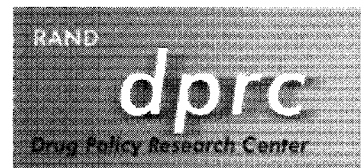


RAND *Europe*



A review of recent advances  
in knowledge about methadone  
maintenance treatment

I. van Beusekom and M.Y. Iguchi

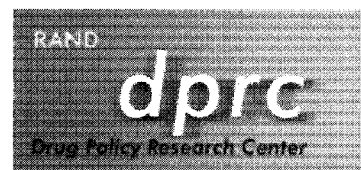
August 2001  
MR-1396/RE/FOPH/DPRC

A project for:



Bundesamt  
für Gesundheit  
Office fédéral  
de la santé publique  
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ISBN: 0-8330-3091-4

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Published 2001 by RAND  
1700 Main Street, P.O. Box 2138, Santa Monica, CA 90407-2138  
1200 South Hayes Street, Arlington, VA 22202-5050  
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## Foreword

Evidence is scarce in many fields of medicine. The evidence that does exist is often disputed. Nevertheless, policymakers and clinical practitioners all do their best to deliver the best possible treatment to persons in need of care. Clinical guidelines contain recommendations for evidence-based practice. They are mostly based on the existing knowledge base, which may or may not be intertwined with opinion statements.

This report summarises the existing evidence on methadone maintenance treatment for opioid dependent persons, in order to provide a knowledge base for the development of practice guidelines development. The Swiss Federal Office of Public Health will use this information, together with a more detailed review of the Swiss situation, as a basis for the development of guidelines for methadone maintenance in Switzerland.

*The authors would like to thank all the people who gave their feedback on previous versions of this report, in particular James P. Kahan, who inspired the authors with his critical readings and ideas and Douglas Longshore, who helped improve this document with his thorough quality review. Furthermore, the support of the Drug Policy Research Centre for Dr. Iguchi's work is highly appreciated. The content of this report remains the full responsibility of the authors.*

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## Executive summary

In 1995, the Swiss Federal Office of Public Health published a report, which summarises literature on methadone maintenance treatment to that date. The Swiss Federal Office of Public Health asked RAND Europe to write a sequel to this report, reviewing the recent (1995-2000) literature on methadone treatment for opiate addiction in all countries except Switzerland, for which a separate review was prepared. The purpose of this report is to provide a knowledge base for the development of clinical guidelines in Switzerland.

We started with a description of guidelines for methadone maintenance treatment in a large number of countries. During the past five years, several institutions have tried to set guidelines for methadone maintenance treatment, both on a national and supranational level. Most guidelines and recommendations agree on a basic set of eligibility criteria. Persons have to be opiate dependent and they get priority for treatment if they are pregnant, HIV-infected or live with a person who is already in methadone maintenance treatment. Many guidelines set a minimum age for treatment entry, but do not explain what should be done with younger persons. Some guidelines explicitly say that these persons may not start methadone maintenance treatment, while others set separate eligibility criteria. The contents, level of detail and quality of the guidelines are still very diverse, however, and will need further improvement. Also, the lack of reference to evidence is concerning. Some guidelines seem to be based on personal opinion of the authors, mixed with clinical evidence. Recommended practice in countries other than Switzerland is summarised in Table. 1.

**Table 1: Guidelines for and clinical practice in methadone maintenance treatment in 17 countries**

Country	Inclusion/eligibility criteria for methadone maintenance treatment	Starting dose	Maximum dose	Injectable methadone allowed?	Take-home doses allowed?	Who may administer methadone?
Australia				Yes, but disputed		
Austria						General practitioner
Belgium	General Practice: person must have medium-long term treatment objectives Prison: to enable detoxification	30 mg/day		No	Possible after six weeks of treatment	Pharmacist
Canada					After stabilisation	
Denmark	Opioid dependence according to ICD-10 criteria		120 mg/day			Publicly employed doctors
Finland	> 20 years of age > 4 years of heroin use Previous attempts at detoxification failed		270 mg/day		If patient co-operates well Max. take-home time: 1 week	One clinic



France	Methadone only in treatment centre or prison; buprenorphine also in general practice			No	No	Treatment centre
Germany	Opiate dependent Goal of abstinence Pregnancy or serious illness		3000 mg/month		After stabilisation	Treatment centre
Greece	> 22 years of age Daily consumption Previous attempts at detoxification failed No severe psychopathologies Priority to pregnant and HIV-infected addicts and to partners of MMT-patients			No		Limited number of treatment centres
Ireland	> 18 of age Addicted according to ICD-10 > 1 year of i.v. drug use Pregnant and HIV-infected addicts and partners of MMT-patients	Average: 55 mg/day		No		General practitioner and treatment centres and their satellite clinics
Italy	n.a.		No maximum	No		Medical doctors in co-operation with treatment centre
Netherlands	> 6 months of heroin dependence Other criteria set by treatment centres					Any medical doctor
Portugal	> 18 years of age HIV-infected Pregnant Long addiction history Failed detoxification attempts Psychiatric comorbidity Severe medical disease	No minimum	No maximum	No		Treatment centres
Spain	Opioid dependence	Average: 60 mg/day		Not forbidden, but not used either	Yes	Treatment centre
Sweden	> 4 years of i.v. drug use > 20 years of age Opiate is dominant drug of abuse Failed previous drug-free treatment attempts Support from social worker <u>Exclusion:</u> imprisonment at time of start		No restrictions			Treatment centre

United Kingdom	n.a.	10-40 mg/day	60-120 mg/day	Only in exceptional cases	Yes	Shared care: medical doctors and treatment centres
United States <sup>1</sup>	n.a.	40 mg/day	80-100 mg/day			Treatment centre

Concerning the **pharmacokinetics** of methadone, the understanding of the role of the hepatic enzyme CYP3A4 has increased significantly in the past five years. This enzyme plays an important role in the metabolism of methadone. Many drug interactions can also be explained now, since many drugs influence the activity of CYP3A4. The field of drug interactions is an area where knowledge has advanced most significantly since 1995. Research on the P450 3A N-demethylation of methadone has resulted in a much better understanding of drug-drug interactions involving methadone and other substances metabolised by hepatic mechanisms. Of great importance is the improved understanding this research provides with respect to interactions with drugs used in the treatment of HIV as well as those used to treat psychiatric disorders.

Furthermore, the past five years have shown a lot of activity in research concerning **treatment outcomes**. The knowledge about the effectiveness of methadone maintenance has increased. Several studies confirmed the effectiveness of methadone as an effective treatment for opiate users and some studies even generate some knowledge about prognostic factors to treatment effectiveness. This needs to be considered with caution, though, because predictors of treatment success are often idiosyncratic. The only factor that has some scientific basis as a predictor is early treatment success. Not surprisingly, success and adherence early in treatment continue to be strongly associated with outcome. Many treatment outcome studies focus on dose and dose administration. Several random assignment and naturalistic studies strongly support the use of higher rather than lower methadone doses, with one study pointing out the need to consider regional variations in heroin availability and purity. The appropriate starting dose and maximum allowable dose are still subject of research and discussion. Several studies noted the equal importance of quality counselling and use of contingent positive incentives to promote abstinence. Weak support is provided for the use of an injectable form of methadone, but numerous reasons for caution are also brought forward.

Research concerning overdose and mortality associated with methadone treatment has also shown significant advances. The literature in this area was surprisingly rich and of generally improved quality when compared to earlier studies of mortality associated with methadone or other opiates. In general, the studies indicate that the probability of overdose death is one-fourth as likely while enrolled in methadone treatment, with highest risk for overdose while on methadone occurring during the first several weeks of treatment. Several studies provide caution regarding overly liberal dispensing policies that make large quantities of unsecured methadone available for inappropriate or accidental ingestion.

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<sup>1</sup> Several guidelines exist in the United States

The current literature concerning treatment modalities reflects expansion of methadone dispensing to settings outside the traditional clinic setting. This includes discussions of methadone utilisation in general practitioner offices, therapeutic communities, pharmacies, and prisons.

A separate chapter was dedicated to the **special populations**: people with HIV-infection or tuberculosis, polydrug users and pregnant addicts. The extensive literature on the latter subject points out the importance of providing a sufficient methadone dose to pregnant women so as to reduce illicit drug supplementation. The trade-off with higher dose is an increased risk of neonatal abstinence syndrome, with net benefit favouring use of an adequate maintenance dose. Two studies provide additional rationale for an increased dose of methadone, as increased elimination and decreased absorption decrease methadone levels in pregnant women. Several studies have focused on breast-feeding by methadone receiving mothers. These studies noted the possibility of NAS resulting from ingestion of breast milk from mothers on high methadone doses. Two studies support the use of incentives and psychosocial interventions for decreasing illicit substance use in pregnant women enrolled in methadone treatment.

Tuberculosis and HIV seem to occur less frequently in patients on methadone maintenance, but problems occur when people do have one of those diseases. In both cases, adherence to therapy for the disease and for the opiate addiction runs at risk. Furthermore, the interaction of drugs for treatment of HIV and tuberculosis with methadone might lead to opiate withdrawal symptoms, for which a methadone dose increase would be the appropriate answer.

One of the greatest challenges facing methadone treatment providers today is the use of illicit and off-prescription drugs during treatment. In the US, numerous studies report the use of treatment vouchers, redeemable for goods or services, as reinforcement for desired behaviours such as group attendance, demonstrating abstinence (submitting a urine testing negative for drug use), or for completing a specified treatment-related task. Other studies focus on other **psychosocial treatment and motivational interventions**. Numerous studies continue to support the use of treatment vouchers to reinforce abstinence and other appropriate behaviours. An area where not much knowledge has been generated is that of take-home incentives and urine tests. Take-home incentives can be used both to lower the threshold for treatment and to reinforce good treatment participation. Evidence exists that take-home incentives can help improve treatment outcomes and stimulate patients to refrain from using illicit opiates. One weak study by Baker et al. describes urinalysis, leaving this controversial issue open to further discussions.

Several studies appear to support the use of family interventions in the treatment of those enrolled in methadone treatment. Furthermore, multiple studies demonstrate that numerous psychosocial interventions may significantly improve treatment outcomes including psychotherapy, inclusion of non-drug using significant others in treatment, the community reinforcement approach, or node-linked mapping. Not much research has been done on non-traditional interventions and no support for acupuncture

or yoga was noted. Finally, several studies have focused on treatment intensity. These studies provide support for the proposition that more intensive treatments will improve treatment outcome when compared to lower intensity interventions.

Research in the past five years has not led to any definitive conclusions on how to cope with the **perceptions addicts may have of treatment**. Experience still seems to be the best advertisement, because addicts who have been in treatment tend to be more positive about it than those who have not. The studies about perceptions of addicts have merely shown that addicts can have different opinions about take-home doses, injectable prescribing, and so on, but they cannot relate this to recommendations for clinical practice and are therefore hardly useful for people developing guidelines.

Methadone is not the only possible substitution drug. In chapter 9, **other substitution drugs** were highlighted. While the effectiveness of buprenorphine and LAAM has been established by now (although, as with methadone, the dosing remains subject of discussion), studies about prescribed heroin are just starting to show results.

The report finished with a set of **recommendations for guideline development**, using the review as an information source. It summarised the findings of the review according to the main phases of methadone treatment: initiation, maintenance and stabilisation, and, for some patients, cessation of methadone maintenance treatment. Within these phase descriptions, important elements for inclusion in guidelines are discussed. The way these elements are filled in is left to the determination of the experts in Switzerland. It will depend on their own medical expertise, but also on their perceptions of drug addicts and addiction treatment and on the current policy in a country.

### **General characteristics of methadone maintenance treatment**

Many patients fail to become abstinent from licit and illicit opiates over the long term. However, the quality of life of opiate dependent persons can be greatly improved and harm reduction can be achieved.

Most authors agree that methadone maintenance will be most successful if

- a) The treatment is provided by a well trained, motivated staff;
- b) The treatment is provided in the appropriate treatment environment;
- c) The treatment aims at maintenance rather than abstinence; abstinence may be a long-term goal.
- d) The treatment is given in a multidisciplinary environment, where general practitioners, pharmacists, specialised drug treatment doctors and nurses co-ordinate their actions
- e) The treatment is multidisciplinary in itself; this means that methadone maintenance is not the only treatment, but that other needs of the patient, be they medical, social, legal, psychiatric or something else are addressed at the same moment. After all, these factors may include the reason for using illicit opiates;

f) Treatment is matched to the patient's individual needs; each patient has his personal history and individual characteristics. Some authors also state that it is important to give the patient a feeling of control over his own treatment.

g) The patient stays in treatment as long as necessary. This may be a period of one or two years, but it may also imply life-long methadone treatment. Research has consistently demonstrated a significant correlation between effectiveness of treatment and treatment retention.

## **Initiation**

Access to treatment for any opioid dependent person who is eligible and motivated for treatment should be facilitated (Verster A. 2000). Lack of treatment capacity could lead to a loss of motivated persons. In order to encourage participation in substitution therapy, a range of treatment options and venues might be considered. Low threshold treatment programs, full service clinics, GP prescriptions, pharmacy dispensing, or even methadone dispensed in residential settings might all play a useful role in attracting opiate abusers into treatment, while other clinics with higher thresholds might be better suited for better motivated patients. Clinic rules should not turn away patients and since each patient is different, different treatment environments will be best able to provide service to all patients.

Guidelines on the first phase of treatment could include the following elements:

### **a) Eligibility criteria**

The physician should assess whether a patient is eligible for treatment entry. Many countries use the (modified) criteria for opioid dependence as defined in the DSM-IV or ICD-10 as the basic eligibility measure and add their own criteria, such as a minimum number of years of opioid use, or proof of opioid use in the past few weeks. At treatment entry, patients should have a clear idea of what they can expect and what is expected of them. This latter point is important, as patients should participate in treatment actively.

Some countries have applied stricter regulations for treatment entry as a consequence of a shortage of capacity. By setting the threshold higher, fewer addicts are eligible for treatment.

### **b) Criteria of possible effectiveness**

Guidelines should assess the patient's specific treatment needs. Specific guidelines might be usefully developed for the treatment of:

- Pregnant patients
- Patients with HIV-infection or AIDS
- Antisocial patients
- Polydrug users, especially cocaine and alcohol users
- Patients with psychosocial or psychiatric comorbid disorders

These factors may lead doctors to provide priority entry into treatment services (e.g. for pregnant and HIV-infected persons) or to pay extra attention to the provision of additional or tailored psychosocial treatment (e.g. for polydrug users, or those demonstrating antisocial behaviours). If

more knowledge about prognostic factors becomes available, this might also help in establishing the optimal treatment options individual patients.

Many patients have psychiatric comorbidities. Co-operation with doctors in internal medicine, psychiatry and other medical specialisations is recommended to complement social reintegration therapy.

All authors agree that the patient should start at a low dose of methadone in order to prevent overdose. There has not been any research on starting doses, but guidelines state starting doses of 10 to 40 mg, depending on the quantity and quality (i.e. purity) of heroin the patient is used to. A starting dose higher than 40 mg/day may be very dangerous. The patient should be monitored closely. If the patient experiences withdrawal symptoms, the dose should be increased slowly and carefully, while it may be decreased if the patient seems to experience adverse effects from the methadone. These adverse effects might also occur as a consequence of interactions with other licit and illicit drugs.

Authors state that, in the early phase of treatment, the patient had better not receive take-home doses, except for exceptional personal circumstances. Daily administration in a treatment setting is the preferred method of treatment in the phase that the patient is not yet on a stable dose of methadone. Furthermore, the patient may have used heroin to suppress depressed feelings or a comorbid psychiatric disorder. Stopping the use of heroin could well initiate the re-emergence of such problems. This is another reason for doctors to monitor their methadone patients carefully in the early phases of treatment, as such psychiatric problems may cause patients to relapse to heroin use.

### **Stabilisation and maintenance**

Once the patient has stabilised on a certain dose of methadone, he or she can start to concentrate on the problems which might have been the underlying factors for starting to use heroin or which are the consequences of the heroin dependence. These problems, along with patient characteristics, should lead the doctor to decide on the most appropriate treatment for this patient.

Basically, the treatment is composed of two components that are closely related: the medical component of methadone prescription and the psychosocial element of therapy and treatment environment.

#### Methadone prescription

The medical component exists of the assessment of the appropriate dose of methadone and of the clinical monitoring of the patient. The following aspects should be taken into account:

- **Stabilisation dose:** this dose may vary between 20 mg/day and 300 mg/day, depending on the needs and desires of the patient. A higher dose (>60 mg/day) has proven effectiveness, because it blocks the euphoric effects of heroin. This way, the patient has no incentive to use heroin. Over the years, the dose may change as patients indicate their

- preferences or when they have to use other medications which influence the metabolism of methadone.
- Administration of methadone: administration of methadone in a liquid oral form is the preferred one in most literature, closely followed by methadone pills. Pills could be crushed and thus used for injection, which would increase the harms associated with drug use again. Adding naloxone to the methadone solution can prevent injection. Naloxone blocks the euphoric effects of methadone when it is injected, while it does allow methadone to do its work when it is taken orally.
  - The position on injectable methadone is still ambiguous in many countries. Some state that injectable methadone can be a good solution for patients who have been using injected heroin for long periods of their lives (see chapter 8). Administering methadone with needles may be a good option to get patients to enter treatment and to remain in treatment. Others consider that one of the objectives of methadone maintenance should be that patients stop using the needle.
  - Time of day of methadone consumption: a small number of studies discuss the time of day methadone could best be administered. As methadone reaches its peak two to four hours after administration and the effect then slowly decreases in the following 20 to 30 hours, it is argued that the dose should be administered in the morning, so that the patient is asleep when the effect is decreasing, while the peak effects of methadone are at the moment when the patient craves most for heroin.
  - Compliance: The literature has discussed several enforcement strategies. Urinalysis is the best known. Urinalysis can be used just to assess whether a patient has used other drugs than methadone. A treatment centre could also decide to enforce sanctions when urine samples are opioid positive or it could reward a number of consecutive negative samples or it could do both, but the evidence base for this is very small. Take-home doses can be an integrated part of treatment for stabilised patients, but it can also be part of an enforcement strategy. For example, patients could get a take-home dose for each three consecutive illicit opiate-negative urine samples, or they could merit the privilege of three take-home doses per week as long as they keep on showing negative results in the urine tests. A sanction could be to stop this privilege if a test shows positive results. Vouchers are a way to reward treatment compliance without using money. Just like take-home doses, they can be given for each compliant action, after a number of consecutive compliant actions and they can be withdrawn in some cases. Vouchers have proven effectiveness for longer abstinence from illicit drugs. The advantage is that patients get a reward in a manner that does not engender craving and drug use, as is the case with monetary rewards.

