PROPOSAL FOR
THE INCLUSION OF METHADONE IN
THE WHO MODEL LIST OF ESSENTIAL MEDICINES

DEPARTMENT OF MENTAL HEALTH AND SUBSTANCE ABUSE
Management of Substance Abuse

HIV/AIDS DEPARTMENT

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Summary of the proposal

The scope and relevance of methadone in the management of opioid dependence is to be seen on the background of *epidemiological data* on the extent of opioid dependence worldwide, the burden of disease due to opioid dependence and the role of opioid dependence in HIV/AIDS epidemics. Most illicit opioid use is heroin use, mainly through intravenous injecting. Heroin users have a mortality risk 13 times higher than the average in the same age group, even without taking into consideration increased mortality associated with HIV epidemics and other blood-borne infectious diseases. In some parts of Europe, heroin injecting accounts for 25-33% of deaths in young adult males. Worldwide, it is estimated that there are 12.6 million injection drug users (IDUs) and that around 10% of HIV infections are associated with injecting drug use. In 2003 injecting drug use (IDU) directly accounted for approximately 420 000 new HIV infections globally. HIV seroprevalence rates as high as 60 to 90% are seen among injecting heroin user populations in various countries of Eastern Europe, South-East Asia and Western Pacific regions.

Methadone is a synthetic opioid that is most commonly used for substitution therapy of opioid dependence. It is one of the most effective types of pharmacological therapy of opioid dependence. Methadone's mechanism of action, like morphine, is mediated by the activation of opioid receptors, principally of the μ type. The *pharmacology* of methadone is well researched and documented, including adverse effects and drug interactions.

Clinical research data on the effectiveness of substitution maintenance therapy with methadone (methadone maintenance treatment) of opioid dependence are well documented. They cover randomised clinical trials, large prospective long-term observational studies, and special research on cost and cost-effectiveness. Methadone maintenance treatment in opioid dependence has been studied in 8 randomized controlled trials using non-active controlled conditions. In three meta-analyses robust effects of methadone compared with controls for retention in treatment, illicit opioid use and criminality were reported. A recent Cochrane review (Mattick et al., 2004) concluded that treatment with methadone is statistically more effective than non-pharmacological approaches in retaining patients in treatment (3 RCTs, RR=3.05; 95% CI: 1.75-5.35) and the suppression of heroin use (3 RCTs, RR=0.32; 95% CI: 0.23-0.44). The long-term observational studies document the attractiveness and the sustained improvements in the outcomes of methadone maintenance treatment. Cost and cost-effectiveness studies suggest that methadone maintenance treatment is a cost-effective option, on the condition of adequate dosing and retention in treatment.

During the last two decades, scientific evidence has accumulated that methadone maintenance, in addition to being an effective treatment for opioid dependence, has a supportive function to enhance *HIV/AIDS prevention, treatment and care.* Methadone maintenance treatment programs provide opportunities for expanded HIV prevention among injecting drug users and a platform for implementation of directly observed antiretroviral therapy for opioid dependent people with HIV/AIDS as well as therapy for opportunistic infections such as tuberculosis (WHO, UNODC, UNAIDS, 2004). Evidence of reduced HIV seroconversion rates among patients on methadone maintenance treatment has been demonstrated repeatedly with associations between length of time in treatment and lower rates of HIV seropositivity (Abdul-Quader et al., 1987). An early review of 15 studies came to the conclusion that methadone maintenance consistently is associated with reductions in the sharing of injecting equipment (Ward et al., 1995). In a meta-analysis of 8 studies, comparing HIV risk behaviours in methadone maintenance patients and opioid users out of treatment, seven studies found significant differences in risk behaviour after 12 months in treatment with significance levels ranged between p=0.00 to p=0.08 (mean p=0.01), and effect sizes from r=0.12 (d=0.24) to r=0.48 (d=1.10), mean r=0.21 (d=0.45) (Marsch, 1998). A more recent review of 33 studies with a total of over 17,000 participants concludes that methadone maintenance

treatment effectively reduces HIV risk behaviors, particularly needle use, and prevents HIV infection (Sorenson & Copeland, 2000).

As methadone maintenance therapy envisages long-term treatment with a significant proportion of patients retained in treatment for many years and in view of the fact that currently a global number of persons with opioid dependence receiving prescribed methadone is estimated to be over half a million, an accumulated *experience with methadone* in management of opioid dependence has to be considered as very substantial.

The accumulated data demonstrate that methadone maintenance treatment is a *major public health tool* in the management of opioid dependence and in HIV/AIDS prevention and care for opioid dependent injecting drug users.

1. Summary Statement of the proposal for inclusion, change or deletion

Methadone is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the management of opioid dependence, including opioid dependence co-occurring with HIV/AIDS, and for HIV prevention among opioid dependent individuals.

2. Focal points in WHO for application

Dr Vladimir Poznyak
Department of Mental Health and Substance Abuse (MSD), Management of Substance Abuse (MSB)

Dr Andrew Ball
HIV/AIDS Department

3. Name of Organisation(s) consulted and/or supporting application:

Joint United Nations Programme on HIV/AIDS (UNAIDS)
College on Problems of Drug Dependence (CPDD), USA

4. International Nonproprietary Name (INN, generic name) of the medicine:

Methadone hydrochloride

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the WHO Model List of Essential Medicines as an individual medicine under section 24 (Psychotherapeutic medicines) and new subsection "Medicines used in substance dependence". A square box symbol is not required.

6. Information supporting the public health relevance (epidemiological information on the disease burden, assessment of current use, target population)

6.1 Epidemiology of opioid dependence

6.1.1 Prevalence of opioid dependence

Even though non-medical opioid use is prohibited by international law, such use occurs in many countries of the world. Table 1 gives an overview of estimated prevalence of "problematic" opioid use in different regions of the world (Degenhardt et al., 2001; WHO, 2000). By the operational definition used by Degenhardt et al (2001), "problematic" opioid users are dependent on opioids as defined by ICD-10 (WHO, 1993). These prevalence rates were estimated based on the UN Drug Control Program's (UNDCP, 2000) Global Illicit Drug Trends for persons over the age of 15 years and the additional assumption that 28% of all users in the past year were "problematic" users or opioid dependent users, the latter fraction being derived from an Australian national survey (Hall et al., 1999). It must be noted that prevalence estimates of use were not available for all countries in all WHO regions. In making estimates for countries which had no reported prevalence estimates, WHO regional estimates of prevalence were used by deriving a weighted average prevalence rate from the data that were available from countries in the region. These estimates have to be considered as rather conservative, because other estimates, e.g. from EMCDDA, tend to be higher than those reported above (e.g. Kraus et al., 2003; EMCDDA, 2003a). Also recent data from the U.S. National Survey on Drug Use and Health study demonstrated that in 2003 in USA 57.4 percent of past year heroin users (0.2 million) were classified with dependence on or abuse of heroin (Substance Abuse and Mental Health Services Administration, 2004).

Table 1: Prevalence (%) of opioid dependence in the past 12 months among persons 15 years and above according to 14 WHO regions for the year 2000.

Regions	**Population ('000s) over 15 years**	**Prevalence of opioid dependence**	**Population ('000s) with opioid dependence**
Europe A (e.g., France, Germany, Italy, Netherlands, Spain, UK)	339,446	0.11	373
Europe B (e.g., Bulgaria, Poland, Romania, Turkey)	161,213	0.09	145
Europe C (e.g., Russia, Ukraine)	152,432	0.19	290
America A (e.g., Canada, USA)	255,420	0.13	332
America B (e.g., Argentina, Brazil, Chile, Costa Rica, Mexico)	297,625	0.03	89
America D (Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru)	44,658	0.07	31
Eastern Mediterranean B (e.g. Islamic Republic of Iran, Jordan, Libyan Arab Jamahiriya, Saudi Arabia, Tunisia)	86,853	0.55	478
Eastern Mediterranean D (e.g., Afghanistan, Egypt, Morocco, Pakistan, Sudan)	204,039	0.41	837
South East Asia B (Indonesia, Sri Lanka, Thailand)	206,870	0.04	83
South East Asia D (e.g., Bangladesh, India)	818,521	0.15	1,228
Western Pacific A (e.g., Australia, Japan)	129,888	0.04	52
Western Pacific B (e.g., China)	1,131,503	0.02	226
Africa D (e.g., Algeria, Niger, Nigeria)	159,577	0.09	144
Africa E (e.g., Congo, Ethiopia, Uganda, South Africa)	190,152	0.01	19
Total	4,178,197		4,327

Letters A-E are based on level of child and adult mortality with A indicating the lowest levels, and E the highest (WHO, 2000)

Prevalence of opioid dependence seems to be concentrated mainly in younger age groups, and higher in men compared to women (Degenhardt et al., 2001; WHO, 2001; 2002). In many countries, especially in developed nations, non-medical opioid users are more concentrated in cities (Bless et al., 1994; Garfield, Drucker, 2001).

