and calling the police. Application of excessive responses for minor breaches of rules will result in many people being discharged when they could have gone on to do well from treatment. Application of no responses to significant breaches of rules risks harm to other patients and staff, and also does not assist the patient in question. Each service will have to decide on its own rules and where it sets its limits depending on cultural norms, the goals of treatment in that setting and the political environment which allows the treatment to continue. Treatment rules are often very different for a withdrawal facility or therapeutic community aimed at abstinence to an opioid agonist maintenance program aimed at reducing mortality and morbidity associated with opioid dependence and improving quality of life. Whatever limits are set, it is vital that they are consistently applied by all treatment staff. In this way patients will learn quickly what the limits are. Some patients will push the boundaries when there is a perceived difference in application of limit setting by staff. Sometimes called "splitting", this risks setting treatment staff against each other with resulting poorer outcomes for the patients. Even if an incident is serious enough to warrant abrupt discharge, agencies should use this as an occasion to review whether they have done all they can not to provoke or permit such behaviour. Treatment services should have a mechanism of reporting incidents when they occur, including "near misses" and unexpected adverse outcomes, which should be reviewed regularly by a team including someone responsible for the clinical governance of the service. Initiatives to reduce such incidents might include measures to train staff in non judgemental and non-confrontational communication strategies, reducing waiting time for appointments and medication, frequent review of patient treatment, family and employment friendly practices, and the presence of security. Are there special measures to be taken before involuntary discharge? Rec: Before involuntary discharge, reasonable measures to improve the situation should be taken including re-evaluation of the treatment approach taken. If the situation does not warrant immediate discharge for the safety of staff and other patients than attempts should be made to resolve the situation without discharge, particularly if discharge is to no treatment. Patients should understand what is expected of them, and there should be clear communication when behaviour crosses those boundaries. When alternative options are not appropriate or have been exhausted, attempts should be made to transfer the patient to another treatment service.

Patient records
Rec: Medical records should include treatment history, present health and social status, diagnosis, treatment plans and their revisions, referrals, consent, prescribed drugs, other medical and social interventions and laboratory findings. Every contact between the health service and the patient should be recorded in the medical record. The record should be contemporary and clearly legible. Each entry should be signed and dated. Rec: Health care providers involved in the treatment of an individual, and patients themselves, should have access to patient data according to national regulations. Rec: Generally health care providers or other personnel involved in patient treatment cannot share information about patients with police and other law enforcement authorities, except if a patient approves, or if required by law. In some circumstances, professional standards may be to breach confidentiality, for example if the life of the patient is at risk of if the life of a child is at risk. In these situations, professional staff should balance the rights of the patient to privacy against the duty to protect and seek advice from their professional body if unsure. Such breaches of confidentiality are generally allowed under law, or may in some cases be required by law. As a general rule, patients should have access to their own medical records. This may be limited in some situations if is not in the patient's best interest to view his or her own records.

Registration of patients

Rec: Central registration of patients receiving agonist treatment is acceptable and is recommended, if feasible, and if access to the register is restricted to health authorities. The benefit of central registration of patients is that it prevents patients from receiving methadone or buprenorphine from more than one source. It can also be used to limit access to other controlled medicines requiring central approval, such as other opioids. The adverse effects of central registration are that it has the potential for breach of privacy and this may deter some patients from entering treatment, it can delay the commencement of treatment, and it uses resources which could otherwise be used for treatment. Should patients have proof of identity before entering treatments? Rec: Patients should have proof of identity before commencing treatment with controlled medicines In most countries, writing a prescription requires identifying the patient, however in some countries anonymous prescription for methadone is allowed. Central registration is not possible without identifying patients.

Public vs. private treatment

Should the public health sector be involved in provision of treatment? Rec: Funding and equitable access to treatment should be assured for the appropriate treatment approaches in each national situation, according to the burden of disease. If the country has a public universal healthcare system, then this should include access to opioid
Payment for treatment of opioid dependence

Should patients be required to pay for their pharmacological treatment of opioid dependence?
Rec: To achieve better coverage and treatment outcomes, pharmacological treatment of opioid dependence should be provided free of charge, or covered by health insurance.

Supervision of methadone/buprenorphine

Should methadone and buprenorphine be supervised? Research indicates that diversion will occur with both methadone and buprenorphine if they are unsupervised. With buprenorphine, the extent of diversion will also depend on the degree of supervision, as it is easier to divert a tablet placed under the tongue than a liquid. The main problems with methadone diversion are the risk of methadone injecting and fatal overdose in non-dependent people. The main problems with buprenorphine diversion are non-medical use of buprenorphine with potential development of dependence syndrome, the risks associated with injecting buprenorphine (Hepatitis C, HIV, endocarditis, local infections). On balance, initiating treatment with supervised dosing, assessing response to treatment, and subsequently allowing unsupervised doses to patients who demonstrate stability, appears to: have a substantial effect in reducing diversion, probably not diminish efficacy, and have support from consumers. The key elements of “stability” appear to include housing, employment, not being dependent on multiple drugs, and ceasing injecting after entering treatment. Supervision of doses of methadone and buprenorphine is recommended for all patients unless they have demonstrated that they are a low risk of diversion. Are there measures to minimize diversion? Rec: Normal legal restrictions, staff training and adequate take away policy can minimize diversion. What are conditions for take home dosages? Rec: Take home dosing can be recommended when stabilization of dose and social situation are achieved, and when there is a low risk of diversion. Rec: To optimize the sustainability of programs, there should be systems to prevent or minimize diversion of pharmacotherapy, and to monitor the benefits of treatment. As a minimum, this would include systems that monitor the extent of diversion.

Appendix
List of natural, synthetic and semi-synthetic opioids (Brunton, Lazo & Parker, 2005)

Natural opioids

Endogenous opioids

Endorphins

Dynorphins

Encephalins

Alkaloids found in opium

Morphine

Thebaine

Codeine

Papaverine

Semi synthetic opioids
Diacetylmorphine (heroin)

Dihydrocodeine

Hydrocodone

Hydromorphone

Nicomorphine

Oxycodone

Oxymorphone

Synthetic opioids

Anilidopiperidines

Fentanyl

Alphamethylfentanyl
10 Maintenance treatment

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Alfentanil

Sufentanil

Remifentanil

Carfentanyl

Ohmefentanyl

Phenylpiperidines

Nocaine

Pethidine (meperidine)

Ketobemidone

MPPP

Allylprodine

Prodine
10 Maintenance treatment

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PEPAP

Diphenylproplamine derivates

Propoxyphene

Dextropropoxyphene

Dextromoramide

Bezitramide

Piritramide

Methadone

Dipipanone

Levo-alphacetylmethadol (LAAM)

Loperamide
Diphenoxylate

Benzomorphane derivatives

Pentazocine

Phenazocine

Oripavine derivatives

Buprenorphine

Etorphine

Morphinan derivatives

Butorphanol

Nalbuphine

Levorphanol

Levomethorphan
Others

Dezocine

Lefetamine

Tilidine

Tramadol

Opioid antagonists

Nalmefene

Naloxone

Naltrexone

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Habrat B., Chmielewska K., Baran-Furga H. Physical status of opiate dependent patients before and after one-year participation in methadone maintenance program. 2002 Przeglad lekarski


10 Maintenance treatment

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Žilvinas Padaiga, Emilis Subata1, Giedrius Vana. Outpatient methadone maintenance treatment program. Quality of life and health of opioid-dependent persons in Lithuania. 2007 Medicine Lithuania

17 Reference of WHO guidelines to be added!