### Complementary treatment

Complementary treatments are elements of treatment that take care of the non-medical part of the addiction. We also discuss the treatment environment as such an element.

- Most methadone prescription programmes offer at least some personal counselling sessions. During these sessions, treatment goals are set with the patient and problems associated with the drug addiction can be

discussed. The counselling sessions are a good way to establish a relationship of confidence between the physician and the patient.

- With treatment environment we mean the setting in which treatment is given. This may be in-patient treatment or outpatient or both. In-patient treatment has the advantage that the patient can be monitored very closely, but the disadvantage that it precludes the possibility of normal daily activities, such as work and education. Outpatient treatment may facilitate success in voluntary residential treatment and post-treatment drug-free status, but is less useful for patients with a high risk of relapse. Furthermore, the orientation of the treatment can be seen as a treatment environment. Research has found that an abstinence-oriented environment is less likely to be successful than an environment in which healthy behaviour is encouraged without the objective of stopping the use of methadone.
- Psychosocial treatments and psychiatric treatments address the psychological, social, legal and psychiatric problems of the patient. These problems have probably come up during the assessment, but might also occur during the first weeks of treatment. Special attention needs to be paid to the specific groups of patients that were mentioned earlier: anti-social and depressed patients, and so on. Most guidelines stress the importance of co-operation between the methadone-prescribing doctors and the therapists in order to establish a good relationship with the patient and to enhance retention in treatment.

### **Reduction of methadone dose**

Over the years, the physician and the patient can decide that a dose reduction or even a total stop of methadone use is appropriate. A patient can have several reasons for stopping the use of methadone. The best reason is when both physician and patient believe that the patient has reached abstinence from illicit drugs and has stabilised his life sufficiently to continue on his own. Stopping the use of methadone does not necessarily mean that concurrent therapies are stopped. It might also be that the patient has to use other drugs for medical reasons that interfere with methadone consumption.

A reduction of the dose of methadone will very probably lead to withdrawal symptoms. Therefore, most authors recommend that such reduction be done very slowly. This is called 'tapering off'. Depending on the patient and his stabilisation dose, the dose can be reduced by 1 mg per fortnight up to 10 mg per day. In the final phase of reduction (one study states: when the patient is at 30 mg/day), the rate of reduction should be slowed down. Tapering off can take a few months for some patients, but a number of years for other patients. As in the early phase of treatment, close monitoring of the patient is recommended.

### **Final thoughts**

If the Swiss government is to disseminate methadone on a broad basis, it should consider the possibilities of monitoring this dissemination, for example through the canton registrations. The monitoring system could try to gain information about morbidity and mortality associated with



methadone use. Furthermore, the guidelines might have to leave some room to future developments. For example, research is being done on methadone dispensers that allow take-home doses, without posing a risk to the environment of the addict. In chapter VI, the death of an infant as a consequence of the use of a baby-bottle for measuring methadone dose is described. A baby-bottle is such a risky measuring device, but this risk of inappropriate use could be easily avoided if doses are provided on a day-to-day basis or in childproof containers with measuring device or both. These options are currently being studied. The results of these experiments might influence the way take-home doses are perceived.

## **I Introduction**

In the European Union, an estimated 1 to 1.5 million people are dependent on illicit opiates, mainly heroin. Many addicts show behaviour that poses serious physical, psychological and social risks to themselves and their social environment (EMCDDA 2000a). One of the main aspects of heroin that induces these risks is the fact that, when people become more dependent on heroin, they need it more frequently and they need a larger dose. Their lives change into a constant quest for drugs and for money to buy them. In this way, a physical dependence becomes a way of life.

One way of helping addicts reduce the unhealthy aspects of their addiction is substitution treatment, i.e. by prescribing a substitute drug for the illicit opiate. The first substitution drug that was used for opiate addiction was methadone (Dole V.P. 1965), which is still the most popular substitution drug. It is estimated that 90% of opiate substitution treatment in European Union countries consists of methadone substitution treatment (EMCDDA 2000). Other substitution drugs currently in use or under discussion are buprenorphine, levo-alpha-acetyl-methadol (LAAM), morphine and heroin. The presumed advantages of substitution treatment are:

- more hygienic administration of drugs;
- care provider contact with the addict; the possibility for starting psycho-social treatments to handle other problems related to heroin addiction, such as psychosocial and legal problems, but also addiction to other drugs (e.g. cocaine);
- a possibility for the addict to stabilise his life, as substitution drugs are administered on a less frequent and more systematic basis
- less mortality (Capplehorn 1996a)

Although methadone is the most established drug for substitution treatment, it is still under continuous discussion. This discussion focuses, among other things, on adequate dosing, the efficacy of methadone as a substitution drug, the role of additional psychosocial treatments and the optimal duration of methadone maintenance treatment.

The Swiss methadone report (Swiss Federal Office of Public Health 1995) summarises literature on methadone treatment until 1995. The Swiss Federal Office of Public Health has asked RAND Europe to write a sequel to this report, reviewing the recent (1995-2000) literature on methadone treatment for opiate addiction in all countries, except Switzerland, for which a separate review was prepared. The purpose of this report is to provide a knowledge base for the development of clinical guidelines in Switzerland.

### **1.1 Outline of this report**

After a description of the methodological design of this literature review, we will start with an overview of regulations and guidelines for methadone maintenance treatment in several countries where methadone

maintenance treatment receives a lot of attention. Then, the outcomes of several clinical outcome studies are summarised to give insight into the most recent developments in methadone maintenance treatment research. Where methadone is compared to other treatments, these are briefly discussed. Each chapter finishes with a conclusion that summarises the main developments in the field over the past five years, where appropriate focusing on what has changed insights since 1995.

This diverse material on methadone will be integrated within a final chapter, which discusses the several phases of methadone maintenance and formulates keypoints for guideline development.

## **2 Study design**

This chapter describes the method of selection of the articles and the main characteristics of the included studies.

### **2.1 Search strategy**

The following databases were searched electronically for all publications pertaining to methadone maintenance treatment that were published after 1995:

- Cochrane Clinical Trials Register (CCTR)
- Cochrane Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane protocols
- Dialog
- Embase
- Medline
- National Guideline Clearinghouse
- Psycinfo
- Scisearch
- Socialscisearch

At first, the search aimed at all existing substitution drugs, but during the course of the searches the focus was narrowed to methadone maintenance alone. During the first phase of searches, no selection on publication types was done; later Medline and the National Guideline Clearinghouse were searched specifically for guidelines.

The search terms (entered separately and concurrently) were:

- Methadone
- Maintenance
- Treatment
- Substitution
- Heroin
- Opiate addiction
- Opiate substitution
- Substitution treatment
- Office-based opiate prescription
- Harm reduction

Also, the bibliographies of major articles and reviews were screened for additional studies and some authors were contacted for their articles.

### **2.2 Inclusion criteria**

As this study focuses on methadone maintenance treatment for opiate addiction, in particular heroin, studies that did not pertain to this were excluded. Randomised clinical trials, clinical trials, guidelines and regulations, case reports, systematic reviews and meta-analyses were included if they had been published between 1995 and 2000. Letters and conference abstracts were generally excluded. Letters were included if they pertained to drug interactions with methadone or to side effects. Only publications describing a human population were included; publications

that described research with methadone on heroin-dependent rats, for example, were excluded. Publications describing the effects of other substitutes, such as buprenorphine and LAAM, were considered only if the substitution drug was compared to methadone. Publications about behavioural treatments were only included when they compared behavioural treatment to methadone maintenance or when it was given in addition to methadone. Articles in English, Dutch, German, French and Spanish were reviewed.

At first, all titles and abstracts that came out of the electronic search were screened for the above mentioned criteria. Articles that clearly classified for inclusion as well as articles for which the abstract did not give enough information, were retrieved for more detailed evaluation. From those, the articles that met the criteria for inclusion were selected.

### **2.3 Results**

The first search led to more than 2000 titles, for which the abstract was read. The abstract selection led to a total of 800 articles retrieved for assessment of inclusion criteria. Many were excluded because, for example, the study did not focus on treatment, it was not about heroin addicts, or it did not consider methadone treatment. Also, some articles turned out to be Swiss – so they would be covered in the Swiss review – while others could not be found. Eventually, 222 articles were included for review.

### **2.4 Assessment of characteristics of study quality and study population**

Because baseline characteristics of study design and of study subjects may affect response to therapy, we studied data on the age of addicts, their functional class, duration and severity of the addiction and prior treatment for patients in all study arms in each study. To assess the quality of the study, we determined whether the study described randomisation, appropriateness of randomisation, blinding, appropriateness of blinding, withdrawals and dropouts. Where relevant, these baseline characteristics are discussed in the literature review. Priority is given to studies of higher study quality; these studies are described more elaborately and have received more weight in the concluding chapter.

### **3 Guidelines and clinical practice recommendations**

Guidelines are statements of recommended clinical practice. This recommendation is based on both clinical evidence and on the policy towards opioid dependence in a country. While the evidence is the same for most countries, the interpretation of this evidence differs per country. Therefore, this chapter will describe current guidelines and clinical practice in the different countries of the European Union, the United States of America, Canada and Australia.

#### **3.1 The scientific basis of the guidelines**

The extent to which the above mentioned guidelines are based on clinical evidence, is not always clear. Some explicitly discuss the literature, while others make statements about dosing seemingly without basing these on any evidence. Furthermore, the writers of guidelines may have chosen to ignore clinical evidence because they judge methadone treatment differently. This chapter should therefore be seen as informative about the way guidelines are structured, but the statements should be assessed critically. In chapters IV and following, we will summarise the clinical evidence.

#### **3.2 General remarks**

Most guidelines state or imply that methadone maintenance treatment is appropriate only for persons who are opiate dependent according to the DSM-IV criteria for substance dependence.

These criteria are defined as follows (Kauffman J F 1995):

- 1) tolerance to the drug, as defined by either of the following:
  - the need for markedly increased amounts of the substance to achieve intoxication or desired effect
  - markedly diminished effect with continued use of the same amount of the substance
- 2) withdrawal, as manifested by either of the following:
  - the characteristic withdrawal syndrome for the substance
  - use of the same (or closely related) substance to relieve or avoid withdrawal symptoms
- 3) the substance is often taken in larger amounts or over a longer period than was intended
- 4) a persistent desire or unsuccessful efforts to cut down or control substance use
- 5) a great deal of time spent in activities necessary to obtain or use the substance or to recover from its effects
- 6) important social, occupational, or recreational activities given up or reduced because of substance use
- 7) continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem that was likely to have been caused or exacerbated by the substance.

Access to treatment also depends on the availability of treatment facilities. Some countries have a limited number of treatment places, resulting in

waiting lists. As drug treatment services are located mainly in cities, regional differences in availability of treatment may occur within countries (EMCDDA 2000a). The European guidelines state that countries should try to have sufficient capacity for all persons who need and want methadone treatment (Verster A. 2000).

Although the conventional wisdom prescribes methadone maintenance only for addicted chronic users, some authors suggest that opioid maintenance treatment is also appropriate for persons who are no longer opioid dependent but have a high risk of relapse. Pregnant addicts should be encouraged to start methadone maintenance, as many studies indicate that this is a safe treatment for both mother and child (California Society of Addiction Medicine 1998). Other guidelines give recommendations for specific groups of opioid dependent persons, such as people with anti-social personality disorder or HIV-infected addicts (Effective Medical Treatment of Opiate Addiction. NIH Consensus Statement 1997; Department of Health 1999).

Furthermore, the risk of addiction to methadone should also be taken into account, although there is no agreement on whether this should be a precluding factor. Some accept that some addicts will never stop using methadone, but consider the goal of methadone maintenance for the patient to remain free of illicit drugs and to reach a stable state of living. Others are afraid that heroin addicts will become dependent on "just another drug" (i.e. methadone). Also, the possibility of a different substitution treatment, for example buprenorphine or LAAM, could be taken into account (California Society of Addiction Medicine 1998).

Most countries apply an age limit for access to treatment. This limit is set at 18 years in most countries, but Sweden, for example, allows people into treatment only if they are over 20 years of age. Furthermore, a person must have been dependent for at least one, two (Finkbeiner 1996), sometimes even four years (Finland, Sweden), while mental illness, homelessness, and incarceration may be exclusion criteria (EMCDDA 2000).

In most countries of the European Union, methadone treatment has a long-term maintenance objective. Only in Greece and Italy does methadone treatment aim at detoxification primarily (EMCDDA 2000).

In the following paragraphs, current practice and guidelines — if existing — in the countries in focus will be discussed. The reader should note that statements about "what should be done" come from the guidelines cited, not from the authors of this review. We will start with a description of guidelines in the European Union, the United Kingdom, the United States, and Australia, because these have the most elaborate guidelines. After that, we will summarise both guidelines and daily practice in several European countries and Canada.

### **3.3 European Union**

The European methadone network (Euromethwork) has established a set of recommendations on methadone maintenance (Verster A. 2000), although the text is in some parts more a review of literature than a recommendation. The text starts with the remark that, although different admission criteria may apply, treatment should be available to all persons who are opioid dependent and need treatment. Treatment would best be started in the morning and early in the week, so that the most important monitoring moments are during the opening hours of the clinic. One should take a number of factors into account:

- The starting dose is different for each patient, depending on his drug use and treatment aims. The initial dose is in general between 10 and 30 mg/day, but if tolerance to methadone proves to be very high, this may be 25-40 mg/day. The dose should be accumulated at a maximum rate of 10-20 mg to a dose of between 60 and 120 mg/day. The patient should be monitored well in the early phase of treatment, as a dose that is too low might lead the patient to seek additional heroin, whereas a high dose might be fatal
- People with a high level of emotional distress or psychiatric disorders should be maintained on a higher dose of methadone
- If a patient continues to use illicit opiates, this may mean several things. It may mean that somebody does not comply with the treatment rules and objectives, but it may also mean that the dose of methadone is insufficiently high, leaving the patient craving for heroin. Doctors should keep this in mind
- Urinalysis is considered a helpful tool that should be applied with care. On the one hand it depicts illicit opiate use and can help monitor patients, on the other hand it does not show the dose of illicit opiates used. Besides, it shows illicit opiate use only in the past few days
- Special attention should be paid to groups of patients with special needs: pregnant women and their (unborn) children, people with HIV or AIDS, poly-drug users and people with mental health problems
- Different treatment settings may necessitate different treatment options: one could think of addicts in hospital, in prison or on holiday (Verster A. 2000)

### **3.4 United Kingdom**

The United Kingdom has a set of recent guidelines for maintenance treatment (Department of Health 1999). The guidelines start with a description of the goals of opiate substitution treatment. These goals are primarily to help the patient to become or remain healthy, by promoting safer drug administration and if possible a reduction of the frequency and rate of illicit opiate use. In order to achieve this goal, medical practitioners should seek co-operation with other professionals who could contribute to such a healthy state of being. The authors call this 'shared care'. This shared care can help increase compliance of the patient to treatment, if all services give consistent and regular feedback. Most of the treatment services have contracts with behavioural therapy service providers (EMCDDA 2000).



Each professional has his own role in the treatment of drug addicts: the general practitioner should detect and manage drug misuse problems as far as possible and refer patients with more complex problems to specialist services. Guidelines for standardised assessment and referral of patients do not yet exist. The guidelines do give recommendations of issues that should be covered during assessment. These are:

- reason for presentation to the doctor
- past and current drug use
- history of injecting and risk of HIV and hepatitis
- medical history
- psychiatric history
- forensic history
- social history
- past contact with treatment services
- other, such as the family situation

Drug addicts in prison should be given the possibility to start or continue treatment (Department of Health 1999).

As soon as a person starts methadone treatment, the doctor should notify him to the Regional Drug Misuse Database.

There are general recommendations on the dose. The guidelines state that "the aim is to provide a dose of a substitute drug that will prevent withdrawal symptoms and reduce or eliminate non-prescribed drug use." The initial dose should be 10-40 mg/day, increased with 5 to 10 mg/day. A total weekly increase should not exceed 30 mg above the starting dose. The total dose should be between 60 and 120 mg/day, depending on the needs of the patient. Such a stable dose can be achieved after about six weeks of treatment, although this also depends on the patient. High doses should be monitored closely, because they may lead to intoxication in combination with alcohol or benzodiazepine use. If a patient has missed three days of methadone dispensing, he should be assessed again and should restart at a lower dose, as his tolerance to methadone may have been reduced in the meantime (Department of Health 1999). In practice, the doses prescribed are quite low: in England and Wales methadone is usually prescribed in doses of up to 50 mg; only 1.5% of the daily doses are higher than 100 mg (Loo 1996;Strang 1998). Injectable methadone is not allowed except for some patients. In such an exceptional case, the patient should be treated in a specialist treatment environment. In practice, general practitioners also prescribe injectable methadone (Department of Health, 1999). Proposals for new legislation to restrict the prescribing of injectable methadone to specialists and authorised licence holders are currently being put forward (EMCDDA 2000).

The guidelines recommend that patients attend the pharmacy six or seven days a week, especially during the early phases of treatment, but doctors have the freedom to decide on the dispensing interval themselves (Marsden 1998). They recommend tighter monitoring and supervision of methadone administration in the early phases of treatment, because patients run a higher risk of overdose in the beginning of treatment. Such monitoring may include urine testing and daily on-site methadone

distribution. Therefore, the guidelines state that take-home doses should not be allowed to patients who:

- show a continued and unstable pattern of drug misuse
- have a significant unstable psychiatric illness
- are suspected to divert their methadone to the market or are suspected to use it in an appropriate manner.

Some patients, however, might fare better on less than daily contact with the doctor, as this would interfere with their work or other obligations. The guidelines also allow patients who comply well to travel with a supply of up to 500 mg. For amounts over 500 mg a Home Office license is required.

Treatment aims and goals should be adjusted according to the patient's individual progress. A dose reduction should only be started if doctor and patient agree to this. Reduction should be done very slowly: 5 to 10 mg per week or per two weeks (Department of Health 1999).

### **3.5 United States**

Clinical guidelines and political reality seem to form two worlds of their own in the United States. The practice still is that doctors are not allowed to prescribe high doses of methadone, and federal rules state that opiate treatment should be abstinence-oriented. The medical associations have very different views. Their guidelines - which cannot always be implemented in the USA - are discussed here, with minor reference to the current situation in practice.