In terms of types of opioid substances used, heroin is the most used opioid, but there are countries or regions where opium or other forms of opioids are more prevalent. Even though the above estimates

mainly reflect injecting drug use, there are other forms like smoking or inhaling, some of them more prevalent in developing countries.

6.1.2 Disease Burden

Long-term heroin users as one significant population of non-medical opioid users have a substantially increased risk of premature death from drug overdoses, violence, suicide and infectious disease-related causes (Darke & Ross, 2002; English et al., 1995; Hulse et al., 1999). Cohort studies of the mortality of heroin users treated before the advent of HIV indicated that they were 13 times more likely to die prematurely than their age peers (English et al., 1995; Goldstein & Herrrera, 1995; Hser et al., 1993). In countries with a high prevalence of HIV infection among IDUs, deaths from AIDS are a major contributor to premature death among heroin users (EMCDDA, 2003b; UNAIDS, 2002).

The risk of fatal opioid overdose is higher among opioid dependent heroin injectors who are male and increases with the duration of opioid dependence. It is also higher among those who use heroin with cocaine, alcohol and benzodiazepines and those returning to heroin use after a period of abstinence (Darke & Zador, 1996; Tagliaro et al., 1998; Warner-Smith et al., 2001).

In large parts of North America, Asia, and Eastern Europe, sharing contaminated needles, syringes and other injecting equipment accounts for a substantial proportion of HIV infections related to non-medical opioid use (Cohen, 2004; EMCDDA, 2003b; UNAIDS, 2002). The prevalence of Hepatitis C virus (HCV) is even higher among IDUs, in some countries up to 90% (EMCDDA, 2003a). Chronic infection has been estimated to occur in 75% of infections, and 3-11% of chronic HCV carriers will develop liver cirrhosis within 20 years (Hepatitis C Virus Projection Working Group, 1998).

Heroin-related deaths (irrespective of the aetiology, i.e. whether by overdose or HIV/AIDS) which primarily occur among young adults males account for a substantial number of life years lost in some developed societies (World Health Organization, 2002). In some parts of Europe, namely, Scotland and Spain, opioid-related deaths account for as many as 25%-33% of deaths in young (15-39 years) males (EMCDDA, 2003b).

Degenhardt et al. (Degenhardt et al., in press) estimated mortality attributable to illicit opioid use in two ways: (1) applying estimated mortality rate from all causes (derived from cohorts of illicit opioid users) to data on the prevalence of illicit opioid use in each WHO region; and (2) summing the separately estimated annual mortality rate from AIDS, drug overdose, suicide and trauma among the estimated number of dependent opioid users in each region. In 2000, the median estimated global number of deaths from opioid use derived using the all-cause method was 197,383 while the equivalent number of deaths derived by adding the separate mortality rates was 240,483. Both estimates had wide uncertainty intervals around them (82,365 to 407,689 for the sum of the four causes of death and 101,751 to 322,456 for the all-cause estimates). When crude estimates of morbidity attributable to illicit drug use were added to mortality, illicit opioid use accounted for 0.7% of global disability adjusted life years.

6.1.3 Opioid dependence and HIV/AIDS

Although people with opioid dependence constitute only a small proportion of the population, because opioids are predominantly used by injection, the contribution of opioid use to the transmission of human immunodeficiency virus (HIV) is significant. IDU is one of the leading modes of HIV transmission globally (UNODC, 2004; UNAIDS, 2004). In the United States of America in 1999 injecting drug users accounted for 18% of the reported HIV cases classified by a specific risk and for at least 36% of all reported AIDS cases (Centers for Disease Control and Prevention, 2001). Between 1990

and 1998, IDUs were the largest group among diagnosed AIDS cases in Western Europe, since 2001 the second largest group in Central Europe and by far the largest group in the Eastern European Region (EuroHIV, 2003). HIV seroprevalence rates of 60 to 93% among injecting heroin users are seen in some countries of Eastern Europe, Eastern Mediterranean, South-East Asia and Western Pacific regions (UNODC, 2004; UNAIDS, 2004). Worldwide, it is estimated that there are 12.6 million IDUs and that around 10% of HIV infections are associated with IDU. Therefore, IDU directly accounted for approximately 420,000 new HIV infections in 2003 (UNAIDS, 2004).

IDU continues to drive HIV epidemics in many countries. Explosive HIV epidemics among injection drug users (with HIV prevalence among IDUs increasing from 0% to 30-50% within a period of one to two years) have been witnessed in most regions, starting with New York City around 1980, followed by epidemics in such cities/regions as Edinburgh in 1984, Bangkok in 1988, Manipur (India) in 1989, Myanmar in 1992, Odessa (Ukraine) in 1994, Ho Chi Minh City (Viet Nam) in 1995, Svetlogorsk (Belarus) in 1996, Yunnan Province (China) in 1996, Kaliningrad (Russian Federation) in 1997, Temertau (Kazakhstan) in 1997, Moscow in 1999 and Narva (Estonia) in 2000. In the past few years new HIV epidemics have emerged among IDU populations in such diverse countries as Argentina, China, Indonesia, Islamic Republic of Iran, Libyan Arab Jamahiriya, Malaysia, Nepal and Uzbekistan. In many regions there is significant overlap of drug using and sex worker populations, providing a bridge for the transmission of HIV to the general population (Ball A. et al., 1998; UNAIDS, 2004; UNODC, 2004).

It has become an international public health priority to reduce the risks of HIV transmission associated with injecting drug use. Methadone maintenance treatment programs provide opportunities for expanded HIV prevention among injecting drug users and a platform for HIV/AIDS treatment and care, including the implementation of directly observed antiretroviral therapy for opioid dependent people with HIV/AIDS as well as therapy for opportunistic infections such as tuberculosis (WHO, UNODC, UNAIDS, 2004;).

6.2 Assessment of current use of methadone

The global number of persons with opioid dependence receiving prescribed *Methadone* is estimated to be over half a million, and to be on the increase in practically all regions of the globe. Originally implemented in the United States and Western Europe, methadone maintenance treatment of opioid dependence is expanding eastwards to Central and Eastern Europe, to the Eastern Mediterranean Region and to South-East Asia. On a global level, methadone maintenance has become the most frequently used therapeutic approach for heroin dependence. There are near 400 000 individuals with opioid dependence treated with methadone in the European Region (EMCDDA, 2003; WHO, 2004). Methadone maintenance treatment covers the estimated treatment needs in some European countries up to over 80%, in others much less. In the European Region, 76% of substitution treatment programmes use methadone (EMCDDA, 2000). In the USA at the end of 1998 179,329 patients were enrolled in methadone maintenance treatment programs (http://www.aatod.org/1999-2.html); current estimates of patients in methadone maintenance range from 200,000 to 300,000. Methadone is being used for treatment of opioid dependence also in Argentina, Australia, Canada, China, Indonesia, Iran, New Zealand, Thailand and some other countries. It is estimated that *a million opioid dependent people would be in methadone treatment within the next five years.*

6.3 Target population

Methadone treatment is indicated for those who are dependent on opioids and can be used as a substitution maintenance treatment or for detoxification and the management of opioid withdrawal. The largest group receiving methadone are heroin dependent persons. The majority of them are injectors, a

minority use heroin by smoking or sniffing, however, in a few countries, such as the Netherlands, the majority are non-injectors. In the European Union Member States it is estimated that sixty percent of opioid dependent drug users are drug injectors. (EMCDDA, 2003).

7. Treatment details

7.1 Indications for use

Management of opioid dependence, either as a maintenance medication or for gradual detoxification and opioid withdrawal management. Methadone maintenance treatment should be restricted to people who meet the clinical criteria for opioid dependence (WHO, UNODC, UNAIDS, 2004). Regulations in many countries prescribe that patients must also be adults, be able to give informed consent and present proof of identity (National Drug Strategy, 1998; Henry-Edwards et al., 2003).