The United States has several guidelines. Most of them are similar; some focus on treatment environment, while others stress the differences between types of users or dosing issues. The National Institutes of Health (NIH) consensus statement has taken a position that reflects recent changes in thinking in the United States about drug dependence treatment: it explicitly states that abstinence is not the most important goal of treatment. It states: "Continuity of treatment is crucial — patients who are treated for fewer than 3 months generally show little or no improvement, and most, if not all, patients require continuous treatment over a period of years and perhaps for life. Therefore, the program has come to be termed methadone "maintenance" treatment" (NIH Consensus Statement 1997). The guidelines of the American Psychiatric Association (1995), which is also the founder of the DSM-IV criteria, and the National Institutes on Drug Abuse (NIDA) support this statement in their guidelines. They recommend a minimum treatment time of 12 months and even repetitive treatment efforts (National Institutes on Drug Abuse (NIDA) 1999). Furthermore, the NIH consensus statement pleads for more loose regulations for methadone maintenance treatment. The regulations of the Food and Drug Administration (FDA) are so detailed that they "limit the flexibility and responsiveness of the programmes". For example, the FDA regulations are in favour of lower doses of methadone, while the effectiveness of using higher doses has been proven (NIH Consensus Statement 1997). Since the publication of these guidelines, the operational responsibility for regulating methadone has been moved to the Centre for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental

Health Services Administration (SAMHSA). CSAT is currently piloting accreditation standards for methadone treatment programmes.

Several guidelines plea, among other things, for fast and flexible treatment entry, especially for pregnant addicts. These recommendations have not been instituted as yet (American Psychiatric Association (APA) 1995; Institute of Medicine 1995; Lewis 1999).

The dose should be assessed for each individual patient. 40 mg per day is considered low; this is often a starting dose (Poehlke 1999), which may rise over time to 80 mg or even more than 100 mg per day. Doses above 80 mg have shown the best results. Although the starting dose is low, this should rise to a stable dose, whatever dose that may be, at which a patient does not feel withdrawal symptoms or other inconveniences (California Society of Addiction Medicine 1998) (Poehlke 1999). A good treatment program would monitor the patient closely during the first days of treatment, constantly adjusting the dose of methadone to avoid withdrawal symptoms and ongoing use of illicit opiates (California Society of Addiction Medicine 1998). The guidelines of the American Psychiatric Association add to this that, in case a higher dose is administered, the plasma methadone concentrations could be monitored (American Psychiatric Association 1995).

As treatment starts, doctors should pay attention to possible comorbid psychiatric disorders that were previously suppressed by heroin use, but that may emerge now that heroin use is stopped. Insufficient treatment of such comorbid disorders may cause patients to relapse to illicit opiate use (American Psychiatric Association 1995).

Substitution treatment can be given in different treatment environments. Currently, methadone may be dispensed only in licensed and heavily regulated outpatient clinical facilities. In the USA, long-term residential treatment and short-term residential treatment are important treatment modalities for heroin dependent persons.

One protocol (Kauffman J F 1995) gives very detailed characteristics of what a good treatment environment should look like. A treatment environment should include at least the following services:

- assessing patients
- dispensing medication
- administering urine tests
- identifying acute medical or psychiatric and neuropsychological problems when they occur
- counselling to reduce substance use
- evaluating and addressing family problems
- referring patients to additional services as needed
- performing clerical functions and keeping records
- providing security.

The NIH consensus statement stresses the importance of the knowledge and emphatic — often culturally sensitive - attitude of staff and the availability of psychotherapy and other counselling services. Training of

personnel should be improved to stress these aspects (NIH Consensus Statement 1997).

### **3.6 Australia**

The Australian National Drug Strategy sets the rules for substitution treatment. The first goal of substitution treatment and concurrent treatment strategies is relapse prevention. Therefore, general practitioners and hospitals are included more and more in the early phases of treatment. The Australian National Drug Strategy aims (among other things) at:

- building stronger links between drug treatment services and mental health services
- improving access to treatment for people in the criminal justice system.
- enhancing participation of family members and community members (National Drug Strategic Framework 1998-99 to 2002-03 1998)

In Australia, the use of injectable methadone syrup has led to a lot of discussion; the harm reduction goals of methadone were only partly achieved, while injecting methadone brings along many disadvantages. For example, the needle needed for methadone is larger than the one used for heroin, so tissue damage does not decrease; it even increases when converting to methadone (Chutuape MA; Silverman K, and Stitzer ML 1998b).

### **3.7 Other countries**

Other countries have less explicit guidelines regarding substitution treatment. Almost all countries have at least a set of eligibility criteria for entrance into methadone maintenance treatment. These inclusion criteria are summarised in table 1. This table shows that regulation regarding other aspects of treatment, such as dosing and modes of administration, is very diverse. In the following, we will highlight some interesting aspects of recommended clinical practice in different countries.

In **Belgium** recommended clinical practice is quite detailed. Methadone is the preferred substitution drug here. Injected methadone is prohibited. Methadone maintenance treatment should start with a dose of 30 mg/day. This dose should be evaluated after 48 hours and adjusted if necessary. For the first six weeks, a pharmacist should administer the dose; then, take-home doses may be considered. General practitioners should limit the number of patients on substitution treatment in their practice and try to focus on patients with medium- and long-term treatment objectives. This means that they have to give priority to patients who aim to stay in treatment, while patients who want to enter treatment just to get some rest from seeking heroin, without the objective to treat their addiction, deserve lower priority. Registration on a specific clinical-case register is considered very useful. In prisons, methadone is administered more often to facilitate withdrawal than as a part of maintenance treatment (EMCDDA 2000).

**Table 1: Guidelines for and clinical practice in methadone maintenance treatment in 17 countries**

Country	Inclusion/eligibility criteria for methadone maintenance treatment	Starting dose	Maximum dose	Injectable methadone allowed?	Take-home doses allowed?	Who may administer methadone?
Australia				Yes, but disputed		
Austria						General practitioner
Belgium	General Practice: person must have medium-long term treatment objectives Prison: to enable detoxification	30 mg/day		No	Possible after six weeks of treatment	Pharmacist
Canada					After stabilisation	
Denmark	Opioid dependence according to ICD-10 criteria		120 mg/day			Publicly employed doctors
Finland	> 20 years of age > 4 years of heroin use Previous attempts at detoxification failed		270 mg/day		If patient cooperates well Max. take-home time: 1 week	One clinic
France	Methadone only in treatment centre or prison; buprenorphine also in general practice			No	No	Treatment centre
Germany	Opiate dependent Goal of abstinence Pregnancy or serious illness		3000 mg/month		After stabilisation	Treatment centre
Greece	> 22 years of age Daily consumption Previous attempts at detoxification failed No severe psychopathologies Priority to pregnant and HIV-infected addicts and to partners of MMT-patients			No		Limited number of treatment centres
Ireland	> 18 of age Addicted according to ICD-10 > 1 year of i.v. drug use Pregnant and HIV-infected addicts and partners of MMT-patients	Average: 55 mg/day		No		General practitioner and treatment centres and their satellite clinics
Italy	n.a.		No maximum	No		Medical doctors in co-operation with treatment centre
Netherlands	> 6 months of heroin dependence Other criteria set by treatment centres					Any medical doctor

Portugal	> 18 years of age HIV-infected Pregnant Long addiction history Failed detoxification attempts Psychiatric comorbidity Severe medical disease	No minimum	No maximum	No		Treatment centres
Spain	Opioid dependence	Average: 60 mg/day		Not forbidden, but not used either	Yes	Treatment centre
Sweden	> 4 years of i.v. drug use > 20 years of age Opiate is dominant drug of abuse Failed previous drug-free treatment attempts Support from social worker <u>Exclusion:</u> imprisonment at time of start		No restrictions			Treatment centre
United Kingdom	n.a.	10-40 mg/day	60-120 mg/day	Only in exceptional cases	Yes	Shared care: medical doctors and treatment centres
United States <sup>2</sup>	n.a.	40 mg/day	80-100 mg/day			Treatment centre

The government of **Canada** changed its policy towards substitution therapy recently. Fischer (Fischer B 2000) states that the number of patients in methadone maintenance treatment increased greatly after the government of Canada decentralised methadone treatment regulation to the provinces. The provinces of Ontario and British Columbia rapidly changed the guidelines to be less restrictive. Physicians have greater discretion with regard to urinalysis results. It is no longer compulsory for them to exclude a patient from treatment if one 'dirty' urine sample is detected. Furthermore, the physicians have the option of additional psychosocial treatment and of giving take-home privileges to patients who have stabilised. In Ontario, guidelines neither state a maximum dose nor a maximum number of patients a doctor may include in treatment.

**Denmark** saw recent changes in its legislation as well. A new law that came into force in 1996, in combination with guidelines from the National Board of Health sets the borders for methadone maintenance treatment in Denmark. The Danish recommendations stress the importance of a comprehensive approach to opiate dependence treatment; apart from the physical dependence on opiates, other factors, such as the client's psychosocial and legal needs, should be taken into account before admitting somebody to methadone treatment.

Only publicly employed doctors are allowed to prescribe methadone; no special licence is needed. Urine tests have to be carried out at least once

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<sup>2</sup> Several guidelines exist in the United States

every month. Further monitoring and possible sanctions are to be decided by the doctors (EMCDDA 2000).

**Finland** has only one full-time substitution treatment unit; furthermore, some psychiatric hospital departments collaborate with this unit in the treatment of heroin-dependent patients. The government is now contemplating the decentralisation of substitution treatment to local treatment units, so that treatment is more easily accessible. Methadone treatment aims at maintenance; if patients want to try to detoxify again, they must be referred to buprenorphine treatment. If patients co-operate well, they may be allowed to take 7 doses of methadone home for a week (EMCDDA 2000).

In **France**, high-dose buprenorphine is the preferred substitution drug. Only substance-abuse specialists may prescribe methadone. Centres offering methadone maintenance treatment must initially administer this within the treatment centre; they must own a safe to keep the methadone and they must carry out regular urine tests for illicit opiate use. Methadone treatment can both be started and continued in prison (EMCDDA 2000).

**Germany** has a number of guidelines, some of which are federal and some of which are only applicable in some provinces. The latest modification to the German Narcotics Act (1998) states that methadone is the preferred drug for substitution. Persons are eligible for substitution treatment if:

- a) they are dependent on opiates and wish to achieve abstinence in the long term;
- b) they have to undergo medical treatment for a serious illness;
- c) they are pregnant or have just given birth to a baby (Ditzel 1999).

Treatment should be embedded in a comprehensive treatment plan, which pays attention to other problems the patient may have.

The Federal Association of Physicians and Public Health Insurance Organisations has drawn up additional guidelines for substitution treatment funded by the Social Health Insurances. These Neue Untersuchungs- und Behandlungsmethode-Richtlinien (new guidelines for diagnosis and treatment) - which may be ignored if the patient has no public health insurance - approve the use of methadone for different types of addicts; opiate dependence is included, but it is not the only admission criterion. The NUB guidelines require doctors to control the urine of the patients frequently for illicit opiate use. If illicit opiate use is detected, patients must be excluded from treatment (EMCDDA 2000).

The **Italian** guidelines leave a lot of freedom to the prescribing doctors. The guidelines suggest that:

- Public treatment centres diagnose the opiate dependence of a person;
- Methadone maintenance treatment should be matched to the individual needs of the patient;
- Methadone does not necessarily aim at abstention from all opiates. It may be prescribed over a longer period of time in order to prevent relapse to illicit opiate use and in order to minimise the harms related to illicit opiate use;

- Medical doctors can prescribe methadone as long as they do this in collaboration with the local public treatment centre (EMCDDA 2000).

In **the Netherlands**, methadone is considered a medical drug and therefore any doctor may prescribe it. The Law on the Provision of Medicines covers the rules for prescription (EMCDDA 2000). Admission criteria are set by the treatment institutions; these admission criteria are often quite loose. In practice, the only admission criterion is dependence on heroin. Patients are even allowed to some moderate use of other drugs (Trimbos Instituut 1999a).

The expansion of the number of HIV infections has led to a concurring increase of methadone substitution services in **Spain**. At first, legislation on methadone provision was very restricted, but as the number of HIV infections increased, the government alleviated the criteria for treatment admission. Nowadays, the only admission criterion is a diagnosis of opioid dependence, without any restrictions on dosage or on duration of treatment. There are no treatment guidelines.

Specialist treatment centres provide most methadone maintenance treatment; general practitioners are hardly ever involved. Treatment by private treatment centres is highly regulated (EMCDDA 2000).

The National Board of Health and Welfare of **Sweden** has set criteria for substitution treatment in Sweden. The criteria are quite strict. The Swedish National Board of Health and Welfare collects data from the methadone maintenance programmes.

### **3.8 Opinions on good methadone maintenance treatment**

The following section describes unofficial or personnel expressions of opinion on good methadone maintenance treatment. These recommendations are not country-specific and they have no official status. Therefore, they are discussed in this separate section.

Sellman et al. (1995) state that an optimal methadone programme has the following phases:

- 1) Stabilisation (0-6 months)  
Goals: cessation of intravenous opioid use through the administration of an adequate dose of methadone; addressing of any concomitant psychiatric or medical conditions; stabilising crisis in social situations.
- 2) Rehabilitation (6-12 months)  
Goals: reduction and cessation of the use of all other psychoactive drugs; start of psychosocial rehabilitation
- 3) Community reintegration (1-2 years)  
Goals: maintaining stabilisation while care is integrated into the primary health care setting; developing an ongoing shared-care arrangement between the specialist clinic and the general practitioner; and providing psychotherapy and crisis intervention as needed
- 4) Withdrawal (6-12 months)  
Goal: negotiating methadone withdrawal on an outpatient basis
- 5) Aftercare and follow-up (1-2 years)



Goal: maintaining the improved status-quo through a detailed individual aftercare plan worked out in consultation with the case manager, medical specialist and general practitioner.

Loo et al. (1996) state that methadone prescription for addicts should be allowed only under strict regulation to prevent its becoming an additional addiction. Although the authors are generally positive about the effects of methadone maintenance, they point out that its effects can be counterproductive when the dose, administration or conditions for retaining in treatment are inadequate. They propose that addicts should be eligible for inclusion in methadone maintenance treatment only if they have been addicted for more than two years. In most guidelines, this limit is set at one year (California Society of Addiction Medicine 1998).

One study focused on substitution treatment in hospitals (Pardieck 1999). The authors consider two kinds of substitution treatment in hospitals: one for substitution patients that need hospitalisation and one for heroin addicts who enter hospital and receive methadone for the time of their stay in hospital (transition or temporary treatment). In the first case, the substitution treatment should be continued as it was; in the second case methadone treatment may facilitate treatment of the disease for which the patient is hospitalised and ease the contact between doctor and patient. Furthermore, methadone maintenance is a good way of keeping patients in hospital. If they do not get any treatment, there is a large possibility that the patient will leave the hospital against the doctor's advice.

Loo et al. (1995) discussed different doses of methadone, but the authors focused on the effect of dose increase on the risk of getting HIV-infected. They state that methadone maintenance treatment in itself is not sufficient to prevent addicts from getting HIV, even though methadone is supposed to keep people from injecting heroin, but when it is given in a sufficiently high dose and is accompanied by psychosocial care, it does prevent people from getting HIV-infection. They remark that the psychosocial element of treatment seems to be more important than the methadone itself. Also, they state that it is essential that the treatment is monitored closely in order to prevent patients from abusing the drug.

Several authors (Kauffman J F 1995; Loo 1996) argue that it is essential to identify psychological and other needs and to treat those along with the physical addiction; this is seen as the only way to treat the cause of the addiction. Those needs may be related to health (including psychiatric disorders) or social aspects, such as employment, education and housing. In Germany, a review of evaluation studies of maintenance treatment programmes revealed that maintenance patients hardly rehabilitate into work and hardly improve on other psychological and social aspects. As a consequence, the authors recommended lower thresholds for methadone maintenance and more provisions for psychosocial therapy, as well as financing of long-term treatment. They state that the politicians did not act upon these recommendations (Kalke 1998).

As stated above, methadone should be considered a long-term treatment. Many patients encounter difficulties in stopping methadone and the risk of

relapse is high (as high as 80% within the first year). Therefore, patients should stop in a controlled manner, slowly decreasing the amount of methadone administered. This is called tapering off. Tapers may be as slow as one mg per two weeks and may consequently take several months or even years if the dosage is over 100 mg. Poehlke (1999) recommends 5 mg per day until the dose has been reduced to 30 mg; then a gradual decrease of 10% of the dose. The patient's physical and mental health should be monitored closely. Other medications, such as clonidine, may be useful to control the discomfort that comes along with tapering off, especially in the final phase (California Society of Addiction Medicine 1998).

### **3.9 Conclusion**

During the past five years, several institutions have tried to set guidelines for methadone maintenance treatment, both on a national and supranational level. Most guidelines and recommendations agree on a basic set of eligibility criteria. Persons have to be opiate dependent and they get priority for treatment if they are pregnant, HIV-infected or live with a person who is already in methadone maintenance treatment. Many guidelines set a minimum age for treatment entry, but do not explain what should be done with younger persons. Some guidelines explicitly say that these persons may not start methadone treatment, while others set separate eligibility criteria. The content, level of detail and quality of the guidelines are still very diverse, however, and will need further improvement. Also, the lack of reference to evidence is concerning. Some guidelines seem to be based on personal opinion of the authors, mixed with clinical evidence. This should be made explicit.



## **4 Methadone: characteristics of the drug**

Methadone has been used as a drug for opiate dependence treatment since the sixties. New information about it is still appearing every day. This chapter summarises the new knowledge about the pharmacokinetics of methadone and about interactions of methadone with other licit and illicit drugs.

### **4.1 Methadone Pharmacokinetics and Dose Formulations**

While racemic methadone is most commonly used, in Germany the l-methadone isomer is used. In a 2-week double-blind trial of 26 opiate addicts, Scherbaum, et al. (1996) compared l-methadone to racemic methadone (delivered at twice the l-methadone dose). They reported no significant differences in withdrawal symptoms and other clinical response measures, although they noted that almost half of the patients receiving the racemic formulation demanded and ultimately received a dose increase of 20 mg. This indicates a level of dissatisfaction not made apparent by withdrawal measures. In a related study, Eap, Finkbeiner, et al. (1996) switched 22 patients from l-methadone to a double dose of racemic methadone. They noted a significant decrease of 16% in the mean serum concentration/dose ratios of the active l-enantiomer after the change. They suggested that the adaptive changes associated with racemic methadone might be due to an increase in demethylation (by the hepatic enzyme CYP3A4) and suggested the need for dose adjustment in some patients. Another group, Hiltunen, et al. (1999) also compared l-methadone and racemic methadone in 50 methadone-maintained individuals. Their findings were very consistent with those of Eap and colleagues (1996) above, in that racemic methadone was associated with greater reports of treatment dissatisfaction, generally alleviated by dose increases. Further, it was noted that the correlation between objective and subjective indicators of treatment efficacy was significantly better for selective measures of l-methadone than for overall plasma levels of methadone. The authors conclude that chiral analyses of methadone should be further explored for therapeutic monitoring of methadone maintenance treatment.

In the United States, concern regarding the comparability of three different methadone formulations (tablets, liquid, and methadone hydrochloride diskets) led to a three-way, double-blind, cross-over comparison trial by Gourevitch, Hartel et al. (1999). They examined differences in methadone pharmacodynamics and subjective symptoms of opiate withdrawal among eighteen patients as they were switched between three different oral formulations of methadone. No statistically significant differences in any of the pharmacodynamic parameters studied were found among the three methadone preparations. No significant differences were noted in the rate and extent of rise and fall in plasma methadone levels during a 24-hour intensive sampling period and subjective symptoms did not correlate with methadone formulation.

Wolff et al. (1997) report that the long terminal elimination half-life of methadone (33-46 hours in healthy subjects and, possibly, longer in opiate users) indicated that accurate measurement of this parameter requires a

duration of sampling longer than that used in this study (57 hrs). There is some evidence that monitoring methadone plasma concentration may be of benefit in dosage adjustment during methadone maintenance therapy for heroin (opiate) dependence. However, the kinetics of oral methadone are incompletely characterised. They also suggest that parameters describing plasma concentrations of methadone after a single oral dose in healthy subjects may not be useful for predicting and adjusting dosage in opiate users receiving methadone maintenance therapy unless coupled with (not yet developed) modelling techniques (for example Bayesian forecasting).

Rostami-Hodjegan et al. (1999) found that a time-dependent increase in the clearance of methadone is consistent with auto-induction of CYP3A4, the enzyme responsible for much of the metabolism of the drug. The time for clearance might reflect both up- and down-regulation of alpha1-acid glycoprotein, the major plasma-binding site for methadone.

Quinn, Wodak & Day (1997) provide a comprehensive overview of the pharmacokinetic and pharmacodynamic principles of both illicit drug use and of treatment of illicit drug users. They note that rapid absorption, rapid entry into the central nervous system, high bioavailability, short half-life, small volume of distribution and high free drug clearance are pharmacokinetic characteristics that predict a high potential for harmful use because these factors increase positive reinforcement. They also note that drug users adapt the method and route of drug administration to optimise the delivery of the drug to the brain while attempting to maximise the bioavailability of the drug. The preventive or reductive pharmacotherapeutics of illicit drug use makes use of several subsets of agents: those which act on the same receptor or system as the illicit drug (such as methadone), those which produce an adverse reaction on consumption of the illicit drug (such as disulfiram) and those which symptomatically attenuate illicit drug withdrawal symptoms (such as clonidine). The most common interactions seen in practice are pharmacodynamic in nature, most often due to the additive effects of different drugs on the central nervous system. Of these the effect of the CYP3A microsomal enzyme in diminishing the efficacy of methadone are the most commonly encountered.

## 4.2 Drug Interactions

Moody et al. (1997) state that the N-demethylation of LAAM, norLAAM, and methadone were significantly inhibited by **ketoconazole**. P450 3A N-demethylation of LAAM, norLAAM, and methadone exceeded the next most active P450, respectively, by at least 2.5, 9.6, and 13.4 times when expressed per milligram protein and by 18.2, 6.0, and 6.1 times when expressed per nanomole P450. These results suggest that P450 3A4 is the primary site of N-demethylation of LAAM, norLAAM, and methadone in human liver. Although other enzymes may also be capable of N-demethylating these compounds, identification of specific enzymes, except P450 3A4, has yet to be established. Knowledge of these enzymatic pathways is essential for assessment of the impact of metabolic drug-drug

interactions on therapeutic success and/or adverse events.

Iribarne, et al. (1996) found that methadone metabolism can be strongly affected by drugs that induce or inhibit P450 3A4. Methadone metabolism was 60-72% inhibited by three mechanism-based inhibitors of P450 3A4 (**gestodene, TAO, and erythralosamine**) and by four reversible inhibitors of P450 3A (ketoconazole, **dihydroergotamine, quercetin, and diazepam**) as well as by two nonspecific inhibitors (**metirapone and SKF-525A**). Conversely, **quinidine** (inhibitor of P450 2D6), **7,8-benzoflavone** (inhibitor of P450 1A), or **sulfaphenazole** (inhibitor of P450 2C) did not significantly inhibit, and may even have activated, methadone metabolism. Four heterologously expressed P450 proteins were able to catalyze the N-demethylation of methadone, namely, P450 2C8, P450 2C18, P450 2D6, and P450 3A4. However, referring to their relative liver content, it was asserted that P450 3A4 is the major enzyme involved in the N-demethylation of methadone. They advised caution in the clinical use of methadone when drugs are co-administered that induce (e.g., **rifampicin**) or inhibit P450 3A4 (e.g., diazepam). Iribarne et al. (1997) then conducted an in vitro study to determine if methadone is an inhibitor of other P450s characterised by their specific catalytic activities. Enzymatic activities specific to P450 2E1, P450 1A, P450 2B and P450 2C were not inhibited by methadone. Conversely, nifedipine oxidation, mediated by CYP3A4, was potently inhibited by methadone by a mixed-type inhibition mechanism. Fluvoxamine, a new antidepressant, was shown to be a potent mixed-type inhibitor of methadone N-demethylation. Finally, methadone appeared to be a mixed-type inhibitor and not a suicide inhibitor of cytochrome P450 3A family. They advised caution in the clinical use of methadone with other drugs that are able to induce or inhibit P450 3A4.

One drug thought to have potential as an inducer of the cytochrome P-450 family is **rifabutin**, a rifamycin derivative like rifampicin, that has been registered for the treatment of pulmonary tuberculosis and for the prophylaxis and treatment of MAC in patients with AIDS. Benedetti (1995) examined rifabutin and concluded that rifabutin is a less potent inducer of CYP3A4 than rifampicin, and that it does not appear to affect cytochrome P-450 1A2. Brown et al. (1996) examined the possibility of a drug-drug interaction between rifabutin and methadone, in 24 methadone-maintained, former injecting drug users infected with the human immunodeficiency virus. The study was an open-label, drug-drug interaction and safety trial in which patients were followed for 15 days. Patients received rifabutin 300 mg as a single dose concomitantly with their individualised methadone dosage. No significant differences in methadone peak plasma concentration, time to peak plasma concentration, area under the plasma concentration-time curve, systemic clearance or renal clearance was observed in the presence of rifabutin. Seventy-five percent of the patients reported at least one symptom of narcotic withdrawal during the study, but these symptoms were mild. Concurrent administration of rifabutin and methadone appeared to be safe in human immunodeficiency virus-infected injecting drug users maintained on stable doses of methadone and is not expected to produce any

significant changes in the pharmacokinetics of methadone in these patients.

In a review of drug interactions with antiviral drugs, Taburet & Singlas (1996) reported that **zidovudine** will increase the AUC of methadone 1.4-fold, while methadone also inhibits zidovudine glucuronidation. Trapnell et al. (1998) report similar findings. They state that zidovudine is primarily metabolised to an inactive glucuronide form, GAZT, via uridine-5'-diphospho-glucuronosyltransferase (UGT) enzymes. UGT enzymes were said to exist as different isoforms, each exhibiting substrate specificity, and that methadone and other drugs will decrease GAZT formation, presumably due to UGT inhibition. Their in vitro study indicated that the concentration of methadone required to produce a 50% inhibition of GAZT was well above the usual clinical concentration.

**Ritonavir, indinavir, and saquinavir**, are all human immunodeficiency virus-1 protease inhibitors and all are extensively metabolised by liver CYP3A4. Iribarne et al. (1998) examined in vitro metabolic interactions between these protease inhibitors and methadone or buprenorphine using a panel of 13 human liver microsomes. The rank order of inhibition potency against metabolism of methadone and buprenorphine was ritonavir > indinavir > saquinavir. Similar findings were reported by Hsu, Granneman & Bertz (1998). They state that ritonavir is primarily metabolised by cytochrome P450 (CYP) 3A isozymes and, to a lesser extent, by CYP2D6. In vitro, ritonavir is a potent inhibitor of CYP3A. In vivo, ritonavir significantly increases the AUC of drugs primarily eliminated by CYP3A metabolism. It also inhibits CYP2D6-mediated metabolism, but to a significantly lesser extent (145% increase in desipramine AUC). Since ritonavir is also an inducer of several metabolising enzymes [CYP1A4, glucuronosyl transferase (GT), and possibly CYP2C9 and CYP2C19], the magnitude of drug interactions is difficult to predict, particularly for drugs that are metabolised by multiple enzymes or have low intrinsic clearance by CYP3A. For example, the AUC of CYP3A substrate methadone was slightly decreased and alprazolam was unaffected. In a single clinical example, Geletko & Erickson (2000) reported a case study involving an HIV-infected methadone maintenance patient receiving methadone maintenance who experienced withdrawal symptoms after ritonavir, saquinavir, and stavudine were added to his regimen. They concluded that the most likely cause of withdrawal symptoms was ritonavir.

Altice, Friedland & Cooney (1999) describe seven cases of opiate withdrawal among patients receiving chronic methadone maintenance therapy following initiation of therapy with the non-nucleoside reverse transcriptase inhibitor, **nevirapine**. Three patients, for whom methadone levels were available at the time of development of opiate withdrawal symptoms, had subtherapeutic methadone levels. In each case, a marked escalation in methadone dose was required to counteract the development of withdrawal symptoms and allow continuation of antiretroviral therapy. Three patients continued nevirapine with methadone administered at an increased dose; however, four chose to discontinue nevirapine. Heelon & Meade (1999) also provide a case report of one patient who experienced

methadone withdrawal symptoms when combining methadone and nevirapine.

Iribarne, Picart, Dreano & Berthou (1998) later examined the co-administration of the serotonin reuptake inhibitors (SSRIs), **fluoxetine** and **fluvoxamine**, with methadone or buprenorphine. Both fluoxetine and fluvoxamine are known to be CYP450 2D6 and 3A4 inhibitors in vitro. They reported that fluoxetine inhibited methadone N-demethylation, but did not inhibit buprenorphine dealkylation, while norfluoxetine inhibited the metabolism of both methadone and buprenorphine. They also reported that fluvoxamine inhibited the metabolism of methadone and buprenorphine. They suggest care in co-administration and note that fluvoxamine is more potent than fluoxetine in inhibiting methadone and buprenorphine metabolism. Baumann (1996) noted that fluvoxamine inhibits with decreasing potency, cytochrome P450 1A2, CYP2C19, CYP2D6 and CYP1A1, but it was also an inhibitor of CYP3A. Eap, Bertschy, Powell & Baumann (1997) examined the interactions of fluoxetine and fluvoxamine with l-methadone and racemic methadone. Their findings suggest that CYP2D6, an enzyme that is strongly inhibited by fluoxetine, preferentially metabolises l-methadone, whereas CYP1A2, which is strongly inhibited by fluvoxamine, metabolises both enantiomers. The authors also suggest possible roles for CYP3A4 or CYP2C19. They recommend that SSRIs with the lowest affinity for CYP1A2, CYP2D6, and CYP3A4 be utilised if a lack of metabolic interaction with methadone is desired. Fluvoxamine is the only SSRI expected to inhibit CYP1A2, while fluvoxamine and norfluoxetine may inhibit CYP3A4. Sertraline and citalopram are the SSRIs least likely to inhibit CYP2D6 and CYP3A4. Paroxetine may also minimally effect CYP3A4. The authors also suggested that fluoxetine and fluvoxamine be considered for their therapeutic potential in methadone patients exhibiting very high rates of methadone metabolism. Consistent with that recommendation, DeMaria & Serota (1999) reported on a patient that could not maintain an effective serum level of methadone — even at a dose of 200 mg/d. They administered fluvoxamine and found a subsequent increase in her methadone blood level and a concurrent reduction in opiate withdrawal symptoms.

At least one clinical example of an SSRI-methadone-diazepam interaction has been reported. Alderman & Frith (1999) reported a case involving a 28-year-old woman hospitalised with severe hypoxaemia and hypercapnia indicating hypoventilation. Medication prior to admission had been stable and included methadone 70 mg daily and diazepam 2 mg twice daily. Three weeks before admission she had commenced treatment with fluvoxamine. At the hospital, methadone was decreased to 50 mg daily and diazepam was tapered to zero. The serum methadone concentration decreased and oxygenation improved considerably.

Cobb et al. (1998) conducted a randomised, double-blinded, placebo-controlled pharmacokinetic and safety trial to determine the effect of **fluconazole** on methadone disposition. Volunteers receiving methadone maintenance therapy were randomised to receive either 200 mg/day oral fluconazole (n = 13) or placebo (n = 12). After 14 days there was a significant (35% average) increase in serum methadone area under the



curve relative to baseline among patients receiving fluconazole. At the same time, mean serum methadone peak and trough concentrations increased significantly by 27% and 48%, respectively, and oral clearance of methadone was significantly reduced by 24%. In contrast, the pharmacokinetics of methadone went unaltered in the placebo group. Renal clearance of methadone was not significantly affected by fluconazole or placebo therapy. Although exposed to increased concentrations of methadone, patients treated with fluconazole did not exhibit signs or symptoms of significant narcotic overdose.

Another drug that appears to inhibit CYP 3A4 is **amprenavir**, a relatively potent protease inhibitor. Decker et al. (1998) report that amprenavir inhibits CYP3A4 to a greater extent than saquinavir, and to a much lesser extent than ritonavir. In a review of ritonavir pharmacokinetics and drug interactions, however, Hsu, Granneman & Bertz (1998) reported that co-administration of ritonavir and methadone decreases the dose normalised C<sub>max</sub> and AUC of methadone. This finding is unexpected as ritonavir is a potent inhibitor of CYP3A metabolism, and methadone is primarily metabolised by CYP3A. They postulate that CYP3A inhibition may be offset by CYP2C9 induction.

Finally, Reimann et al. (1999) investigated the effects of **fusidic acid therapy** on the hepatic CYP (CYP450) enzyme system. Thirty HIV-seropositive l-methadone-substituted injection drug users were randomised into 3 groups (A - C). Ten patients were treated with fusidic acid 500 mg/day over a period of 14 (group A) or 28 days (group B), respectively. Patients in group C served as a control group and did not receive any medication apart from l-methadone. No effects on antipyrine pharmacokinetics and pharmacokinetics of antipyrine metabolites were found in group A after 14 days of fusidic acid intake and in the control group without therapy. However, in contrast an activation of the CYP450 enzyme system was observed in group B after 28 days of fusidic acid therapy with an increase of total antipyrine clearance as well as clearances to all metabolites. Antipyrine half-life was significantly reduced and some patients developed clinical signs of l-methadone underdosage. The results suggest that fusidic acid has a time-dependent activating effect on the CYP450 enzyme system.

### **4.3 Conclusion**

Concerning the pharmacokinetics of methadone, our understanding of the role of the hepatic enzyme CYP3A4 has increased significantly in the past five years. This enzyme plays an important role in the metabolism of methadone. Many drug interactions can also be explained now, since many drugs influence the activity of CYP3A4. The field of drug interactions is an area where knowledge has advanced most significantly since 1995. Research on the P450 3A N-demethylation of methadone has resulted in a much better understanding of drug-drug interactions involving methadone and other substances metabolised by hepatic mechanisms. Of great importance is the improved understanding this research provides with respect to interactions with drugs used in the treatment of HIV as well as those used to treat psychiatric disorders.



## **5 Treatment outcome studies**

The guidelines discussed in the chapter 3 are based on literature that had been published by then. Since the publication of these guidelines, a large array of new evidence has appeared in the medical literature. This chapter describes studies that have tried to establish the effectiveness of treatment. The academic discussion about the appropriate dose has continued, while a start has been made with research about prognostic factors to treatment effectiveness, treatment modalities, and the possibilities and pitfalls of urine tests.

### **5.1 Effectiveness of methadone maintenance treatment**

Methadone can be very effective for the treatment of heroin dependence. It saves many people's lives, because they are less likely to die from heroin overdose or suicide while on methadone treatment (Caplehorn 1996b). Methadone maintenance with a long-term treatment perspective is found to be significantly more effective than abstinence-oriented treatment (Caplehorn 1998). Two studies (Bell James 1995a; Sees KL 2000) found that abstinence-oriented treatment may even have a negative impact on treatment outcomes, while methadone maintenance increases abstinence from illicit opiates and has positive outcomes on other outcome measures. Sees et al. (2000) compared methadone maintenance treatment plus psychosocial therapy with psychosocially enriched detoxification for 180 days. Total treatment time for both groups was one year. They found that methadone maintenance with psychosocial therapy is more effective in decreasing heroin use and motivating addicts to stay in treatment. In the detoxification group, more persons dropped out or used cocaine or both.

Farrell et al. (1994) conducted a thorough review of articles on methadone maintenance treatment. They state that the following factors of treatment are associated with good treatment outcomes:

- higher doses of methadone (>50 mg);
- treatment goal of successful ongoing maintenance rather than abstinence;
- good quality counselling;
- good staff-patient relationships;
- clinics with low staff turnover rates and good management;
- no withdrawal of privileges in case a patient does not comply to treatment regulations (withdrawals of privileges are associated with lower retention rates).

The use of injectable methadone as opposed to oral methadone is still under lively discussion. Although the arguments in favour of injectable methadone for some patients are appealing, there is no evidence that people will enter into treatment more easily if they can continue injecting (Farrell M. 1994).

Patients who end treatment with the approval of their treating staff do better than patients who leave for other reasons. Most patients (70%), however, start using illicit opiates after treatment ending anyway. The

evidence suggests that patients with a shorter history of opioid dependence do better after leaving treatment than those with a longer history.

Marsch (1998) published a meta-analysis of articles on methadone maintenance interventions. She included studies about the effect of methadone maintenance on one of the following three outcome measures:

1) Illicit opiate use (11 studies with 2056 participants)

The author found an overall significant favourable effect on illicit opiate use.

2) Criminal activities (24 studies with 7173 participants)

The effect on the reduction of the criminal activities of the participants was significant and favourable.

3) HIV risk behaviours (8 studies with 1797 participants)

The author found an overall significant favourable effect on HIV risk behaviours.

Marsch does not link any conclusions to these findings, as she herself doubts whether any generalisation can be made on the basis of the data.

O'Connor and Fiellin (2000) wrote a comprehensive review on pharmacological treatment of heroin-dependent patients. One of their findings is about the setting of pharmacological treatment. The authors state that the physician's office may be a good setting for treatment as it minimises the stigma on drug addicts and limits contact with other drug-using patients. This setting is mostly appropriate for patients that are stabilised in methadone maintenance treatment.