7.2 Dosage regimens

The appropriate dosing for methadone treatment is divided into the *induction phase* of dosing involving the initial starting dose and the stabilization dose, and then dose adjustment for ongoing *maintenance therapy* or dose reduction for *withdrawal* from methadone.

Induction phase: Starting and stabilization doses

The objectives during induction to methadone are to retain individuals in treatment by reducing the signs and symptoms of withdrawal and to ensure their safety. There is a need to achieve a balance between adequate relief of withdrawal symptoms and the avoidance of toxicity (which may result in death) during the induction phase (Humeniuk et al., 2000). The first dose of methadone should be determined for each patient based on the severity of dependence and the level of tolerance to opioids. A dose of less than or equal to 20mg for a 70kg patient can be presumed to be safe, even in opioid naïve individuals as this is the lowest dose at which toxicity has been observed. Caution should be exercised for starting doses of 30 mg or more and extreme caution and supervision of the patient are required if an initial dose of methadone exceeding 40 mg is considered necessary (Humeniuk et al., 2000).

Doses can be increased by 5-10mg every three days based on presence of observable withdrawal signs, and patient complaints of withdrawal symptoms, but total weekly increases in dose should not exceed 20mg, with the maximum daily dose at the end of the first week of dosing normally not exceeding 40mg.

During the first two weeks of methadone substitution treatment the aim is to stabilise the patient so that they are not oscillating between intoxication and withdrawal. Patients should be carefully monitored during this time and should be observed daily for signs of intoxication or withdrawal (Henry-Edwards et al., 2003). Stabilization of the patient's dose usually can be achieved at doses of 30-50mg, which are generally able to eliminate withdrawal signs. For most patients this dose range will also alleviate but not necessarily eliminate withdrawal symptoms. Therefore, to maximize patient comfort and satisfaction with treatment the daily dose can be adjusted carefully upwards.

An expert workshop on the induction and stabilisation of patients onto methadone (Humeniuk et al., 2000) recommend the following dose titration procedure.

- Do not increase the methadone dose for at least the first three days of treatment unless there are clear signs of withdrawal at the time of peak effect (i.e. 3-4 hours after dose).
- Consider dose increments of 5-10mg every three days subject to assessment.
- Total weekly increase should not exceed 20mg.
- The maximum dose at the end of the first week should typically be no more than 40mg.

Maintenance therapy daily dose range

Doses should be determined for individual patients but generally a higher dose is required for maintenance than is required for initial stabilisation. Maintenance doses for effective methadone substitution treatment are typically 60-100mg/day.

Some individuals can be safely maintained at doses lower than 50mg. However, Methadone doses in excess of 60mg/day are most clearly associated with better retention in treatment and maximal suppression of heroin use (Ward et al., 1992; Ward et al., 1998). Cross tolerance to heroin increases as a function of increasing methadone dose and results in the blockade of the euphoric effect of concurrent heroin use. A daily methadone dose of 60mg or greater should be sufficient to ensure a substantial level of tolerance to the effects of heroin in the majority of individuals (Henry-Edwards et al., 2003, Gowing et al., 2001, Ward et al., 1998). Doses in excess of 100mg/day may be necessary to achieve successful maintenance with patients who have a fast methadone metabolism but there is no evidence from treatment outcome studies that routine dosing at levels in excess of 100 mg/day results in any additional benefit for the majority of patients (Henry-Edwards et al., 2003, Ward 1998). However, the maximum dose and maximum length of treatment should be left to the practitioner's clinical judgement, based on the assessment of the individual patient (WHO/UNODC/UNAIDS 2004).

Ideally, doses should be tailored to the individual patient's needs. Where withdrawal symptoms are causing the patient discomfort, doses should not be artificially limited by clinical policies.

Withdrawal dose regimen

Gradual reduction of the dose of methadone can be utilized to achieve withdrawal. The withdrawal process should be gradual and tapered as the dose level drops. The recommended rate of reduction is 10mg per week until a daily dose of 40mg is reached, and then reductions of 5mg per week. The rate of reduction is best negotiated with the patient to maximize patient involvement. Adjunctive symptomatic medications to minimize severity of withdrawal symptoms should be provided along with supportive counselling.

7.3 Duration of therapy

Treatment termination should occur as the result of negotiation between the clinician and the client and the majority of terminations are initiated at the request of the client. Length of time in treatment is predictive of an improved treatment outcome and it is recommended that patients be encouraged to remain in treatment for at least 12 months to achieve enduring lifestyle changes (Ward et al., 1998, Henry-Edwards et al., 2003). Abrupt cessation of methadone treatment will result in the development of the opioid withdrawal syndrome. Dose reduction should occur at a rate that does not cause physical or psychological distress to the patient (National Drug Strategy, 1998), using the withdrawal dose regimen described above. It is recommended that the methadone dose be reduced by 10mg/week to a level of 40 mg/day and then by 5 mg/week. Rates of reduction should be negotiated with patients, and dose changes should occur no more frequently than once a week. If more rapid cessation of treatment is required, abrupt cessation of methadone from a dose of 40 mg/day in conjunction with

clonidine and symptomatic medications to manage withdrawal signs and symptoms can be considered (Henry-Edwards et al., 2003; Gowing et al., 2000).

7.4 Reference to existing WHO and other clinical guidelines

The World Health Organisation, United Nations Office on Drugs and Crime and The Joint United Nations Programme on HIV and AIDS Position paper on substitution maintenance therapy is an important international statement on the role of substitution maintenance treatment, including methadone maintenance treatment, in the management of opioid dependence and HIV/AIDS prevention, treatment and care (WHO, UNODC, UNAIDS, 2004) (http://www.who.int/substance_abuse/publications/en/PositionPaper_English.pdf).

The WHO Expert Committee on Drug Dependence in its 30th Report acknowledged that "methadone maintenance treatment has grown substantially to become the dominant form of opioid substitution treatment globally" and that the "weight of evidence for its benefits is substantial" (WHO, 1998) (http://whqlibdoc.who.int/trs/WHO_TRS_873.pdf).

WHO Guidelines "Scaling up antiretroviral therapy in resource-limited settings" affirms that "opioid agonist pharmacotherapies, such as methadone maintenance treatment… have the advantage of allowing direct observation of the concomitant administration of ART" and recommends that "where feasible, countries promote and support the development of integrated programmes involving the direct observation of therapies for management of both drug dependence and HIV infection among IDUs (WHO, 2002). The same WHO guidelines provide recommendations on potential drug interactions between antiretroviral (ARV) medications and methadone and potentially necessary dosage adjustments of the medicines (http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf).

The evidence-based *treatment rules* for running a Methadone programme and for training purposes are internationally acknowledged and available in a number of sub-national, national (e.g. in Australia, Canada, Hong Kong, Indonesia, Islamic Republic of Iran, Lithuania, Myanmar, United Kingdom, USA), and international (Verster and Buning, 2000) guidelines.

The Commission on Narcotic Drugs at its 47th Session in March 2004 invited WHO to develop guidelines on pharmacological therapy of opioid dependence, including therapy with methadone, and these guidelines are in the process of development in WHO and are expected to be published in 2005.

WHO guidelines on "Comprehensive Treatment and Care of HIV-infected Injection Drug Users" is currently under development and will be published in early 2005. The guidelines will address issues related to opioid agonist pharmacotherapy, including methadone treatment of opioid dependence.

7.5 Need for special diagnostic or treatment facilities and skills

There is no need for special diagnostic facilities per se, but clinical skill in the diagnosis of drug dependence and the recognition of opioid dependence as a diagnosis separate from occasional opioid use or other illicit drug use is required (Bell et al., 1992; Mattick & Hall, 1993; Ward et al., 1992; Ward et al., 1998). In view of frequently observed psychiatric and somatic comorbidity in need of treatment, the respective clinical diagnostic screening also must be assured.

Arrangements for controlled intake of prescribed methadone must be made during the induction phase and for patients in unstable situations, in order to avoid overdose and diversion. A record of doses received is necessary to efficiently manage patient dosing and ensure appropriate doses are administered.

Urine drug testing can be a useful tool in diagnosis of drug dependence and for monitoring treatment adherence and effectiveness (Ward et al., 1998). Facilities for collecting and testing urine samples would be of benefit, but are not necessary to the adequate delivery of opioid replacement therapy (Ward et al., 1998). In fact, in settings with constrained economic resources there would be an argument for testing urine samples only during the induction period. However, the presence of heroin metabolite (morphine) in urine can be a trigger for counselling and dose adjustment upwards to reduce ongoing illicit opioid use.

Clients may need to be registered in a central register of patients in opioid substitution therapy. This register can assist clinicians and others to oversee the functioning of the program, the extent and duration of patient enrolment, and to ensure patients do not register twice to receive methadone from more than one source.

8. Summary of comparative effectiveness

8.1 Updated review of randomised clinical trials in a variety of clinical settings

8.1.1 Search strategy

Literature search 1966 to 1 July 2004. No language restrictions.

- MEDLINE
- The Cochrane controlled trials register (CCTR)
- The Cochrane Data-base of Systematic Reviews
- Reference lists of retrieved articles

Searched terms :

- Methadone
- Maintenance treatment
- Substance use disorders
- Randomized controlled trials

Study selection :

- Randomized controlled trials (RCT:s) comparing maintenance treatment with methadone and controlled conditions in opioid dependence
- Meta-analysis and systematic reviews of this type of studies

Data-collection and retrieval :

- Two researchers independently retrieved the data base.

8.1.2 Previous meta-analysis and systematic reviews

An updated Cochrane review of all randomised clinical trials of methadone maintenance therapy, compared with either placebo maintenance or other non-pharmacological therapy for the treatment of opioid dependence, identified 6 relevant studies (2 double-blind), with a total number of 954 participants. The method of concealment of allocation was adequate in one study. Based on the meta-analysis, methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment (3 RCTs, RR=3.05; 95%CI: 1.75-5.35) and in the suppression of heroin use (3 RCTs, RR=0.32; 95% CI: 0.23-0.44). Conclusion of the review: methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy (Mattick et al., 2004).

8.1.3 Summary of available data

In Table 2 the design and outcome of the 8 randomized controlled studies on methadone maintenance compared with non-active control conditions are presented. Two studies were placebo-controlled, 2 used a gradual withdrawal group as controls and 4 studies used untreated controls. A total of 1428 subjects have been included in the different studies. RCT-studies comparing methadone with other active drugs are more fully reviewed in Berglund et al. (2003).

8.1.4 Meta-analytic procedures

Standardized mean difference effect-sizes, d, were used in the meta-analytic calculations. The Hedges' correction was used (Hedges and Olkin, 1985) in order to adjust for small sample-size bias. For categorical data odds ratios were transformed according to Shadish and Haddock (1994). The Comprehensive Meta-Analysis Software Program was used for the calculations including heterogeneity testing and moderator analysis (Borenstein and Rothstein, 1999). Although no strict clinical interpretation of effect-sizes is agreed upon, many apply the convention that 0.2 is a small but relevant effect, 0.5 a moderate effect and 0.8 a large effect.

8.1.5 Results

Outcome measures for retention, illicit opioid use and criminality are presented as meta-analyses. The outcome results are heterogeneous and therefore a random model is used. Type of control was a significant moderator for abuse and retention and the outcome measures are divided according to type of control. In the subgroups most of the results were homogeneous with the exception of untreated controls (abuse and retention) and detox controls (retention). In the Strain et al. study the 20 mg/d methadone group was excluded from the analysis. The Dolan et al. study was performed inside a prison and is presented separately.

In Figures 1a-c the results of the meta-analyses for retention, opioid abuse and criminality are presented. The summary standard mean differences, d:s, are .90, .61, and .48, respectively. They are all significant. In the study by Dolan et al. in prison objective and subjective measures of opioid use were significantly reduced in the methadone group (d = .30, and .53, respectively).

8.1.6 Conclusion

Methadone maintenance treatment in opioid dependence has been studied in 8 randomized controlled trials using non-active controlled conditions. All 8 studies reported significantly positive effects of methadone compared with controls. In three meta-analyses robust effects of methadone compared with controls were found for retention, opioid abuse and criminality, respectively. In one study methadone maintenance treatment reduced abuse of illegal opioids in prison. Thus, according to its efficacy, methadone maintenance treatment should be made available for subjects with opioid dependence.

Figures 1a-c. Results of randomized controlled studies of methadone maintenance treatment