One study found that, one year after recruitment for methadone maintenance or methadone reduction ('maintenance-to-abstinence') treatment, patients showed substantial reductions in the use of illicit opiates, stimulants and non-prescribed benzodiazepines. Reductions in drug injecting behaviour, alcohol use and criminality were also found, but not for patients who had poor treatment response (Gossop; Marsden; Stewart, and Rolfe 2000). Byrne followed-up a group of 86 heroin addicts nine years after the start of a methadone maintenance programme and found that 56% of them were well and functional; the most optimistic interpretation of the data was that 81% were well at follow-up (Byrne 2000). In Australia, methadone maintenance had a significantly beneficial effect on the long term. After 22 years, patients who had been on methadone maintenance significantly reduced their use of heroin while on treatment. Some had even stopped using illicit drugs (Reinert 2000).

Two studies compared a group of addicts in methadone maintenance treatment with a group that received no methadone. Fischer et al. (1999) retrospectively compared heroin dependent persons who had been on methadone maintenance with heroin addicts who had not. The dose of methadone and the treatment strategy were not mentioned. They concluded that the basic health status and the criminal justice involvement of the persons was equal in both groups, but that the group of persons who had been in treatment, had:

- less illegal income generation at a statistically significant level
- less illicit and other drug use at a statistically significant level

- less illicit market activities at a statistically significant level
- needed less emergency care
- more socio-economic integration.

The authors state that the basic health status and criminal justice involvement might improve in the long term for the methadone maintenance group, as these effects often present with a delay. They also state, however, that these results in favour of methadone maintenance may be biased, because of self-selection effects: less harmful, more motivated persons will enter into treatment more easily than addicts who are not willing to change their way of life.

Rosenbach and Hunot (1995) studied patients in a clinic that started giving only counselling and later added methadone maintenance to the treatment programme. While retention in the study was 13% in the counselling-only group, 83% of the patients in the methadone maintenance treatment group remained in treatment - a significant difference. Furthermore, the methadone maintenance group did significantly better in the rates of abstinence from use of needles and use of illicit drugs, they were less involved in crime and developed better personal relationships.

## **5.2 Dose**

As the dose is important to the success of methadone treatment (National Institutes on Drug Abuse 1999), many studies focus on this aspect of treatment. The dose should be assessed and monitored on an individual basis, depending on the patient's health and dependence(s). The dose that is appropriate for one person may be an overdose for the other (Furet 1999).

### Studies Using Random Assignment

Three studies used a randomised assignment procedure to compare treatment outcomes associated with 40-50 mg versus 70-90 mg of methadone in the treatment of opiate dependence. Strain et al. (1999) compared a group receiving 40 to 50 mg with a group receiving 80 to 100 mg of methadone. One hundred ninety-two patients were enrolled in a 40-week randomised, double-blind clinical trial. Intent-to-treat analysis through week 30 demonstrated that patients (n=97) in the higher-dose group had significantly lower rates of opioid-positive urine samples compared with patients (n=95) in the lower-dose group. These differences persisted during a planned withdrawal from methadone. Nineteen (33%) of 57 patients in the high-dose group and 11 (20%) of 54 patients in the moderate-dose group completed detoxification. Both the lower- and higher-dose methadone treatments resulted in decreased illicit opioid use during methadone maintenance and detoxification. The higher-dose group had significantly greater decreases in illicit opioid use.

Rhoades et al. (1998) examined two major methadone treatment factors, visit frequency and methadone dose. One hundred fifty opiate-dependent subjects randomly assigned to four groups received 50 or 80 mg of methadone and attended a clinic 2 or 5 days per week. Survival analysis indicated significantly higher dropout rates for groups having five vs. two visits per week. Lower methadone doses were associated with higher

proportions of opiate-positive urinalysis results. Preston et al. (2000) studied a group of patients who continued to use drugs despite methadone maintenance treatment. Patients were randomly assigned to one of four treatment groups:

- 1) Standard methadone maintenance treatment, which consisted of 50 mg/day oral liquid methadone and weekly counselling sessions;
- 2) Standard methadone maintenance treatment plus vouchers for each illicit opiate-negative urine sample; the value of the vouchers started at \$2.50 and increased by \$1.50 for each consecutive negative urine sample. For every 3 consecutive negative samples, patients would receive an additional \$10 voucher;
- 3) Methadone dose increase to 70 mg/day;
- 4) Methadone dose increase to 70 mg/day plus vouchers.

Contingent vouchers and a methadone dose increase each significantly increased the percentage of illicit opiate-negative urine samples during the study. If considered after the study, patients who had received contingent vouchers, with or without dose increase, had a longer abstinence of illicit opiates. Patients who had received a dose increase, with or without contingent vouchers, reported less frequent use of illicit opiates and less craving for heroin. The authors concluded that abstinence reinforcement and a methadone dose increase were each effective in reducing opiate drug use. When combined, they did not dramatically enhance each other's effects on any single outcome measure. Other studies found the same result (Bell James 1995b)(Saxon AJ and others 1996).

Contrary to the above results, Curran et al. (1999) report that patients in their study reported significantly increased craving for heroin as the methadone dose was increased. Not only did the patients crave relief of their withdrawal symptoms, which would indicate an insufficient dose of methadone, they also craved the 'positive' effects of heroin: the high. The authors conclude that this effect must have appeared because the use of methadone primed the need for heroin, just as one sip of alcohol can make abstinent (former) alcohol addicts crave for alcohol. Although the study was a randomised double blind, placebo-controlled study, it only included a small number of participants and two test days in an unknown study period.

### Naturalistic Studies

Several naturalistic studies provide support for the view that some methadone is better than no methadone at all and that higher methadone doses are preferable to lower, with a few caveats. In a prospective cohort study conducted in Amsterdam, Van Ameijden, Langendam & Coutinho (1999) demonstrated that low-threshold methadone maintenance effectively reduces overdose mortality. In their study, 498 Dutch injecting drug users (IDU) provided 1,969 person years of follow-up (1989-1995). Forty-four IDU died in this period, 15 due to illicit drug overdose. Compared to IDU not in maintenance, the adjusted relative risk for overdose mortality among those receiving 5-50 mg, 55-70 mg, and 75+ mg were 0.35, 0.13, and 0.11, respectively ( $p < .05$ ). Current injection use and HIV-seropositivity were independent predictors for overdose

mortality. They note that previous studies indicated effectiveness of methadone-assisted detoxification and high-dose maintenance programs in reducing mortality, and that these findings suggest low-threshold maintenance programs also reduce overdose mortality, with higher dosages being most protective. Hartel et al. (1995) examined factors associated with heroin use during methadone maintenance treatment using logistic regression to examine data obtained in a cross-sectional sample of 652 methadone patients. They report that heroin use during the 3 months prior to interview was greatest among patients maintained on methadone dosages of less than 70 mg/day and among patients who used cocaine during treatment, independent of treatment duration, treatment compliance, alcohol use, and socio-economic factors. Cocaine users were more likely than nonusers of cocaine to use heroin at all methadone dosage levels were. Maddux, Prihoda & Vogtsberger (1997) followed a cohort of 610 opioid users admitted to methadone maintenance for 1 year. The maximum dose during treatment ranged from 10 mg to 110 mg, with a mean of 52 mg. Higher doses were associated with increased retention through the dose range of 60 mg-69 mg. Dose was not related to the likelihood of a positive morphine test but was related to the likelihood of a positive cocaine test. In this study, with flexible dosing and patient participation in dose decisions, patients were said to be retained on methadone about as well as was reported in a previous study using a fixed dose of 80 mg.

For many addicts, it is important to have a high dose of methadone to counter the withdrawal effects of heroin and to prevent persons to continue the use of heroin and other illicit drugs (California Society of Addiction Medicine 1998)(Ezard 1999;Rhoades 1998;Ling W; Wesson DR; Charuvastra C, and Klett CJ 1996a;Richard 1998). A high dose is often considered a dose of more than 60 mg/day. At this dose the effects of heroin, if used, are totally blocked out - including the euphoric effects (Maxwell 1999). Richard et al. (1998) remark that a dose of more than 100 mg is not advisable, but reports exist of patients receiving up to 300 mg/day (Strang 1996).

Johnson et al. (2000) also found that high-dose methadone (60-100 mg/day) is more effective for illicit opiate and cocaine use and for study retention than low-dose methadone (20 mg). Considering the extremely low dose of 20 mg, this comes as no surprise. Meissner et al. found that of the 43 patients in München, who had been maintained on an average dose of 110 mg/day for more than six months, not one used heroin anymore and the number of people without a place to live had decreased by 50%. In the first six months, cocaine use had increased greatly at first, possibly to compensate for the lack of euphoria, but decreased during the course of the study (Meissner 1997).

The reason for bad treatment retention in abstinence oriented methadone treatment programmes may result from the lower doses used in these programmes (Caplehorn 1996a).

One study examined the impact of very high methadone dosing. Maxwell & Shinderman (1999) treated 164 patients in a methadone maintenance



program with doses of methadone exceeding 100 mg/d. The mean dose of these higher dose (HD) patients was 211 mg/d (range 110-780 mg/d). A comparison group (C) of 101 patients was randomly selected from the general clinic population (mean dose 65 mg/d). At intake the HD group reported \$153/day of heroin use versus \$87/day in the C group. The HD group had more patients whose opiate of choice was an oral pharmaceutical (30% versus 2% of the C group). Sixty-three percent of the HD group had comorbid Axis I psychiatric diagnoses compared to 32% of the C group. Response to psychopharmacologic treatment was enhanced by increased methadone dose in HD patients with "refractory" psychiatric disorders. Urine toxicologies described as "before" were collected prior to increase over 100 mg/d in the HD group or at the first routine urine toxicology collection of the calendar year for the C group. These results were compared to the most recent urine toxicologies for both groups ("after"). The percentage of toxicologies positive for illicit drugs in the HD group dropped from 87% "before" to 3% "after." The C group was 54% positive "before" and 37% positive "after." The authors conclude that doses of methadone in excess of 100 mg/d (range 110-780 mg/d in our sample of 164 patients) are safe and necessary to prevent illicit opiate use, stabilise psychiatric symptoms, and diminish abuse of alcohol and benzodiazepines in many patients. The same group (Maremmani I. 2000) studied 90 opioid-dependent subjects, 38 with one or more additional Axis I diagnosis and 52 with no psychiatric comorbidity. There were significant differences between these two groups regarding the methadone dose required for clinical stabilisation, but not in the rate of retention in treatment. Dual diagnosis patients, those with psychiatric comorbidity, required an average stabilisation dose of 154 +/- 84 of methadone compared to 99 +/- 49 mg/day for patients whose only Axis I diagnosis was opioid dependence. In the 990-day period considered there were no differences between the two groups of patients in terms of retention in treatment.

Bach & Lantos (1999) examined the relationship between heroin prices and average methadone doses reported in multiple US cities between 1988 and 1995. They found that the amount of pure heroin obtainable for US\$100 increased 3-fold (on average) between 1988 and 1995. They also report a significant relationship between average heroin price and the average methadone doses observed in clinics within the same cities. The authors concluded that determination of appropriate methadone dose needs to include consideration of the local price and purity of heroin.

### **5.3 Overdose and mortality associated with methadone treatment**

Numerous large-scale reviews of methadone and mortality in many countries support the effectiveness of methadone with respect to decreased rates of mortality when compared to mortality rates for illicit opiate users not enrolled in treatment. Several studies indicate, however, that methadone diversion poses a significant health threat to opiate users not enrolled in methadone treatment.

Caplehorn et al.(1996a) reviewed an admission cohort of 296 Australian methadone maintenance patients followed over 15 years. The relative risks of death in and out of maintenance were calculated for two age groups, 20-29 and 30-39 years. Heroin addicts in both age groups were one-quarter as likely to die while receiving methadone maintenance as addicts not in treatment. Methadone maintenance had no measurable effect on the risk of death through nonheroin overdose, violence or trauma, or natural causes. A meta-analysis showed the reduction in overall mortality was consistent with the results of cohort studies conducted in the United States, Sweden, and Germany. The combined results of the five studies again indicated that methadone maintenance reduced addicts' risk of death to a quarter, RR 0.25 (95% CI 0.19 to 0.33). In New South Wales (NSW), Caplehorn and Drummer (1999) estimated the effects of methadone programs on mortality using a retrospective, cross-sectional examination of all 1994 New South Wales coroner cases in which methadone was detected. Cases were people identified as patients in NSW methadone maintenance programs or those whose deaths involved methadone syrup diverted from maintenance programs. The relative risk of fatal accidental drug toxicity for patients in the first two weeks of methadone maintenance was 6.7 times that of heroin addicts not in treatment (95% CI RR, 3.3-13.9) and 97.8 times that of patients who had been in maintenance more than two weeks (95% CI RR, 36.7-260.5). Ten died from iatrogenic methadone toxicity and diverted methadone syrup was involved in 26 fatalities. They emphasise that doctors should carefully assess and closely monitor patients being admitted to methadone maintenance and limit the use of takeaway doses of methadone.

Valmana, Oyefeso, Clancy & Ghodse (2000) examined methadone-related deaths among all cases of inquest on drug-related cases in 18 coroners' jurisdictions in England during a six-month period in 1997. In 154 deaths, methadone, either prescribed or not prescribed, was reported to be the substance directly implicated in the death of 40 individuals. The majority of deaths involved methadone that had not been prescribed (72%) and a significant difference in age was noted between the methadone prescribed (median = 22 years) and non-prescribed groups (median = 37 years). The authors suggest more stringent controls around the prescription and dispensing of methadone, along with measures to alert opiate abusers of the hazards of using methadone in a non-controlled fashion. Similar problems were noted in the City of Manchester. Cairns, Roberts & Benbow (1996) reviewed City of Manchester coroner records (1985-1994) for deaths associated with methadone. Of 602 alcohol/drug deaths, 90 were attributed at least in part to methadone, 52 of 90 attributed solely to methadone. Inquest verdicts were misadventure (57), suicide (6), and accident (1). Four criminal inquests involved the deaths of children (aged 2-3). 36 of the 90 victims used prescribed methadone, 32 used diverted methadone (4 purchased the drug), and 22 were probable diversions as source was unknown. Deaths rose steadily over time - with a jump in 1990 - probably due to a public health approach that rapidly increased prescribing. Increased availability has coincided with increased deaths. In the south east of Scotland, Bentley & Busuttill (1996) reported that a review of deaths of chronic drug abusers revealed a total of 179 fatalities in a six-year period (1989-1994). There was an almost linear increase in

the number of such deaths per year over this period, rising from 14 in 1989 to 45 in 1994. The majority of deaths (86%) were seen in males and the peak age at death was in the third decade of life. In the majority of cases (60%) death was deemed to be accidental and most were due to accidental drug overdoses, with methadone being the drug most commonly detected on toxicological analysis.

Neeleman & Farrell (1997) examined accidental, undetermined, and suicidal poisonings involving methadone (with or without heroin) and heroin (without methadone) in England and Wales, with an emphasis on trends over time (1974-1992). They report that the proportions of poisoning deaths involving methadone (alone or in combination with heroin) rose by 80% per 3-year period. The proportion of poisoning deaths involving heroin without methadone rose by 76% per 3-year period. They concluded that methadone's involvement in these deaths has not risen disproportionately in relation to that of heroin up to 1992, and that the rising rates of death by poisoning may reflect the growth of the addict population. Other studies cited below provide some reason to believe that the rise in methadone-related deaths might be prevented.

In both the Republic of Ireland and the United Kingdom, methadone patients may be dispensed a weekly dose of methadone, with prescribed daily doses then administered at home each day. Harkin, Quinn & Bradley (1999) reported a survey conducted by 9 GPs in Dublin, Ireland regarding their client's use of a baby bottle to measure or store their methadone dose. A surprising 48 of 186 (26%) methadone patients stated that they had used a baby bottle to measure their methadone in the past month, with 21 of 186 (11%) reporting use of a baby bottle to store the methadone in the past month. A follow-up telephone survey of 10 pharmacists in Dublin and Manchester revealed that 8 of 10 offered a measuring device to new clients at a charge of 30-50p. A previously discarded graduated 30ml plastic device was also offered — although it was thought to be unsuitable for repeated use. The authors recommend that clients be asked how they measure their daily dose and that a free measuring device be included with each prescription.

Zador & Sunjic (2000) sought to determine the number and causes of deaths in methadone maintenance treatment (MMT) in New South Wales (NSW), Australia. A total of 288 patients died while registered in MMT from 1990 to 1995. The most common cause of death was drug-related (44%), followed by medical illness (24%). Fifty deaths (21%) occurred in the first week of MMT, 88% of which were drug-related. In 92% of these drug-related deaths, there was evidence of polydrug use. In all, 42% of all drug-related deaths occurred during the first week of MMT. Nearly half the cases of drug-related death (46%) in the first week were noted by the medical practitioner at assessment to have a history of polydrug abuse or dependence. Four (9%) drug-related cases were prescribed doses of methadone in excess of the-then current national methadone clinical guidelines. The authors caution that the first 7 days of MMT is a high-risk period. Inadequate clinical review of subjects' tolerance to methadone and/or subjects' use of other central nervous system (CNS) depressant drugs probably contributed to most of these cases' deaths during

induction. The study reinforces the importance of a thorough drug and alcohol assessment of people seeking MMT, cautious prescribing of methadone, frequent clinical review of patients' tolerance to methadone during induction and education about the dangers of additional drug use during this period.

Williamson et al. (1997) assessed the safety of prescribing methadone tablets and syrup in South Australia (1984-1994) by investigating overdose deaths of patients using prescribed methadone and non-patients using illegally obtained methadone. Per capita prescription of methadone tablets for chronic pain in South Australia was the highest in Australia in 1994. A large increase in deaths, due mainly to methadone tablets prescribed for chronic pain, occurred in 1993-1994. Illegal diversion of methadone to non-patients was responsible for half of the deaths during these two years. Deaths from overdoses of methadone syrup prescribed in maintenance therapy for drug dependence declined from 1984 to 1994. The relative risk for patient deaths due to methadone tablets versus methadone syrup was estimated to be 7.29 (95% confidence limits, 2.15-31.48). Psychotropic drug combinations were present in 86% of deaths. The authors concluded that the methadone syrup program for drug dependence is relatively safe, but raised concerns about prescribing methadone tablets for chronic pain. They recommend better prescriber education and accountability, as well as improved patient assessment and supervision and advice to patients about concurrent use of alcohol and benzodiazepines.