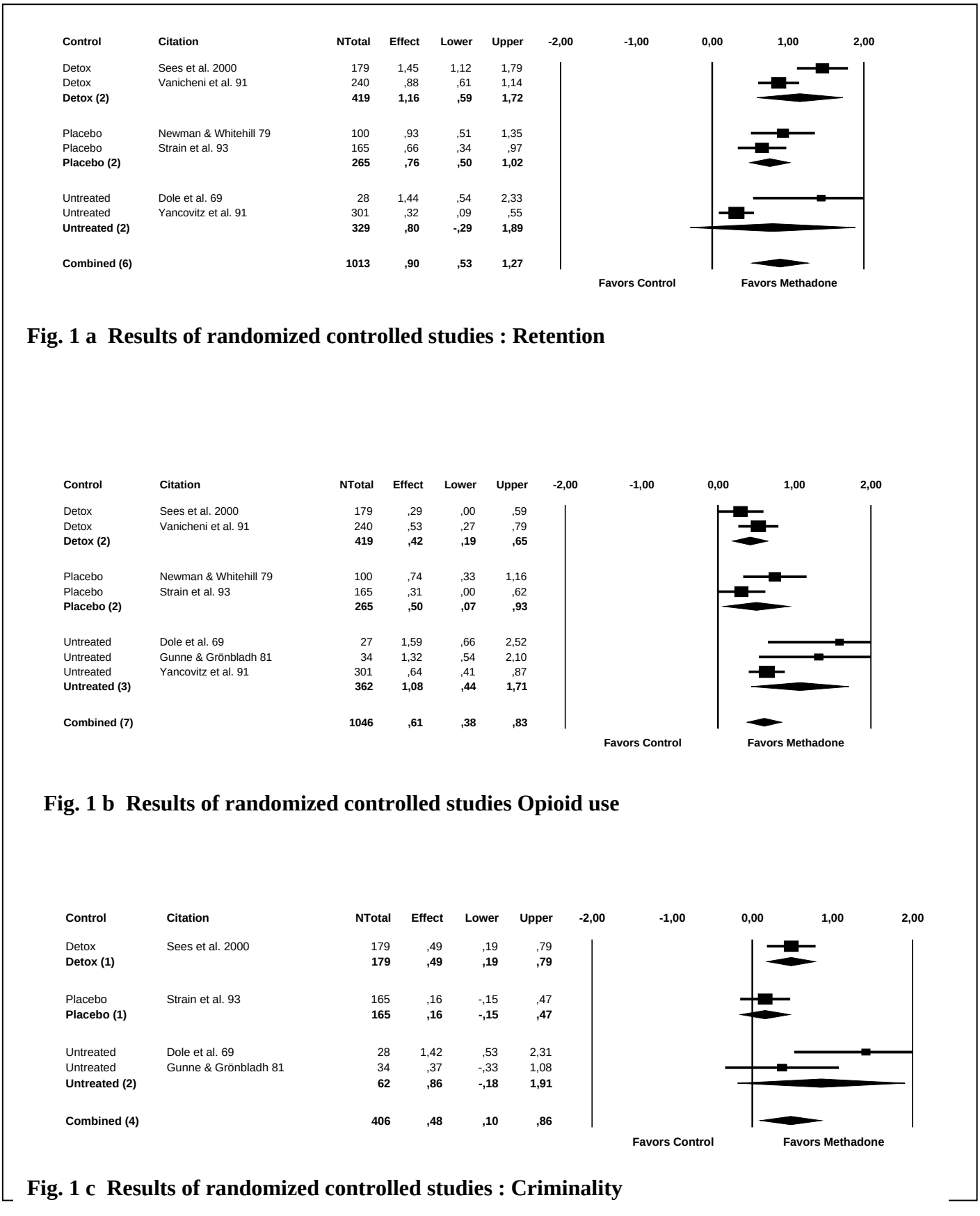

Fig. 1 a Results of randomized controlled studies : Retention

Fig. 1 b Results of randomized controlled studies Opioid use

Fig. 1 c Results of randomized controlled studies : Criminality

Table 2. Results of methadone maintenance treatment in comparison to controls

Study	Subjects/ Setting	Design	Treatment duration	Outcome measures			
				Opioid abuse	Retention	Criminality	Others
Dole et al., 1969	28 Outpatient clinic, US	1. Methadone 35 mg/d 2. Untreated control	50 weeks	**Re-addicted** 1. 0% 2. 100%	1. 75% 2. 6%	**Reincarceration** 1. 25% 2. 94%	Job/school 1. 50% 2. 0%
Newman & Whitehill, 1979	100 Outpatient clinic, Hong Kong	1.Methadone 97 mg/d 2.Placebo	156 weeks	**Persistent use, heroin** 1. 23% 2. 63%	1. 56% 2. 2%	✷**Conviction rate per 100 man-months enroled** 1. 1.41 2. 3.17	Deceased 1. 6% 2. 2%
Gunne & Grönbladh, 1981	34 Research centre, Sweden	1.Methadone (dose not reported) 2. Untreated control	104 weeks	**Drug free** 1. 71% 2. 6%	-	**In prison (2 yrs)** **1. 0%** 2. 12%	Deceased 1. 0% 2. 12% Rehabilitated 1. 76% 2. 6%
Yancovitz et al., 1991	301 Interim methadon clinic, US	1.Methadone 80 mg/d 2. Untreated control	64 weeks	**Positive urine (1 month)** 1. 29% 2. 60%	1. 72% 2. 56%		Cocaine pos urine 1. 68% 2. 70%
Vanichseni et al., 1991	240 Narcotics clinic, Thailand	1.Methadone 74 mg/d 2. Methadone 58 mg/d [gradual withdrawal]	6 weeks	**Positive urine** *(all samples)* 1. 28% 2. 53%	1. 76% 2. 34%		-
Strain et al., 1993, 1994	95(247) Methadone treatment research clinic, UK	1.Methadone 50 mg/d 2. Methadone 20 mg/d 3. Methadone 0 mg/d	26 weeks	***Positive urine*** 1. 56% 2. 68% 3. 74%	Week 20 1. 52% 2. 52% 3. 21%	**ASI legal status** *composite score* 1. 0.11 2. 0.18	Cocaine pos urine 1. 53% 2. 62% 3. 67%

						3. 0.14	
Study	**Subjects/ Setting**	**Design**	**Treatment duration**	**Outcome measures**			
				Opioid abuse	**Retention**	**Criminality**	**Others**
Sees et al., 2000	179 Research clinic, US	1.Methadone 86 mg/d 2. Methadone [gradual withdrawal]	26 weeks	***Heroin use*** 1. 67% 2. 88%	Median days 1. 438 d 2. 174 d	**ASI legal status** *composite score* 1. 0.05 2. 0.13	**Employment, family (ASI)** *Sex-related HIV risk behav* 1. No diff 2. No diff
Dolan et al., 2003	382 Prison, AUS	1.Methadone 60 mg/d 2. Untreated controls (waiting list)	17 weeks	***Hair analysis*** 1. 27% 2. 42% Heroin injection 1. 32% 2. 74%	-		Shared syringes 1. 20% 2. 50%

✸ not used in meta-analysis

8.2 Long-term observational cohort studies

The USA National Institute on Drug Abuse (NIDA) has funded three large-scale national treatment evaluations in the United States covering the past three decades. These observational studies were conducted in natural settings and designed to determine whether the nation's treatment systems were delivering effective services based on current drug use patterns and client needs. They include the Drug Abuse Reporting Program (DARP; see Simpson & Sells, 1982; 1990), the Treatment Outcome Prospective Study (TOPS; see Hubbard et al., 1989), and the Drug Abuse Treatment Outcomes Studies (DATOS; see Simpson & Curry, 1997; Simpson & Brown, 1999), respectively. Collectively, they have examined during treatment performance and predictors of follow-up outcomes for stratified samples of 65,000 admissions to major types of treatment in 272 community-based programs throughout the U.S. Findings from approximately 250 publications based on this research give consistent and broad field-based support for the effectiveness of drug dependence treatments, particularly for clients with adequate lengths of stay.

Data from the most recent evaluation (DATOS) were collected from over 10,000 clients admitted to 99 treatment programs in 11 U.S. cities between 1991 and 1993, representing methadone maintenance, short-term residential (e.g., 28-day hospital programs), long-term residential (therapeutic communities), and outpatient drug-free services. A sub-sample (n=4,229) of the eligible clients who completed the two-stage intake interviews was selected for 1-year follow-up (using a stratified random design). Altogether, 74% (n=3,147) were located, including 70% (n=2,966) who were successfully interviewed, 1.5% (n=64) who were deceased, and 2.7% (n=117) who refused to participate. Gender, ethnicity, and average age were not significantly different between the intake and follow-up samples (Flynn et al., 1997).

Outpatient Methadone Treatment (OMT) programs administered methadone medication under medical supervision to reduce cravings for heroin, in addition to providing counselling and case management services. Some provided methadone as long-term maintenance for clients and others reduced methadone dosage over time with goals of drug abstinence. Private for-profit methadone clinics, non-profit community-based programs, hospital-based outpatient clinics, and county-managed programs were represented. There were 29 OMT programs with 1,540 clients in the DATOS sample.

Admissions to OMT were 60% male, 52% African American or Hispanic, and 82% were over 30 years of age. In addition, 67% had graduated from high school (or equivalency), 40% were married or living as married, 3% were referred to treatment by the criminal justice system, and 10% had private health insurance (Hubbard et al., 1997). Previous drug treatments were reported by 77%; of these, 92% had accumulated more than 3 months in treatment. Principal indicators of problems in pretreatment functioning (other than heroin or other opioid drugs) were weekly cocaine use (42%), no full-time work (85%), and illegal activity (29%).

At least half of the OMT programs in DATOS expected clients to stay in treatment for 24 months or more (ranging from 24 to 30 months). However, the median length of stay was 12 months; in the program with the lowest average retention rate, only 15% of the clients stayed 12 months or longer, versus 76% of the clients in the program with the best retention rate. Comparisons between OMT programs identified several factors related to their overall retention rates; these involved complex variations in age and gender, treatment history, psychological problems, cocaine and alcohol dependence, and needle sharing among clients admitted to different programs (Simpson et al., 1997).

The length of time clients stayed in treatment was directly related to improvements in follow-up outcomes, replicating findings from previous national treatment evaluations (DARP and TOPS). In OMT, for example, clients who remained in treatment for a year or longer were 4 times less likely than early

dropouts (i.e., treated under 3 months) to use heroin weekly during the 1-year follow-up. There was a 69% drop in the number of weekly heroin users and a 48% decline in weekly cocaine users. Unemployment did not change significantly, but illegal activity declined 52%. Rates for being jailed in the year before versus after treatment dropped from 63% to 21%. Further treatment during follow-up was reported by 74% of the OMT sample.

Long-term (5-year) follow-up outcomes were classified into five distinct patterns over time (using latent-class analysis with a subgroup of the 1-year follow-up sample). An estimated 51% showed *Sustained Improvement* (low rates of weekly drug use and high treatment involvement at both time points), 19% showed *Delayed Improvement* (high weekly drug use at the first interview with low use rates later), 10% showed *Substitution* (high use of alcohol or drugs other than heroin and cocaine at both time points), 12% showed *Delayed Relapse* (low use at the first interview that increased by the second), and 8% showed *Continued Use* (high use of heroin and cocaine at both time points). The Sustained Improvement group was less likely to have problems with cocaine or alcohol at admission and was more satisfied with treatment. These findings indicate many methadone treatment clients improve their behaviour in connection with treatment and maintain these improvements over an extended period of time.

Longer retention in methadone treatment was associated with greater crime cost savings, leading to significant favourable returns on treatment investments for both discharged and continuing clients. However, greater net economic benefits were realized from continuing clients. Cost-containment and ideological practices opposed to methadone maintenance and longer lengths of stay in treatment can diminish the benefits from averted crime associated with methadone treatment (Flynn et al., 2003).

Attributions regarding reasons for long-term recovery from opioid dependence were obtained from former DATOS OMT clients in the 5-year follow-up interview. They were first classified into two groups – recovering and non-recovering – strictly defined and based on both biological and self-report measures of no opioid or cocaine use, less than daily use of alcohol, and no arrests or illegal activity during the year prior to interview. The 28% who were in recovery at Year 5 reported that they had relied primarily upon personal motivation, treatment experiences, religion/ spirituality, family, and their job/career. Particular value was placed on the support from family and close friends, indicating the importance of stronger efforts to develop social networks for support of drug-free functioning, especially among clients who lack these resources or need them strengthened (Flynn et al., 2003).

Findings from DATOS are highly consistent with other large-scale treatment evaluations, including the National Treatment Outcome Research Study in England (NTORS; Gossop et al., 2000). Prominent treatment policy reports in the U.S. have also consistently judged methadone maintenance as an effective but underutilized treatment (Gerstein & Harwood, 1990; Lamb et al.,

1998). However, inappropriate dosage has limited its effectiveness levels, and this is sometimes related to whether a program follows a philosophy of methadone maintenance or tapering (see Gossop et al., 2001). Other issues related to treatment effectiveness include engagement in the psychosocial therapeutic process and access to needed social services (Simpson & Brown, 1999), as well as organizational functioning of the treatment system (Delany et al., 2001).

8.3 Studies on methadone maintenance treatment as a prevention of blood-born infections

Transmission of blood-borne infections, particularly hepatitis B and C and HIV is one of the most significant risks of injection drug use. The main transmission modes for HIV and other blood-born infections among users of illicit drugs are unsafe injection practices (using contaminated needles, syringes, other

injecting equipment and drug solutions) and unsafe sexual practices (unprotected penetrative sex). Measures for a reduction in HIV risk behavior in methadone maintenance patients are:

1. Reduction of HIV seroconversion rates in HIV-negative opioid users
2. Reduction in injecting drug use
3. Reduction in unsafe injection practices
4. Reduction in unsafe sexual practices

Reduction can be measured in 1 through laboratory findings, in 3 & 4 through self-report data, and in 2 through both types of sources (urine analysis and/or self-report). In addition to reducing the risks of HIV (and other blood-borne infections) transmission, improving compliance with HIV/AIDS treatment and care (including anti-retroviral treatment) in cases of HIV seropositivity, and contributing to a reduced progression of HIV-related or other disease symptomatology also are potentially protective functions.

8.3.1 Reduction of seroconversion rates

Evidence on reduced seroconversion rates for HIV in patients on methadone maintenance treatment has been demonstrated repeatedly. Ward et al. (1995) have reviewed the earlier studies. Abdul-Quader et al. (1987) found an association between length of time in treatment and lower rates of HIV seropositivity. The longer the time spent in methadone maintenance, the lower the level of seropositivity (Schoenbaum et al. 1989). Patients in methadone maintenance were found to be less likely to be HIV positive than persons awaiting treatment (Chaisson et al., 1987). Marmor et al. (1987) found lower rates in methadone maintenance patients as compared to patients in detoxification programmes.

A Swedish study evaluated results of yearly re-testing of all methadone patients entering treatment in 1984 who had tested negative for HIV on entry. No seroconversion was detected in any of these patients between 1984 and 1990, while among applicants for methadone maintenance treatment seroprevalence rates increased from 16% to 59% (Blix & Groenbladh, 1991).

A prospective study compared a cohort from methadone maintenance programmes with a cohort of out-of-treatment opioid injectors over 36 months, with a total of 255 probands. Seropositivity in the treatment group increased during this period from 13% to 18% (all seroconversions took place in persons who had left treatment), while seropositivity in the out-of-

treatment group went up from 21% to 39% (Metzger et al., 1993). Another prospective study found in a cohort of 681 opioid injectors during a 5-year-period a significant relation between those staying in treatment for less than 1 year as compared to those staying longer (Moss et al., 1994). Serpelloni et al. (1994) described an increase of 70% for the risk of an HIV infection for every 3 months spent out of treatment in the year prior to data collection.

8.3.2 Reduction of injecting drug use

Evidence for a reduced frequency of drug injecting is presented from many studies. Hall et al (1995) published a review of earlier studies, including both randomised controlled trials and observational studies. They concluded that observational studies generally support the findings from RCTs in showing that heroin use decreased while opioid dependent individuals remained in methadone maintenance treatment, although there were substantial differences in outcome between studies. Differences relate to dosages, duration of treatment, and patient characteristics.

8.3.3 Reduction of unsafe injection practices

Not all patients in methadone maintenance treatment quit injecting totally. Also, the reduction of injecting drug use develops over time. A supplementary target of treatment therefore is to reduce risk-taking injection practices if injecting drug use continues.

An early review of 15 studies came to the conclusion that methadone maintenance consistently is associated with reductions in the sharing of injecting equipment (Ward et al., 1995).
Eight studies were included in a meta-analysis, comparing HIV risk behaviours in methadone maintenance patients as compared to opioid users out-of-treatment, or comparing pre-post values, various durations of treatment or continuous versus interrupted treatment (Marsch, 1998). A total of 1781 persons were participating in the studies. Outcome measures : injection drug use and/or needle sharing; 3 studies also asked about sexual risk behaviour. Seven studies found significant differences in risk behaviour after 12 months in treatment; one study measuring outcome after only 1 month in treatment found no significant difference in outcome. Significance levels ranged between p=0.00 to p=0.08 (mean p=0.01), and effect sizes from r=0.12 (d=0.24) to r=0.48 (d=1.10), mean r=0.21 (d=0.45). The efficacy of methadone maintenance treatment to reduce HIV risk behaviour is considered to be small to moderate.

A more recent review of 33 studies with a total of over 17 000 participants concludes that methadone maintenance treatment effectively reduces HIV risk behaviors, particularly needle use, and prevents HIV infection (Sorenson & Copeland, 2000). Reduction of needle sharing is less obvious. However, the British National Treatment Outcome Research Study NTORS investigated changes in injecting and sharing of needles and syringes in 732 drug "misusers" in methadone maintenance treatment and in residential drug-free programmes. Clients from residential programmes were more likely to be abstinent at 1-year follow-up, methadone clients were more likely to be injecting but not sharing (Gossop et al., 2003).

8.3.4 Reduction of unsafe sexual practices

There is less available evidence regarding changes in risk taking sexual behavior. Only 3 of the 8 studies analysed by Marsch (1998) used risk taking sexual behavior as an outcome measure. A more recent study including 123 drug injectors (50% in methadone maintenance treatment, 50% out-of treatment) found a higher rate of sexual partners, of unprotected sex and of high-risk sexual partners in the out-of-treatment group (Lollis et al., 2000). It remains open if this result is a consequence of treatment, or if it reflects a more positive attitude of patients who engage in treatment to protect their health.

8.3.5 Adherence to anti-retroviral therapy

Progression of non-symptomatic and symptomatic HIV disease depends among other factors on HIV/AIDS treatment and care, including the prophylaxis and treatment of opportunistic infections and the use of highly active anti-retroviral therapy (HAART). HAART involves life-long treatment with a combination of at least three anti-retroviral drugs. Good adherence to HAART is critical to prevent treatment failure, disease relapse and emergence of anti-retroviral resistant strains of HIV. Treatment adherence support is a key element of any HAART and other anti-retroviral therapy programme. To date there is limited research on the impact of methadone maintenance treatment on HIV/AIDS treatment outcomes, including HAART adherence. The adherence of patients to antiretroviral therapies has been studied by Arnsten and colleagues who showed that self-reported adherence to antiretroviral therapies is lower than actual adherence documented with use of MEMS caps (one week adherence by self report: 78%, one week adherence demonstrated by MEMS cap monitoring: 53%) (Arnsten et al., 2001). Anti-retroviral compliance improves in the stabilisation phase of methadone maintenance treatment. At entry

into treatment, less than 80% reported adherence to the treatment regimen, and a significant increase in adherence was found during the first 4-week stabilisation phase (Avants et al., 2001).

8.3.6 Conditions for successful reductions of HIV-related risks through methadone maintenance

The protective value of methadone maintenance treatment against blood-born infectious disease shows differences when comparing outcomes across services. Two factors improving outcome in HIV protection have been identified :

- Duration of treatment : maintenance treatment of 12 months or longer (Moss et al., 1994, Marsch, 1998);
- Dosage: higher average methadone dosages (Brown et al., 1989; Serpelloni et al., 1994).

8.4 Conclusion

During the last three decades, the scientific evidence has accumulated that methadone maintenance is an effective treatment for opioid dependence that has a supportive function to enhance HIV/AIDS treatment and care. In conjunction with evidence for a superior capacity of

methadone maintenance therapy for recruiting opioid-dependent injecting drug users into treatment, retain them in treatment and reduce risky behaviours associated with HIV transmission, methadone maintenance treatment is a major public health tool in the management of opioid dependence and in HIV prevention, treatment and care among opioid dependent drug users.