Neale (2000) provides a qualitative investigation of the role of methadone and methadone treatment in non-fatal illicit drug overdose that is consistent with the above cited studies. During 1997 and 1998, semi-structured interviews were conducted with 33 individuals in six hospital accident and emergency departments in two Scottish cities. The research identified four overdose situations related to methadone/methadone treatment. These were: topping up a legitimate methadone prescription; abusing another's methadone prescription; preferring illegal drugs to prescribed methadone; and failing to obtain prescribed methadone.

Stenbacka, Leifman & Romelsjo (1998) investigated the impact of methadone treatment on inpatient care admissions and mortality among 331 methadone-maintained patients compared with 1,483 similar untreated opiate misusers. Mortality was lower for methadone patients than for the comparison group and those patients who had left treatment. The annual incidence rate decreased from 1.4 inpatient care admissions per year for those who had stayed 0-1 year, less than 1 for those who stayed more than 2 years, and 0.3 for those who had stayed longer (>4 years) in methadone treatment. A similar decrease occurred in both sexes. The incidence rate decreased more among the HIV-negative than the HIV-positive patients did. The low incidence of inpatient care during treatment may be due to treatment but may also be partly due to selection factors.

Zanis & Woody (1998) examined mortality among 507 patients in a methadone program over a 1-year period. Mortality was determined for

patients in treatment (n = 397), and 12 months later for those discharged (n = 110). Of discharged patients, 8.2% had died, of which six were caused by heroin overdose. Comparatively, only 1% (4/397) of patients died while enrolled in treatment. They recommend that efforts be made to retain these at-risk patients in methadone treatment even though treatment response may be sub-optimal.

Karch & Stephens (2000) conducted a retrospective review of case notes in the records of the San Francisco Medical Examiner's office. They compared the findings in cases where methadone was deemed the cause of death with findings in cases where methadone was an incidental finding, and with 50 age-matched, disease and drug free, trauma victims. In all, methadone was detected in 38 cases out of 3317 during 1997-1998. Cases were mostly male 28/38 (74%) and white, 28/38 (74%). In 17 of 38 cases death was attributed to methadone toxicity. For the group the mean blood methadone concentration for all 38 patients, was 957 ng/ml (SD = .681, SE = .14). The mean blood concentration of the main methadone metabolite (EDDP) was 253 ng/ml, SD = 529 ng/ml, SE = .089. The mean ratio of methadone in the blood to EDDP in the blood was 13.6:1. Values were not significantly different between cases in which methadone toxicity was the cause of death and in those in which it was an incidental finding. Cocaine, or the cocaine metabolite benzoylecgonine, was detected in the blood or urine of 16/38 cases (42%); morphine in one-third (13/38) and methamphetamine in only one. Pulmonary edema was evident in all cases, coronary artery disease in 9/38 (24%) and cirrhosis in 7/38 (18%) of the methadone users. Necrotising fasciitis was the cause of death in 4 of the 38 methadone users (11%). Nationally, a sizeable percent of methadone deaths are from drugs diverted from treatment programs. The presence of methadone is often an incidental finding during postmortem examination and is unrelated to the cause of death. They concluded that postmortem measurements of methadone or its metabolite, or both, cannot be used in isolation to identify which deaths are associated with methadone toxicity.

Milroy & Forrest (2000) examined deaths in which methadone was mentioned in the cause of death. Deaths were divided into those associated with methadone only and deaths in which the cause of death was a combination of methadone and other drugs. One hundred and eleven cases were analysed and compared with previously published data. In 55 cases, methadone poisoning was given as the sole cause of death. Fifty victims were adults, age range 17-51 years (median, 23), with five victims under 14 years of age. The mean methadone concentration in the adult deaths was 584 micrograms/litre (median, 435; range, 84-2700). In 56 cases, age range 15-49 years, (median, 28), death was ascribed to a combination of methadone and other drugs. The mean methadone concentration in these deaths was 576 micrograms/litre (median, 294; range, 49-2440). In 26 cases, multiple site sampling was performed. This revealed that there could be a 100% discrepancy between methadone concentrations, and other drugs, in samples collected in different sites in the same body. There is an overlap between quoted therapeutic methadone concentrations and methadone concentrations seen in fatalities, however, those dying from methadone poisoning might not be

the same as those enrolled in a methadone program. Caution must be exercised in determining a fatal concentration because of the phenomenon of postmortem redistribution. A similar finding was reported by Benbow, Roberts & Cairns (1997). They discuss a case in which a post-mortem exam detected far higher concentrations of methadone than were found in a blood sample taken 28 hours prior to death. Two hypotheses were offered. First that the liver may have stored and then released the methadone unchanged - perhaps stimulated by improvements brought on by intensive care. Second, that blood methadone concentrations may vary by a factor of three at necropsy without systematic relations.

Blaney & Craig (1999) reported no significant differences on any outcome variable (illicit drug use, treatment retention, missed medication days, and ratings of patient progress by assigned counsellor) among 265 patients in a Department of Veterans Affairs Methadone Maintenance Treatment Program. They did find a significant effect by assigned therapist, independent of dose. Both studies concluded that individual and interpersonal aspects of methadone maintenance treatment may be as important as dose in determining the effectiveness of methadone maintenance.

#### Mortality in HIV-infected and intravenous drug users

Fugelstad, et al. (1995) reviewed the cause of death in all diagnosed HIV-positive IDUs in the Stockholm area, 1986-90, and then estimated the relative risk of death of those who received methadone treatment with that of those never admitted to or discharged from the program. In Sweden 90% of all IDUs are HIV-tested and most deceased IDUs receive a forensic exam - including HIV testing. During the five-year observation period, 472 HIV-infected IDUs were reported from the Stockholm area. Of these, 135 participated in the methadone maintenance treatment program (MMTP) for a shorter or longer time during the study period. Most had received the HIV-diagnosis more than 1 year before entering the program. Sixty-nine subjects died during the observation period, 52 (75%) from violence or poisoning, 17 (25%) from somatic complications of drug abuse. Nine had an AIDS diagnosis. Eight of the deceased had participated in the MMTP. The relative risk of death from external violence and poisoning was 0.25 (95% confidence interval 0.1-1.0) for HIV-infected IDU participants in the MMTP compared to HIV-infected IDUs never attending the program. When all causes of death were compared, the relative risk was 0.8. Patients discharged from the MMTP had a higher mortality rate than those who never participated. In an earlier study, Fugelstad, Annell, Rajs & Agren (1997) reported on a cohort of 1640 hospitalised drug addicts reviewed over an 8-year period. The cohort consisted of 678 heroin users, 578 amphetamine users and 384 users of other drugs. In total, 234 addicts were HIV-positive, most of them heroin users. During the observation period, 214 deaths occurred in the cohort. The total mortality was 2.2% annually. Death linked to injection of heroin was the main cause of death not only among heroin users but also among subjects classified as users of amphetamines or other drugs. During the observation period, a total of 222 addicts (115 of whom were HIV-positive) entered methadone treatment. No deaths occurred among the HIV-negative subjects who

were participating in methadone treatment. A total of 15 HIV-positive subjects died while taking part in the program - 13 of these subjects from natural causes (mostly HIV/AIDS). One additional study by Fugelstad, Agren & Romelsjo (1998) analysed the mortality, hospitalisations, and arrests in a cohort of severe intravenous heroin users divided into three groups: those in methadone treatment, those discharged from treatment, and those who never received treatment. The study population consisted of 101 heroin users, of whom 56 were HIV-seropositive. Mortality was lower in the methadone group, and all seven deaths were related to HIV-infection. Outside the program, 24 of 29 persons died from external violence and poisoning.

In Amsterdam, Van Ameijden, Langendam & Coutinho (1999) used a prospective cohort study (1989-1995) to evaluate the effectiveness of low-threshold methadone maintenance in reducing overdose mortality. 498 IDU provided 1,969 person years of follow-up. Forty-four IDU died in this period, 15 due to illicit drug overdose. Compared to IDU not in maintenance, the adjusted relative risk for overdose mortality among those receiving 5-50 mg, 55-70 mg, and 75+ mg were 0.35, 0.13, and 0.11, respectively ( $p < .05$ ). Current injection use and HIV-seropositivity were independent predictors for overdose mortality. The study findings suggest that low-threshold maintenance programs reduced overdose mortality, with higher dosages being most protective. Van Ameijden, Krol, Vlahov, Flynn, van Haastrecht & Coutinho (1999) also conducted an intriguing study comparing mortality and morbidity between injecting drug users in Amsterdam ( $n = 624$ ) and Baltimore ( $n = 2,185$ ) in order to generate a hypothesis about the role of different health care systems and drug user policies (universal care and harm reduction versus episodic care and criminalisation, respectively). Surprisingly, overdose/suicide mortality was twofold higher in Amsterdam. Other independent "risk factors" for overdose/suicide mortality were recent injecting, polydrug use, and HIV-seropositivity. High dose methadone maintenance was associated with lower mortality. Incidence of hospitalisations and emergency room visits was substantially lower in Amsterdam, suggesting that greater access to primary care in Amsterdam lowers (inpatient) hospital visits and presumably societal costs.

### Teenage mortality

Oyefeso et al. (1999) examined illicit drug use and associated fatalities in successive cohorts of addicts in England and Wales aged 15-19 years, followed up over a 20-year period covering 1974 to 1993. The investigators report on: (1) trends in all-causes mortality; (2) teenage-specific mortality (deaths during ages 15-19 years); (3) excess teenage-specific mortality; and (4) the main underlying causes of teenage-specific death in this population. Overall mortality rate in the study population ( $N = 9491$ ) was 4.7/1000 person-years. The median age at death was 23 years (semi interquartile range = 3), with the majority (91.3%) of deaths occurring between ages 15 and 29 years. Excess teenage-specific mortality in the population was 10.7 in males and 21.2 in females (general population = 1), and increase in excess mortality in both sexes was evident in the last 5-year period of study. The majority of deaths (64.3%)

resulted from accidental poisoning. Methadone and heroin/morphine accounted for about two-thirds of accidental poisoning deaths, while suicide accounted for 11.4% of teenage-specific deaths. They recommend that treatment services be more responsive to the need for careful prescribing, dispensing and administration of substitute medication to teenage addicts in their care. In a relevant study, Hall et al. (2000) compared data on rates of opiate overdose mortality in the UK and Australia between 1985 and 1995. The proportion of all deaths attributed to opioid overdose increased in both countries between 1985 and 1995. The proportion of all deaths attributed to opioid overdose was substantially higher in Australia than in the UK, but methadone appeared to contribute to more opioid overdose deaths in the UK (50%) than in Australia (18%). A plausible hypothesis is that the greater availability and ease of access to methadone maintenance in the UK contributes to both the lower rate of opioid overdose mortality and the greater apparent contribution that methadone makes to opioid overdose deaths in the UK.

#### **5.4 Prognostic factors to treatment effectiveness**

The success of treatment has been estimated to be predictable as early as the second week of treatment. Morral et al. (1999a) studied a group of 59 patients who had been addicted to heroin for an average of 15.9 years. The patients were on methadone maintenance treatment for their first time and received either standard methadone maintenance or methadone maintenance with a token economy intervention. However, the authors soon distinguished only between successful and non-successful patients. Successful were those who remained in treatment until the end of the study and if less than 4 out of 8 urine tests revealed illicit drug use. They found out that those patients who submitted drug-free urine samples and attended all counselling sessions in the first two weeks of treatment were successful, while all others were not. They used significantly fewer illicit drugs such as heroin and cocaine. The patients who were not successful were consistently using opiates and/or cocaine. The authors discuss the way these findings can be interpreted. Either patients who are compliant early in treatment are very motivated, therefore having a bigger chance of persisting the treatment, or the counselling sessions stimulate them to continue the treatment (Morral A.R. 1999a). This conclusion seems to be supported by another study, that found that methadone maintenance patients with an abstinence goal performed better in treatment, while those who continue to use marijuana run a greater risk of relapse to heroin use. The authors hypothesise that this is the case because patients who keep on using other illicit drugs have more difficulty quitting heroin (The college of physicians and surgeons in Ontario 1996).

Although Morral et al. state that patient characteristics do not reliably predict treatment outcomes across different studies, Staedt (Staedt J. 1996) did find an effect of gender on retention in treatment and rates of opioid- and cocaine-positive urine tests. In a study with 116 patients (80 male, 36 female), female patients had significantly higher rates of abstinence from illicit opioids and had lower rates of positive opioid toxicology tests. Furthermore, the women remained in treatment longer. Readers should note, however, that the number of women in this study



was low. Heinbach found that pre-treatment demographic variables do not predict outcome, except for one: in his study, patients who were single used less illicit drugs than married respondents did (Heinbach 1997). Persons with depressive symptoms often stay in treatment for a longer time (Broome 1999b).

## **5.5 Dose administration**

Methadone can be administered in a solid form - a pill - and in a liquid form, normally potable, but in some instances injectable. The possible disadvantage of the liquid form is that people start injecting it because they want to use the needle. This impedes the harm reduction goal of potable methadone (Servais 1999). It was found that some addicts are 'dependent' on the use of the needle and consider this a reason not to enter methadone treatment. Therefore, Metrebian (1998b) offered heroin addicts the choice between injectable heroin and injectable methadone, that way lowering the threshold for study entrance. 64% of the patients chose injectable heroin and 36% chose injectable methadone. Both groups showed significant reductions in illicit drug use, illicit drug-injecting risk behaviour and criminal activity, and significant improvements in social functioning, health status and psychological adjustment. Felder, Uehlinger and Eap (1999) examined 15 patients participating in an injectable methadone trial and 15 patients enrolled in oral methadone maintenance treatment, who admitted injecting part or all of their methadone take-home doses. Both groups were compared to 20 patients in maintenance treatment who use methadone exclusively by mouth. They reported that methadone injecting was associated with poorer general health, higher levels of emotional, psychological or psychiatric problems, greater use of illicit drugs, and more problems related to employment and support. They also reported higher plasma concentrations of l-methadone in the injection group as the oral route is subject to bio-inefficiencies associated with gut absorption and first pass effects. These results need to be considered with some caution, because only a small number of patients participated.

### Moment of methadone administration

The time of day of methadone administration can be of great importance to the success of methadone treatment. Early administration is more effective in keeping patients from using heroin, because the peak effect of the methadone will then occur on the moment of the day that patients would crave most for heroin. Patients who take their methadone in the late afternoon or evening are protected during the night — when they sleep anyway — while the effect of methadone will have ended by the morning. On the other hand, one could also argue that patients that take their methadone dose later in the day deliberately delay their intake until after they have taken heroin (Best D 1997).

Many methadone maintenance clinics are open seven days per week to enable daily administration of methadone, but a study in Israel revealed that the closure of a clinic one day a week does not affect treatment outcomes. Therefore, the authors state that it would be good if clinics cut their opening hours; it reduces the workload for the personnel and enables

the clinic to function more economically (The national addiction centre 1995).

## **5.6 Treatment modalities**

For some patients, outpatient care is appropriate, while others run the risk of relapse to heroin use if they do not stay in an inpatient facility. The Drug Abuse Treatment Outcome Study (DATOS) retrospectively compared patients in four treatment settings:

- 1) outpatient drug-free programme;
- 2) outpatient methadone maintenance;
- 3) short-term inpatient programme;
- 4) long-term residential programme.

Preselection played a big role; patients that used less drugs, went to the outpatient programme, while patients with a serious dependence went to the inpatient and opiate maintenance facilities.

Patients in the residential programme reduced their heroin use by 72%, those in the methadone maintenance programme by 73%, compared to 50% and 55% in the drug-free programme and the short-term inpatient programme, respectively. Overall, the methadone patients still showed the least improvement on heroin and cocaine use. These outcomes confirm the preselection mentioned above: the most difficult patients entered methadone maintenance. When considering only heroin use, the drug-free programme performed worst. This programme appeared to be less able to treat the patients who were severely dependent (Hser Y.I. 1998).

In Amsterdam (Van Ameijden 1999), a three-layer system divides addicts into different treatment groups:

- 1) Low-threshold treatment is open to any drug addict. Three methadone dispensing centres and one mobile methadone dispensing bus dispense methadone for free every day, without any regulations. Continued illicit drug use is thus tolerated.
- 2) In the medium-threshold treatment, general practitioners and psychiatrists administer methadone to their own patients, with individual treatment arrangements.
- 3) In the high-threshold addiction clinic, addicts receive free methadone, but they have to submit urine samples regularly, their illicit drug use is a 'point of attention' and they have to be motivated to improve their condition. Only 5% of the Amsterdam heroin addicts attend this treatment.

If a patient is better able to regulate his behaviour, he moves up to a higher-threshold programme; if he relapses, he moves down. The authors consider this treatment with ambiguity: "on the one hand there is an attempt to keep in touch with the addicts to prevent their degradation, and on the other there is the risk of unnecessary dependency on methadone." As treatment retention is also a predictive factor of success in the sense that addicts use less illicit drugs, this implies that those addicts who remain in treatment longer and that way improve their lives might become addicted to methadone. Although the authors do not provide data to support this hypothesis, they did find that low-threshold patients had a

significantly higher risk of leaving the programme within two years: 67% compared to 55% in the high-threshold group. This effect could, however, both be attributed to the low threshold as well as to the fact that patients in the high-threshold programme are very motivated, thus pre-selecting the successful ones from the ones that are bound to fail.

Patients in a community-based methadone programme considered this an acceptable way of methadone service delivery and a good alternative to clinic-based treatment. Patients in the community-based programme used significantly less heroin than before their entrance in the programme (Ezard 1999). Treatment in a therapeutic community was also found to be more effective than standard methadone maintenance treatment (Strain et al 1996b).

According to Desmond et al. (1996a) compulsory supervision of adherence to methadone maintenance is not an effective way to treat drug dependence. In their study, 296 methadone patients who were under compulsory supervision because they were on probation or parole stayed in treatment for a shorter period of time, showed less productive activity and higher rates of incarceration than a group of methadone patients who did not experience such compulsory supervision. In the discussion of the results, the authors state that the differences between the groups might come from greater social impairment or antisocial behaviour in the patients in the compulsory treatment group.

The (possible) role of the general practitioner is still unclear. The English guidelines recommend that GP's only prescribe methadone in co-operation with a specialist treatment agency (Marsden 1998). Several studies recommend that GP's only handle stabilised patients, while in-patient or specialised centres treat unstable, difficult patients (van Brussel 1995). In order to facilitate methadone treatment in the general practice for the patient, a methadone dispensing facility — "the methadone machine" — has been installed in Stuttgart. A pharmacy owns this machine, which is placed in the office of a general practitioner, and supplies it with methadone. The machine is connected to a computer in the pharmacy, which contains data about the patients in the practice, their daily dose, and so on. It also registers whether a patient has received his daily dose yet. This gives the doctor flexibility in giving daily doses or giving a patient take-home doses. So far, there are no data on the happiness of doctors and patients with the machine (Ditzel 1999).