9. Summary of comparative evidence on safety

9.1 Estimate of total patient exposure to date

Methadone has been widely used for pain management and since 1960s - for the management of opioid dependence. Since that time millions of opioid-dependent people were treated with methadone both for detoxification purposes and maintenance treatment, and the total number of treatment episodes can be estimated in tens of millions. As methadone maintenance therapy envisages long-term treatment with a significant proportion of patients retained in treatment for many years and in view of the fact that currently the global number of persons with opioid dependence receiving prescribed methadone is estimated to be over half a million, the accumulated experience with methadone in management of opioid dependence has to be considered as very substantial.

9.2 Description of adverse effects/reactions

Side effects and toxicity of methadone are similar to those described for morphine, another full opioid agonist. Adverse effects include: respiratory depression; anorexia, nausea, vomiting (particularly in initial stages), constipation; euphoria, hallucinations, dizziness, drowsiness, confusion, headache; dry mouth, spasm of urinary or biliary tract; hypotension, postural hypotension, vertigo, bradycardia, tachycardia, palpitations, headache, sweating, miosis, hypothermia; decreased libido; rash, facial flushing, urticaria, pruritus.

Methadone is subject to accumulate in the body and has a more prolonged effect than morphine. Long-term treatment with methadone results in tolerance to its analgesic, sedative and euphoric effects, with minimal toxicity.

Methadone can contribute to cardiac complications by prolonging the QT interval, in particular when high doses are prescribed (IC50 for (R,S)-methadone for blocking HERG potassium current in transfected HEK cells: 9.8 µM) (Katchman et al., 2002). Case-reports of Torsade de Pointe in patients receiving methadone have been described. The largest series describes 17 methadone treated patients who developed Torsades de Pointes, with a mean QTc interval of 615 ± 77 msec (Krantz et al., 2002). Fourteen patients had however a predisposing risk factor for arrhythmia and the mean daily methadone dose was high (397 mg/day; SD: 283 mg/day) (Krantz et al., 2002).

9.3 Variation in safety due to health systems and patient factors

Respiratory depression can be a serious problem, particularly in patients initiating methadone maintenance treatment, who are only partially tolerant to opioid agonist effects and the risk of overdose is the highest during the induction period. The risk factors to be identified are the starting

dose, the use of other drugs, e.g. alcohol, benzodiazepines and heroin, and the general health condition (Humeniuk et al., 2000). Deaths reported among opioid dependent drug users in the first week or two weeks of methadone treatment (Gardner, 1970; Drummer et al., 1992; Zador & Sunjic, 2002; Wagner-Servais & Erkens, 2003) have been attributed to: (a) patient factors including commencement on doses of methadone that are too high for the level of physical tolerance, and slowing the metabolism of methadone caused by the use of other drugs (especially sedatives) and/or individual variation (e.g., due to liver disease); and (b) clinician factors including poor assessment of physical tolerance, poor understanding of the accumulation of methadone in tissue in the initial days of dosing, and inadequate observation of the patient and supervision of dosing.

Departure from methadone treatment in a planned way results in ongoing reduced risk of mortality (Oppenheimer et al., 1994). Unplanned departure and ongoing illicit drug use will result in a return to baseline risk rapidly (Zanis et al., 1998). Mortality increases significantly in patients who discontinued methadone maintenance treatment (Langendam et al., 2001), while the mortality risk decreases again after readmission (Grönbladh et al., 1990).

An increase in methadone maintenance programmes does not invite an increase in methadone-related death, even if take-away doses are allowed (Bryant et al., 2004). Mortality rates during methadone maintenance treatment are significantly lower in comparison to heroin addicts out of treatment. Heroin injectors who enter and stay in treatment will reduce their risk of mortality over three fold if they consistently stay in treatment (Mattick et al., 2003; Stenbacka et al., 1998).

9.4 Use of methadone in pregnancy

Methadone has been used for the management of opioid dependence in pregnancy for several decades. Methadone should be used in pregnancy if the potential benefits justify the risk to the mother and foetus (Finnegan, 1991). However, it is a category C medication in Australia and the USA, indicating that due to its pharmacological effect it can cause harmful effects on the foetus or neonate without causing malformations. It may cause respiratory depression in newborn infants, and withdrawal symptoms may be observed in infants born to methadone maintained mothers. A neonatal opioid withdrawal syndrome may occur 72 hours after birth, characterised by CNS, gastrointestinal and respiratory disturbances, and requires symptomatic management. It resolves without ongoing sequelae. These infants are of lower birth-weight compared with infants of non-drug exposed mothers (Finnegan, 1988).

These observations need to be viewed within an appropriate understanding of the risks to pregnant heroin users and their new-born infant. Heroin-dependent pregnant women are a high-risk group, lacking in access to adequate antenatal care, frequently poorly nourished, experiencing poor living conditions, exposed daily to marked fluctuations in blood-morphine levels, frequently abusing a range of licit and illicit drugs and exposed to contaminants, and often suffering from infectious diseases such as hepatitis (HBV and HCV) or HIV/AIDS. Methadone maintenance in pregnancy replaces a short-acting illicit drug of dependence of unknown quality (i.e., heroin), with a pure opioid administered within a medical framework. Providing a pregnant woman with a daily dose of methadone reduces exposure to fluctuating blood-morphine levels and a range of unknown drug contaminants, increases access to adequate antenatal care, and produces longer pregnancies with fewer birth complications for infants who are larger for their gestational age than from heroin dependent women who do not enter such methadone treatment (Ward et al., 1998).

Breastfeeding is permissible in mothers in methadone treatment. During lactation methadone can be found in breast milk, and infants should be monitored for sedative effects. A review of the literature on methadone maintenance treatment and lactation is available (Jansson et al., 2004).

9.5 Drug interactions

Methadone is metabolized by several isoforms of the cytochrome P450 family and co-medications that are inhibitors or inducers of these isoforms can increase or decrease, respectively, methadone plasma levels.

Drugs such as some antiretroviral drugs (delavirdine), a range of antibiotics (ciprofloxacin, fluconazole, ketoconazole, erythromycin, clarithromycin, troleandomycin), anxiolytic and antidepressant drugs (diazepam, moclobemid, fluoxetine, fluvoxamine, paroxetine, nefazodone, sertraline), anti-migraine drug (dihydroergotamine), urinary alkalinizers (sodium bicarbonate) and some fruits (grapefruit and its juice) may increase serum methadone levels and its effects.

Drugs such as a range of anti-retroviral drugs (abacavir, amprenavir, efavirenz, lopinavir, ritonavir, nelfinavir, nevirapine), barbiturates, anticonvulsants (carbamazepine, phenytoin), corticosteroids (dexamethasone), some antibiotics (rifampicin, rifampin/isoniazid), diuretic spirinolactone, herbal medicine St. John's wort and urinary acidifiers like ascorbic acid can decrease methadone plasma levels and may lead to withdrawal symptoms, severe in some cases.

Other opioid agonists, like buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine can displace methadone on μ-opioid receptors to cause withdrawal (DeMaria, 2003; Kalvik et al., 1996). Opioid antagonists, like naltrexone, nalmefene, naloxone also displace methadone from opioid receptors causing severe withdrawal syndrome. The synthetic analgesic tramadol potentially may cause withdrawal in persons already taking opioids.

A review of methadone-drug interactions is available (Leavitt, 2004).

9.6 Summary of comparative safety against comparators

Compared to other opioid agonists used in the management of opioid dependence, methadone is the most frequently used medicine and has the longest history of clinical use with well researched and documented profile of adverse effects and drug interactions.

10. Summary of available data on comparative cost and cost-effectiveness

10.1 Range of costs of proposed medicine

The cost of methadone is not provided in the International Drug Price Indicator Guide. The costs per patient/year (based on average daily dosage of 80 mg) vary from USD$29 (SLOVAKOFARMA, Slovak Republic), USD$60 from BUFA B.V. (the Netherlands) to USD$110 (Biomed Limited, New Zealand), USD$200 (Nycomed, Denmark) and up to USD$512 from Aventis Pharma Deutschland GmbH (Germany) and USD$700 from L. MOLTENI & C (Italy).

10.2 Results of cost-effectiveness analysis

The first economic evaluation of methadone maintenance treatment was conducted in the early 1970s. Methadone maintenance was costed for all aspects of treatment delivery compared with other treatments costed in the same way. Methadone maintenance treatment was reported to be as effective as a therapeutic community intervention, but the cost of providing methadone was one-quarter the cost of therapeutic communities. In conclusion, methadone maintenance treatment was found to be twice as cost-effective (Goldschmidt, 1976). More recently, a cost-effectiveness analysis of methadone maintenance treatment using life-years of survival (Barnett 1999) has showed an incremental cost-effectiveness ratio of $5915 per life-year saved. This study included all costs of treatment provision in the analysis, based on a separate analysis of costs from 600 methadone maintenance programs. Subsequently, Barnett and Hui drew on this earlier work and found methadone maintenance treatment to be cost-effective with an incremental cost-effectiveness ratio of less than $1100 per quality-adjusted life year. They reported this ratio to be more cost-effective than many widely used medical therapies (Barnett and Hui, 2000). Additionally, they found the use of low doses of methadone were less cost-effective than adequate doses and that short episodes of methadone treatment of less than six months are not likely to be cost-effective compared to other options.

In a comparator analysis, Barnett showed that methadone may almost always be more cost-effective than buprenorphine as a maintenance agent (Barnett et al., 2001). However, analysis of data from the largest randomised controlled trial of methadone to date (Mattick et al., 2003) showed no significant difference in cost-effectiveness when methadone was compared to buprenorphine (Doran et al., 2003). This latter article presents the cost-effectiveness of buprenorphine versus methadone in the management of heroin dependence. The trial used a flexible dosing regime that was tailored to the clinical need of the patients, with high maximum doses, using the marketed tablet formulation, under double-blind conditions. A total of 405 subjects were randomised to treatment at one of three specialist outpatient drug treatment centres. The costs included both direct patient costs and operating (facility) costs. The primary outcome measure used in the economic analysis was change in heroin-free days from baseline to the sixth month of treatment. Mean costs of methadone and buprenorphine treatment over a 6-month period were $1,415 and $1,729 respectively.

Recent modelling of the impact of increasing the availability of methadone maintenance programs on reducing the extent of HIV transmission has also shown that increasing such treatment availability is a cost-effective way of providing benefits to communities (Zaric et al., 2000).

10.3 Results of cost-benefit analysis

The most comprehensive cost-benefit/offset study to date is that conducted in the Californian Drug and Alcohol Treatment Assessment (CALDATA) study (Gerstein and

Harwood, 1994) that examined the effects of methadone programs on drug use, health, health care utilisation, and crime. The costs of all aspects of methadone treatment delivery, and the economic value of treatment both to taxpayers and society were included. The benefits following treatment were substantial, with the benefit to cost ratios for those in treatment being 4.78:1 and 4.66:1 for the taxpayer and society, respectively. This results indicates a US$4-US$5 return to the community for each dollar expended on methadone maintenance treatment.

11. Summary of regulatory status of the medicine

Methadone is a narcotic drug under international control in the United Nations Drug Control Conventions of 1961, 1971, and 1988 and is included in Schedule 1 of the 1961 Single Convention on Narcotic Drugs.

In those countries where methadone is available for the treatment of opioid dependence it is subject to strict regulation to ensure that it is used in accordance with high quality medical practice and to minimise the risk of diversion of prescribed medication to the illicit market (Butler, 2002, Boekhout van Solinge, 1997; Farrell, 1995; Jaffe and O'Keefe, 2003; Newman, 2001; National Drug Strategy, 1998; Tuffs 2001). Most countries base their regulations on the 1961 Convention and have specific controls on opioid drugs including methadone (Farrel, 1995).
Regulations typically require that methadone can only be prescribed by authorised prescribers (e.g. in Australia, Germany, Ireland) or provided by accredited opiate treatment programmes (e.g. in US, Sweden, France, Italy, Spain). In addition, most jurisdictions require that drug users receiving methadone prescriptions be registered with a central authority and/or that each prescription be notified to a central register (e.g. in Belgium, Denmark, Germany, Ireland, Luxembourg, Spain, UK, Australia).

12. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Methadone hydrochloride
OS: *Methadone Hydrochloride BANM*
IS: *A 4624, Algolysine, Amidon, AN 148, Doloheptan*
H.E.S., Hoechst 10820, Mecodin, Moheptan, Panalgen, Phenadone, Polamidon, Polamivet
PH: *Methadone Hydrochloride Ph. Eur. 3, USP 24*
PH: *Methadonehydrochloride Ph. Eur. 3*
PH: *Methadoni hydrochloridum Ph. Int. II*
PH: *Méthadone (chlorhydrate de) Ph. Eur. 3*

Formulations of methadone:
- Methadone Hydrochloride Oral Concentrate (10 mg methadone hydrochloride per ml) [a]
- Methadone Hydrochloride Oral Solution (1 mg methadone hydrochloride per ml) [a,b]
- Methadone Hydrochloride Injection (10 mg methadone hydrochloride per ml) [a,b]
- Methadone Hydrochloride Tablets [a,b]
- Methadone Linctus [b]
    - [a] US Pharmacopoeia
    - [b] British Pharmacopoeia

13. Proposed text for the WHO Model Formulary

Methadone hydrochloride

Drug subject to international control under the Single Convention on Narcotic Drugs (1961)

Oral solution, concentrate (Powder for oral concentrate), methadone hydrochloride 5 mg/ml, 10 mg/ml
Oral solution, methadone hydrochloride 5mg/5ml, 10mg/5ml

Uses: detoxification and maintenance therapy in opioid dependence; therapy of opioid withdrawal state.

Contraindications: acute respiratory depression; known hypersensitivity to methadone.

Precautions: severe impairment of hepatic, pulmonary or cardiac function; cardiac arrhythmias; increased intracranial pressure; myxedema or hypothyroidism, adrenocortical insufficiency; convulsive disorders; severe inflammatory bowel disease, prostatic hypertrophy or urethral stricture; renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); **overdosage:** section 4.2.2; **interactions:** Appendix 1.
SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving, especially during induction phase and dose adjustment.

Dosage: The first dose 10-20 mg of methadone should be determined for each patient based on the severity of dependence, the level of tolerance to opioids, use of other psychoactive substances as benzodiazepines or alcohol, as well as on the other relevant clinical factors.

Induction phase of maintenance treatment or detoxification: initial dose of methadone hydrochloride, *by mouth,* 10-20 mg a day, in single or divided doses. Patients should be carefully monitored during this time and should be observed daily for signs of intoxication or withdrawal. It is recommended not to increase the initial methadone dose for at least the first three days of treatment unless there are clear signs of withdrawal at the time of peak effect (3-4 hours after dose). Afterwards the dose can be increased by 5-10 mg based on presence of observable withdrawal signs, and patient complaints of withdrawal symptoms. The maximum dose at the end of the first week of dosing normally does not exceed 40 mg.

Stabilisation phase of maintenance therapy: during the first two weeks of methadone treatment the aim is to stabilize the patient so that they are not oscillating between intoxication and withdrawal. Doses can be increased by 5-10 mg every three days to suppress withdrawal symptoms, but total weekly increases in dose should not exceed 10-20 mg. For most patients 30-50 mg daily, *by mouth*, will alleviate but not necessarily eliminate withdrawal symptoms.

Maintenance phase: generally a higher dose is required than for initial stabilisation. It is recommended that subsequent dosage increases do not exceed 10mg per week. Steady maintenance dosage usually range from 50 to 100 mg daily, *by mouth*; sometimes higher dosage is required.

Detoxification in opioid dependence. After a period of stabilisation or maintenance the dose reduction process should be gradual. The recommended rate of reduction of methadone is 10 mg per week until a daily dose of 40 mg is reached, and then 5 mg per week.

ADMINISTRATION. In maintenance treatment of opioid dependence, methadone may be administered only as an oral solution and the dose of methadone hydrochloride usually is diluted in at least 90 ml of liquid.

Adverse effects: respiratory depression; anorexia, nausea, vomiting (particularly in initial stages), constipation; euphoria, hallucinations, dizziness, drowsiness, confusion, headache; dry mouth, spasm of urinary or biliary tract; hypotension, postural hypotension, vertigo, bradycardia, tachycardia, palpitations, headache, sweating, miosis, hypothermia; decreased libido; rash, facial flushing, urticaria, pruritus.

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