In any case, if different doctors and institutions treat the same patient, good co-ordination between the services is essential (Delile 2000).

One particular treatment environment is the prison. Many prisoners have a history of drug use. Although all countries except Sweden have some kind of provision for substitution treatment in prisons, the provisions differ widely among the countries. Some offer substitution treatment only to prisoners who already were in substitution treatment before they entered the prison, while others encourage prisoners to begin treatment when they enter the prison. In many countries, the methadone treatment in prison

aims at detoxification. Psychosocial care along with substitution treatment is hardly ever institutionalised (EMCDDA 2000).

## **5.7 Conclusion**

The past five years have shown a lot of activity in research concerning treatment outcomes. The knowledge about the effectiveness of methadone maintenance has increased. Several studies confirmed the effectiveness of methadone as an effective treatment for opiate users and some studies even generate some knowledge about prognostic factors to treatment effectiveness. This needs to be considered with caution, though, because predictors of treatment success are often idiosyncratic. The only factor that has some scientific basis as a predictor is early treatment success. Not surprisingly, success and adherence early in treatment continue to be strongly associated with outcome. Many treatment outcome studies focus on dose and dose administration. Several random assignment and naturalistic studies strongly support the use of higher rather than lower methadone doses, with one study pointing out the need to consider regional variations in heroin availability and purity. The appropriate starting dose and maximum allowable dose are still subject of research and discussion. Several studies noted the equal importance of quality counselling and use of contingent positive incentives to promote abstinence. Weak support is provided for the use of an injectable form of methadone, but numerous reasons for caution are also brought forward.

Research concerning overdose and mortality associated with methadone treatment has also shown significant advances. The literature in this area was surprisingly rich and of generally improved quality when compared to earlier studies of mortality associated with methadone or other opiates. In general, the studies indicate that the probability of overdose death is one-fourth as likely while enrolled in methadone treatment, with highest risk for overdose while on methadone occurring during the first several weeks of treatment. Several studies provide caution regarding overly liberal dispensing policies that make large quantities of unsecured methadone available for inappropriate or accidental ingestion.

The current literature concerning treatment modalities reflects expansion of methadone dispensing to settings outside the traditional clinic setting. This includes discussions of methadone utilisation in general practitioner offices, therapeutic communities, pharmacies, and prisons.



## 6 Special populations

Although every person is different, some groups of particular patients can be distinguished. These patients are in a situation that requires extra attention from the treating physician and probably treatment that is tuned to this particular situation. After some short notice on polydrug users and drug users with HIV-infections, the main part of this chapter focuses on pregnancy of heroin addicted women and on their infants.

### 6.1 Polydrug users

Polydrug users form a high-risk group for HIV and criminal activities. Especially cocaine-using heroin addicts are difficult to treat. Their criminal activities and continued cocaine use during methadone maintenance treatment pose an obstacle to effective treatment. Treatment for these persons should target at needle use and sex work in order to decrease the risk of HIV infection (Desmond 1996b). Furthermore, doctors should pay attention to polydrug use, because it might lead to unexpected overdoses. For example, if a drug slows down breathing, just like methadone does, this might lead to a situation in which the patient stops breathing (Lapostolle 1999).

### 6.2 Methadone and HIV-infections

Methadone treatment generally seems to have a large positive effect on the percentage of persons who get HIV-infection. This clearly has to do with reduced risk behaviours, because addicts move away from injectable heroin towards oral methadone (Greenwood 1996;Reisinger 1997). Langendam et al. (1999) found that an increase in frequency of methadone programme attendance and an individual methadone dose increase significantly influence HIV incidence among heroin users (i.e. fewer users become HIV-infected), while the frequency of the visits or the dose in itself did not help decrease the incidence of HIV. The risk of HIV-infection deserves extra attention for female addicts, as they often work as prostitutes in order to earn money for their addiction. Methadone maintenance treatment can be a significant harm reduction policy for them. Withdrawing financial support for methadone maintenance may even lead to harm increase (Grella; Anglin, and Annon 1996;Knight 1996;Rosenbaum M. 1996).

#### HIV Medication Adherence Among Methadone Maintenance Patients

Wall, et al. (1995) randomly assigned 27 HIV-infected methadone maintenance clients demonstrating poor medication adherence to receive either eight weeks of weekday supervised AZT therapy (1<sup>st</sup> dose only) and weekday AZT dispensing of remaining doses (n=14) or to eight weeks of treatment as usual (a monthly AZT prescription) (n=13). Participants in the supervised therapy demonstrated significantly better adherence than treatment as usual during the period of active observation, but not during the weekends, or during the period following the trial. In a later adherence trial, Sorensen, Mascovich, Wall, DePhilippis, Batki, and

Chesney (1998) randomly assigned 12 HIV-infected methadone maintenance clients demonstrating poor medication adherence to receive either eight weeks of weekday supervised AZT therapy (1<sup>st</sup> dose only) and weekday AZT dispensing of remaining doses (n=6) or to eight weeks of the same intervention plus use of a paraprofessional medication manager. This small trial provided some evidence that the addition of medication management to the supervised therapy might prove beneficial as the enhanced group demonstrated better (though not significant) medical clinic attendance in weeks 1-4 (90% vs. 62%), and weeks 5-8 (74% vs. 53%).

A few cross sectional studies describe factors correlated with adherence. Demas et al. (1998) assessed 135 HIV seropositive injection drug users regarding their HIV treatment behaviours, psychosocial adjustment, and HIV-medication specific attitudes and beliefs. They report that the belief that zidovudine (ZDV) is a source of disease control and hope was significantly associated with medication acceptance, adherence, and duration of treatment. Lower adherence was associated with symptomatic disease stage and alcohol/drug coping. Being female and on public assistance was correlated with shorter treatment duration. Stein et al. (2000) examined adherence in 42 HIV seropositive methadone maintenance patients, of which 22 were on dual therapy and 20 were on triple therapy. Individuals on triple therapy reported higher rates of adherence and were more likely to have undetectable levels of HIV RNA. Ongoing illicit drug injection was the only factor significantly associated with multiple measures of non-adherence, but not with HIV RNA levels.

One additional factor that might effect medication adherence among methadone maintenance patients is the occurrence of medication side effects. McCance-Katz et al. (1998) report pharmacokinetic data collected from 8 injection drug users receiving ZDV (before and during methadone treatment. Acute methadone treatment increased oral ZDV in the area under the curve (AUC) by 41% (p=.03) and intravenous ZDV AUC by 19% (p=.06). Clearance was also significantly reduced for both routes. Chronic methadone treatment increased oral ZDV AUC by 29% (p=.15) and intravenous ZDV AUC by 41% (p=.05). Clearance was also significantly reduced for both routes. The study confirmed that methadone maintenance clients receiving standard ZDV therapy experience greater ZDV exposure and may be at greater risk for side effects and toxicity.

### **6.3 Tuberculosis in methadone maintained patients**

The occurrence of tuberculosis (TB) is often associated with HIV-infection. One study found that HIV-positive addicts were at greater risk for tuberculosis than those who were HIV negative (95% confidence interval 1.2-22.7) (Conover et al 2001). Gourevitch et al. (Gourevitch; Wasserman; Panero, and Selwyn 1996) found that tuberculosis therapy has a higher chance of success if done under directly observed antituberculous therapy, despite ongoing drug use of the attending patients.

Other studies about tuberculosis in opioid dependent persons focus on the

interaction of TB medications with methadone. For example, Rifampicin has shown on several occasions to reduce the serum concentration of methadone, as well as rifabutin (Benedetti 1995; Raistrick; Hay, and Wolff 1996; Wada 1998). Wada (1998) advises close supervision of patients on rifampicin and methadone, especially monitoring the liver functions. Often a dose increase for methadone will be necessary.

#### **6.4 Methadone and pregnancy**

For heroin addicts who become pregnant, methadone is the healthiest way of being pregnant for the mother but not always for the child (California Society of Addiction Medicine 1998). Methadone infants have a significantly higher birth weight than children of mothers who do not enter methadone treatment during pregnancy. Women in methadone maintenance treatment live in more stable socio-economic conditions and take better care of their children. Withdrawal symptoms are, however, more intense in methadone babies (Ziegler 2000). Comprehensive psychosocial treatment may help to diminish the problems of mother and child and may alleviate delivery problems (Ladewig 1999).

Fabris, Prandi, Perathoner & Soldi (1998) place this issue in larger perspective. They state that over the past 20 years there has been a steady increase in the number of Neonatal Abstinence Syndrome (NAS) cases observed per year. They state that heroin alone or in association with methadone now represents the drug used by approximately 80% of addicted mothers. The mean age of mothers has increased; the number of drug users who do not appear to be addicts has also increased, and a number of cases have lately been discovered only on the basis of neonatal symptoms, without any previous anamnestic indication. NAS is the most striking effect of fetal exposure to drugs; pharmacological treatment can consist of either sedatives or replacement drugs whose dosage depends on the severity of withdrawal symptoms evaluated using a score system. NAS symptoms are usually resolved within a few days although some signs, especially irritability and tremors, may persist until 3 months of age. They also note that few long-term neurologic or cognitive deficits are directly associated with heroin or methadone use during pregnancy. The main concern at present regards the future of these neonates. The most severe risk to which they are exposed, after HIV infection, is social; during the past few years in over 50% of cases parental authority has been suspended by the juvenile court.

Hulse et al. (Hulse; Milne; English, and Holman 1998) report on a meta-analysis estimating the relationship between neonatal mortality and use of opiates in three groups of women: 1) those using illicit heroin throughout pregnancy; 2) those stabilised on methadone at the time of conception or shortly after; and, 3) those using heroin well into pregnancy with late entry into methadone treatment, or who continued to use illicit heroin during pregnancy while receiving methadone. The pooled estimates of the relative risks of neonatal mortality for separate heroin and methadone use were both near unity: 1.47 (95% CI 0.88-2.33) and 1.75 (95% CI 0.60-4.59), respectively. The result for heroin may be due to the inclusion in the meta-analysis of a particularly large study, which, unlike the two other



smaller studies included found a relative risk near unity. When the larger study was excluded from the meta-analysis the pooled estimate of the relative risk of neonatal mortality for heroin use was 3.27 (95% CI 0.95-9.60). In contrast to the results for use of methadone only, the pooled relative risk associated with heroin and methadone use was 6.37 (95% CI 2.57-14.68). The increased relative risk for neonatal mortality associated with women using heroin and methadone during pregnancy, compared to those stabilised on methadone, was attributed to the chaotic and high-risk life-style associated with illicit heroin use and not to the use of heroin or methadone per se. They recommend that women who use heroin well into pregnancy with late entry into methadone treatment or who continue to use illicit heroin during pregnancy while receiving methadone receive special attention over and above that provided to women stabilised on methadone. In another review of methadone and pregnant women (covering 1988-1998), Wang (1999) found the literature to be unsuitable for meta-analyses and also commented on the lack of formal guidelines. The review confirmed that methadone is the standard of care for the opiate-using pregnant woman, but raised questions regarding its benefits and efficacy in women who continue to use illicit drugs. Wang also emphasised that methadone treatment is most effective for pregnant women who receive care in a comprehensive service centre.

Several studies highlight the problem of illicit substance use by women enrolled in methadone treatment during pregnancy. Brown et al. (1998) evaluated 32 women receiving methadone maintenance during pregnancy, matched by gestational age to women with a positive urine screen for cocaine at delivery and to drug-free controls. Head circumference for methadone infants was significantly less than controls, but not different from infants of cocaine users. Women using cocaine had a significantly higher incidence of meconium in labour compared with methadone and controls. Of the 32 women taking methadone, 84% were positive for other drugs of abuse in the last screen before or at delivery. Cocaine (38%), other opiates (41%), and marijuana (44%) were prevalent. Neonatal withdrawal occurred in 72% of methadone exposed infants. The neonates of women using less than 50 mg of methadone were as likely to withdraw as those women using more, 62% versus 79%, ( $p =$  not significant). Three neonates in the methadone group (9.3%) had major congenital anomalies, with 2 of 3 resulting in mortality. They concluded that birth outcome was not significantly different between methadone and cocaine users, as women receiving methadone maintenance are likely to abuse other drugs. Coghlan et al. (1999) conducted a retrospective maternal and infant record review related to 43 infants admitted with neonatal abstinence syndrome (Finnegan score  $>8$ ) over a 12 month period to a neonatal intensive care unit in Dublin. Of the 37 reporting use of methadone 31 (84%) also reported use of benzodiazepines, heroin, or both. Hospital days averaged 23.5 days per infant, with symptom duration noted to be longer when benzodiazepines were involved. Kelly, Davis & Henschke (2000) conducted an audit of all Chemical Dependency Unit (CDU) mothers and babies delivered at the Royal Women's Hospital, Melbourne, Australia during 1997. Ninety-six infants born to CDU mothers were compared with a control group of 200 infant/mother pairs. The majority of women in the CDU clinic were treated for narcotic addiction

with methadone (90%) but most continued to use heroin during pregnancy (68%). Infants born to CDU mothers were significantly less mature and lighter than control infants. Fifty-three (55%) CDU infants required admission to the Special Care Nursery either because of neonatal abstinence syndrome ( $n = 29$ ) or other medical reasons ( $n = 24$ ). The median length of hospital stay was significantly longer in CDU compared with control infants (8 vs. 3 days). Mayes & Carroll (1996) examined the effect of concomitant cocaine and methadone use on the neonatal withdrawal syndrome in a group of 68 infants born to mothers participating in a methadone maintenance program. Fifty-three (78%) of the mothers in the sample reported regular use of cocaine during their pregnancy and/or had positive urine screens. Infants exposed to both cocaine and methadone had significantly higher first withdrawal scores. However, cocaine exposed infants did not require more medication for withdrawal management either in terms of dosage or of days treated. Additionally, there was no difference in the occurrence of intrauterine growth retardation, prematurity, or early perinatal complications such as respiratory distress.

In a prospective examination of this issue, Bunikowski et al. (1998) examined 34 drug-exposed (opiates and nicotine) and 42 reference infants (nicotine exposure only) from birth to 1 year after delivery. At the time of delivery, 12 of 34 mothers used opiates without medical control. Twenty-two mothers participated in a methadone maintenance programme. At 1 year, the average Griffiths Developmental Quotient (DQ) was significantly lower in the drug-exposed group (mainly due to lower subscales "locomotor" and "intellectual performance"). Severe developmental retardation mean DQ ( $-2$  SD) was diagnosed in 2 drug-exposed infants. Mild developmental retardation was found in 7 drug-exposed and in 3 reference infants. Neurological abnormalities were found more often in the drug-exposed group (11 vs. 3 infants;  $P < 0.01$ ). Among the opiate-exposed infants, the subscales "hearing and speech" and "intellectual performance" were lower in the uncontrolled drug-using than in the methadone group. They summarised that infants prenatally exposed to opiates were at risk for mild psychomotor developmental impairment, although methadone was preferable to "uncontrolled" opiate use. Eyler & Behnke (1999) provide relevant comment regarding methodological limitations of the peer-reviewed studies of developmental outcome during the first 2 years in children prenatally exposed to drugs of abuse. They point out that reported effects vary by specific drug or drug combinations and amount and timing of exposure; however, few thresholds have been established. Drug effects also appear to be exacerbated in children with multiple risks, including poverty, and nonoptimal caregiving environments. Although prenatal exposure to any one drug cannot reliably predict the outcome of an individual child, it may be a marker for an array of variables that can impact development. Appropriate intervention strategies require future research that determines which factors place exposed children at risk and which are protective for optimal development. Further, as pointed out by Vance et al. (1997) many problems such as intrauterine growth retardation, observed in a cohort of infants born to narcotic dependent mothers (INDM), may not be as problematic one year later. Their data

indicated that by 12 months, there had been some catch up growth, and that there was little difference from the rest of the community.

Hagopian et al. (1996) examined the relationship between maternal methadone exposure, neonatal head circumference, and the abstinence syndrome. They examined the records of 172 opiate-addicted pregnant women enrolled in a methadone maintenance program in an urban hospital over a 2-year period. Higher doses of methadone in the third trimester were associated with increased head circumference reflecting both increased gestational duration and improved overall growth. Neonatal withdrawal was positively correlated with gestational age at delivery and race, with nonblack infants exhibiting higher neonatal abstinence scores than blacks following adjustment for maternal dose and gestational age at delivery. Selection of optimal methadone dosage is a complex problem in which the favourable neurobehavioral outcome associated with increased growth and gestational age must be weighed against the risks associated with more severe neonatal withdrawal. Their findings of improved overall foetal growth and gestational duration associated with higher methadone doses suggest that more liberal methadone dosing in pregnancy may improve long-term neonatal outcome. Their findings are also consistent with the suggestion that the high rates of illicit drug use observed in pregnant women receiving methadone might be associated with sub-optimal dosing. Jarvis et al. (1999) add another dimension to this issue. They studied 23 pregnant and 16 non-pregnant opioid-dependent patients to evaluate pregnancy-dependent changes in methadone pharmacokinetics. In the first phase, pregnant patients had a statistically significant higher elimination rate constant ( $k$ ) and lower half-life (19 vs. 30 hours) compared to non-pregnant controls. In the second phase, the apparent clearance ( $Cl/F$ ) was significantly greater during pregnancy, with preliminary data suggesting that this observation results from a decrease in the fraction of dose absorbed ( $F$ ). Increased doses and decreased intervals should both be considered as necessary considerations. DePetrillo & Rice (1995) report data consistent with the recommendations by Jarvis et al., (1999). They retrospectively reviewed compliance and drug toxicology screens for 45 pregnant women enrolled in methadone maintenance. They found that earlier program entry was associated with decreased opiate and cocaine use as well as compliance with urinalysis requests. A comparison of individuals receiving a single daily dose vs. a split-dose revealed differences only in Trimester III with respect to urine toxicology compliance rates, 23.8 vs 0.5%, as well as percentages of urine positive for cocaine, 15.3 vs. 0.3%. The observation that split dosing resulted in significantly fewer opiate positive urine screens might be interpreted as being the result of adequate methadone dosing. It might also be interpreted as being due to increased supervision opportunities or a more compliant population of women.

The call for higher doses must be balanced against observations of Neonatal Abstinence Syndrome correlated with maternal methadone dose. Ziegler et al (2000) found that the abstinence syndrome was much more intense in infants whose mothers had been receiving methadone during their pregnancy than in infants whose mothers used heroin without methadone treatment. Malpas et al. (1999) reviewed the charts of 67

drug-abusing mothers and their 70 infants to determine patterns of drug usage and the severity of neonatal withdrawal. Of these, 40 women were on a methadone programme. There was a strong relationship between maternal methadone dose at delivery and severity of neonatal withdrawal as assessed by the Neonatal Abstinence Score, length of stay and duration of treatment. Children whose mothers received methadone had mean peak symptom scores greater than 10 whereas the group receiving no methadone had mean scores of less than 4 ( $p < 0.001$ ). These effects tended to increase with increasing doses of methadone. Length of stay and duration of neonatal treatment showed significant increases ( $p < 0.001$ ) with increasing methadone dose. Maternal methadone dose appears to be strongly related to the severity of neonatal withdrawal.

#### Additional issues associated with neonatal withdrawal

A few studies reported additional problems associated with neonatal withdrawal from methadone. Martinez, Kastner & Tausch (1999) conducted a retrospective chart review for all infants at San Francisco General between 1992 and 1995, born to women receiving methadone maintenance during their pregnancy. Forty-four infants were identified and the data obtained from hospital medical records. The daily oral intake of these infants was recorded during the first month of life and the incidence of hyperphagia (oral intake  $> 190$  cc/kg/day) was measured. The incidence of hyperphagia was 26% by day 8 and 56% by day 16 of life in the infants, but was not associated with maternal methadone dose or with infant withdrawal scores. Despite significantly greater intake, the hyperphagic infants did not gain weight more rapidly during the first month of life compared with those infants with lower oral intake. Hyperphagia was not associated with either increased neonatal weight gain or with adverse gastrointestinal consequences. Hyperphagia may occur in infants withdrawing from methadone who have high metabolic demands due to clinical signs not controlled by opiate treatment. Robinson (2000) commented that opioid drugs such as methadone or buprenorphine are generally thought of as nonteratogenic and preferable to repeated cycles of withdrawal in utero. However, evidence exists that perinatal exposure to these opioids delays and disrupts cholinergic development, particularly in the striatum. Acetylcholine (ACh) content and the expression of choline acetyltransferase protein and mRNA are reduced in the early postnatal period by prenatal opioid exposure in the rat. Although these indicators of the cholinergic phenotype return to normal levels over time, the activity of the cholinergic neurons remains disrupted, with a large increase in ACh turnover rate. The mechanism of these effects is unknown, but may involve changes in the expression of nerve growth factor, which is reduced by opioid exposure.

One study suggested that for select patients, opioid detoxification may be accomplished safely during pregnancy. Dashe et al. (1998) evaluated the safety of antepartum opioid detoxification in selected pregnant women. Between 1990 and 1996, women with singleton gestations who reported opioid use were offered inpatient detoxification. Predetoxification sonography was performed to confirm gestational age and to exclude fetuses with growth restriction and oligohydramnios. Women with mild

withdrawal symptoms were given clonidine initially, and methadone was substituted if symptoms persisted. Objective signs of withdrawal were treated with methadone from the outset. Antenatal testing was performed once gestations reached 24 weeks. Newborns were observed for signs of neonatal abstinence syndrome and were treated as necessary. Obstetric and neonatal outcome data were collected. In all, thirty-four pregnant women elected to undergo opioid detoxification at a mean gestational age of 24 weeks. The median maximum dose of methadone was 20 mg per day (range 10-85 mg), and the median time to detoxification was 12 days (range 3-39 days). Overall, 20 women (59%) successfully underwent detoxification and did not relapse, ten (29%) resumed antenatal opioid use, and four (12%) did not complete detoxification and opted for methadone maintenance. There was no evidence of foetal distress during detoxification, no foetal death, and no delivery before 36 weeks. Fifteen percent of neonates were treated for narcotic withdrawal.

#### Methadone and breast feeding

Wojnar-Horton et al. (1997) quantified the distribution and excretion of methadone in human milk during the early postnatal period and investigated exposure of breast fed infants to the drug. Blood and milk samples were obtained from 12 breast-feeding women who were taking methadone in daily doses ranging from 20-80 mg (0.3-1.14 mg per kg of bodyweight). Blood was also obtained from eight of their infants, methadone concentration in these samples was quantified by high performance liquid chromatography (h.p.l.c), and the infants were observed for withdrawal symptoms. The mean (95% CI) milk/plasma ratio was 0.44 (0.24-0.64). Exposure of the infants, calculated assuming an average milk intake of 0.15 l per kg of bodyweight per day and a bioavailability of 100% was 17.4 (10.8-24) microg/kg/day. The mean infant dose expressed as a percentage of the maternal dose was 2.79 (2.07-3.51)%. Methadone concentrations in seven infants were below the limit of detection for the h.p.l.c. assay procedure, while one infant had a plasma methadone concentration of 6.5 microg/liter. Infant exposure to methadone via human milk was insufficient to prevent the development of a neonatal abstinence syndrome, which was seen in seven (64%) infants. No adverse effects attributable to methadone in milk were seen. They concluded that exposure of breast fed infants to methadone taken by their mothers is minimal and that women in methadone maintenance programs should not be discouraged from breast feeding because of this exposure. In a related paper, Geraghty, Graham, Logan & Weiss (1997) reported 2 cases of breastfeeding mothers on high doses of methadone and they include a literature review that supports the suggestion that minimal transmission of methadone into breast milk occurs regardless of the mother's methadone dose. They conclude that the current American Academy of Pediatrics recommendations that only women in drug treatment programs on less than 20 mg/day of methadone be advised to breastfeed should be reconsidered.

One cautionary paper by Malpas & Darlow (1999) reported on two infants who appeared to develop neonatal abstinence syndrome, after abrupt discontinuation of breast-feeding by women receiving 70 mg and 130 mg

of methadone. They recommended that women on high doses of methadone should be counselled to wean breast-feeding gradually.

#### Interventions to improve methadone treatment for pregnant women

Luthar & Suchman (2000) presented preliminary evidence on the efficacy of a Relational Psychotherapy Mothers' Group (RPMG), a developmentally informed, supportive psychotherapy designed to serve heroin-addicted mothers with children up to 16 years of age, aims at addressing psychosocial vulnerabilities, and facilitating optimal parenting, among at-risk mothers. RPMG was used as an "add on" treatment in comparison with standard methadone counselling alone. At the end of the 24-week treatment period, mothers receiving RPMG plus standard methadone counselling demonstrated lower levels of risk for child maltreatment, greater involvement with their children, and more positive psychosocial adjustment than women who received methadone counselling alone. Children of RPMG participants also reflected fewer problems in multiple areas. At 6 months post-treatment, RPMG recipients continued to be at a relative advantage, although the magnitude of group differences was often attenuated. Notably, urinalyses indicated that RPMG mothers showed greater improvements in levels of opioid use over time than comparison mothers.

Svikis, Lee, Haug & Stitzer (1997) reported on the effectiveness of behavioural incentives for improving treatment participation and retention in samples of methadone-maintained ( $n = 66$ ) and non-methadone-maintained ( $n = 76$ ) pregnant drug dependent women. Subjects were randomly assigned to receive \$0 (standard care) and \$1, \$5, or \$10/day for attending at least 4 h of interdisciplinary treatment programming during the first 7 consecutive days after transfer from residential to outpatient care, with payment dispensed in the form of gift certificates. Methadone-maintained women attended nearly twice as many full treatment days as those not receiving methadone (5.2 vs. 2.8 days;  $p < 0.001$ ) and were retained in treatment significantly longer (86.4 vs. 28.9% active in treatment at 30 days). There was no main effect of incentives and no effect on attendance in methadone patients. However, non-methadone patients offered higher magnitude incentives (\$5/\$10) attended 3.3 days out of 7 on average, compared to 2.3 days for those offered \$0 or \$1 per day ( $t = 1.73$ ;  $p < 0.05$ ). The study confirmed that methadone maintenance is a powerful therapeutic adjunct that is associated with significantly better treatment retention and participation in ancillary programming than is abstinence-based treatment. It was also found that modest financial incentives facilitate treatment participation for abstinence-based patients. However, more potent interventions would be needed to match the effectiveness of methadone in this regard. In a related study, Jones, Haug, Stitzer & Svikis (2000) utilised an identical design as above, but this time incentive subjects could earn only US\$5/day in vouchers during the first 7 days of an intensive outpatient treatment. US\$5/day did not significantly improve attendance in abstinence-treated patients or impact drug abstinence in methadone-treated patients. They suggested that although US\$5/day had some utility in improving

attendance in methadone-treated patients, more potent interventions are needed to improve attendance and maintain abstinence in this population.

## **6.5 Conclusion**

The extensive literature on this subject points out the importance of providing a sufficient methadone dose to pregnant women so as to reduce illicit drug supplementation. The trade-off with higher dose is an increased risk of neonatal abstinence syndrome, with net benefit favouring use of an adequate maintenance dose. Two studies provide additional rationale for an increased dose of methadone, as increased elimination and decreased absorption decrease methadone levels in pregnant women. Several studies have focused on breast feeding by methadone receiving mothers. These studies noted the possibility of NAS resulting from ingestion of breast milk from mothers on high methadone doses. Two studies support the use of incentives and psychosocial interventions for decreasing illicit substance use in pregnant women enrolled in methadone treatment.

Tuberculosis and HIV seem to occur less in patients on methadone maintenance, but problems occur when people do have one of those diseases. In both cases, adherence to therapy for the disease and for the opiate addiction runs at risk. Furthermore, the interaction of drugs for treatment of HIV and tuberculosis with methadone might lead to opiate withdrawal symptoms, for which a methadone dose increase would be the appropriate answer.

## **7 Studies describing psychosocial and other non-pharmacological aspects of treatment**

One of the greatest challenges facing methadone treatment providers today is the use of illicit and off-prescription drugs during treatment. In the US, numerous studies report the use of treatment vouchers, redeemable for goods or services, as reinforcement for desired behaviours such as group attendance, demonstrating abstinence (submitting a urine testing negative for drug use), or for completing a specified treatment-related task. Other studies focus on other psychosocial treatment and motivational interventions.

### **7.1 Using incentives to promote behaviour change**

#### Treatment Vouchers

Iguchi et al. (1997) examined the effectiveness of using low value vouchers to reinforce either the provision of urine samples testing negative for illicit drugs (UA group) or the completion of objective, individually defined, treatment-plan-related tasks (TP group). A third group was assigned to the clinic's standard treatment (STD group). Participants were randomly assigned to groups after a 6-week baseline-stabilisation period. Urine specimens were collected thrice weekly throughout the study. In the UA condition, participants earned US\$5 in vouchers for each drug-free urine submitted. In the TP condition, participants earned up to US\$15 in vouchers per week for demonstrating completion of treatment plan tasks that were identified and objectively defined by participants in collaboration with their counsellors. Contingencies were in effect for 12 weeks, after which all participants received the clinic's standard treatment. Urinalysis results indicate that the TP intervention was significantly more effective in reducing illicit drug use than either the UA or STD interventions. These effects were maintained with a trend toward continuing improvement for the TP groups even after contingencies were discontinued. The authors hypothesised that reinforcement of appropriate treatment-plan related behaviours resulted in the development of environmentally supported behaviour chains that were incompatible with substance use.

Silverman, Chutuape, Bigelow & Stitzer (1996) evaluated the use of voucher reinforcement for maintaining attendance of seven chronically unemployed methadone patients in a work skills development program involving multiple 2-hour data entry training sessions. The vouchers were exchangeable for goods and services. During the first 6-week condition, daily vouchers were initially worth \$8, increased by \$0.90 for every consecutive day of attendance to a maximum of \$34.10, and reset to \$8 following any day of missed attendance. During the second 6-week condition, voucher values decreased each day by 20% of that individual's earnings on the previous day. During a final 4-week condition, the highest pay level previously achieved by each individual was reinstated and stayed at that level for the remainder of the condition, except that voucher values reset back to \$8 following any missed session. Five of 7 participants completed the study. For those 5 participants, 94% and 98% attendance



rates were sustained during first and second high pay conditions, respectively. All participants acquired data entry skills and reliably rated the work experience as 'interesting', 'enjoyable', 'challenging', and 'helpful'. The authors state that their data show that voucher-based reinforcement can promote sustained attendance of chronically unemployed substance abusers in intensive employment training programs and support the continued evaluation of these incentive procedures under a wider range of work-site training conditions.

In another study, Silverman, Higgins et al. (1996) randomly assigned 37 methadone patients demonstrating heavy cocaine use during a baseline period to either a condition receiving voucher-based reinforcement of cocaine abstinence or to a group receiving non-contingent voucher presentations. Patients exposed to abstinence reinforcement received a voucher for each cocaine-free urine sample provided three times per week throughout a 12-week period; the vouchers had monetary values that increased as the number of consecutive cocaine-free urine samples increased. Control patients received non-contingent vouchers that were matched in pattern and amount to the vouchers received by patients in the abstinence reinforcement group. Patients receiving vouchers for cocaine-free urine samples achieved significantly more weeks of cocaine abstinence and significantly longer durations of sustained cocaine abstinence than controls. Nine patients (47%) receiving vouchers for cocaine-free urine samples achieved between 7 and 12 weeks of sustained cocaine abstinence; only one control patient (6%) achieved more than 2 weeks of sustained abstinence. Among patients receiving vouchers for cocaine-free urine samples, those who achieved sustained abstinence ( $>$  or  $=$  5 weeks) had significantly lower concentrations of benzoylecgonine in baseline urine samples than those who did not achieve sustained abstinence. Patients receiving voucher reinforcement also rated the overall treatment quality significantly higher than controls. In a related study, Silverman, Wong et al. (1996) used a within-subject reversal design to assess the effectiveness of voucher-based abstinence reinforcement in reducing opiate use in patients receiving methadone maintenance treatment in an inner-city program. Throughout the study subjects received standard methadone maintenance treatment involving methadone, counselling, and urine monitoring (three times per week). Thirteen patients who continued to use opiates regularly during a 5-week baseline period were exposed to a 12-week program in which they received a voucher for each opiate-free urine sample provided: the vouchers had monetary values that increased as the number of consecutive opiate-free urines increased. Subjects continued receiving standard methadone maintenance for 8 weeks after discontinuation of the voucher program (return-to-baseline). The percentage of urine specimens that were positive for opiates decreased significantly when the voucher programme was instituted and then increased significantly when the voucher programme was discontinued during the return-to-baseline condition, although rates of opiate positive urines in the return-to-baseline condition remained significantly below the rates observed in the initial baseline period. As previously cited, Preston, Umbricht & Epstein (2000) evaluated a behavioural intervention, a pharmacological intervention, and a combination of both interventions. Contingent vouchers, with or without a methadone dose increase,

increased the duration of sustained abstinence as assessed by urine screenings. Methadone dose increase, with or without contingent vouchers, reduced self-reported frequency of use and self-reported craving. The authors concluded that abstinence reinforcement and a methadone dose increase were each effective in reducing opiate drug use. When combined, they did not dramatically enhance each other's effects on any single outcome measure.

Recognising that voucher-based reinforcement approaches often work for many but not all patients, Silverman, Chutuape, Bigelow & Stitzer (1999) designed a study to determine if they could promote cocaine abstinence in a population of treatment-resistant cocaine abusing methadone patients by simply increasing the magnitude of voucher-based abstinence reinforcement. Participants were 29 methadone patients who previously failed to achieve sustained cocaine abstinence when exposed to an intervention in which they could earn up to \$1155 in vouchers (exchangeable for goods/services) for providing cocaine-free urines. Each patient was exposed in counterbalanced order to three 9-week voucher conditions that varied in magnitude of voucher reinforcement. Patients were exposed to a zero, low and high magnitude condition in which they could earn up to \$0, \$382, or \$3480 in vouchers for providing cocaine-free urines. Analyses for 22 patients exposed to all three conditions showed that increasing voucher magnitude significantly increased patients' longest duration of sustained cocaine abstinence and percent of cocaine-free urines, and significantly decreased patients' reports of cocaine injections. Almost half (45%) of the patients in the high magnitude condition achieved four or more weeks of sustained cocaine abstinence, whereas only one patient in the low and none in the zero magnitude condition achieved more than 2 weeks. Reinforcement magnitude was a critical determinant of the effectiveness of this abstinence reinforcement intervention.

In acknowledgement of the need to identify non-monetary reinforcers that might be applied in a voucher reinforcement program, Chutuape, Silverman & Stitzer (1998b) used three different survey techniques to assess relative patient preference for a variety of incentives available within a methadone treatment setting. Methadone patients (n = 111) rated preference for three service incentives (take-home medication, dose increase, additional counselling sessions) using three different survey techniques (rank order, visual analogue scales, and multiple choice). Mean and individual responses were highly consistent across surveys and indicated that, in general, take-homes were the most preferred, followed by dose increases and then counselling. The rank order survey also assessed an additional 18 service items (e.g., rent, food or gas payments; employment assistance; medical care). Consistent with other measures, most patients (64%) placed take-homes within their top five rankings, indicating a high level of preference, but this survey also revealed wide individual differences in preference ranking. The authors state that the surveys can be used to identify preferred incentives for clinic-wide use in contingency management programs or they can be used to select individualised incentives for each patient, potentially maximising utilisation of clinic resources.

Jones, et al. (2000) examined the effectiveness of low-magnitude behavioural incentives in improving attendance for abstinence-treated patients and sustaining illicit-drug abstinence for methadone-treated patients. Subjects were randomly assigned to either incentive or control conditions, with target behaviours differing for the two patient groups (attendance for abstinence-treated and abstinence for methadone-treated patients). Controls received no incentives, whereas incentive subjects could earn \$5/day in vouchers during the first 7 days of an intensive outpatient treatment. Results showed that \$5/day did not significantly improve attendance in abstinence-treated patients or impact drug abstinence in methadone-treated patients. The data suggest that low-magnitude voucher incentives enhanced treatment attendance by methadone-treated subjects. Although modest monetary incentives had some utility in improving attendance in methadone-treated patients, more potent interventions are needed to improve attendance and maintain abstinence in this high-risk population.

In another interesting demonstration of voucher utility, Robles et al. (2000) assessed the effectiveness of a brief abstinence reinforcement procedure for initiating cocaine abstinence in methadone maintenance patients. On Monday of the test week, 72 cocaine-abusing methadone patients were offered a \$100 voucher if urine samples collected on Wednesday indicated that they had abstained from cocaine across that 2-day period. A patient was considered abstinent and the voucher delivered if the urine benzoyllecgonine concentration decreased by 50% from Monday to Wednesday (quantitative criterion) or if the concentration of Wednesday's urine sample was  $\leq$  300 ng/ml. Overall, 79% of study patients showed urinalysis evidence of abstinence from cocaine between Monday and Wednesday of the test week. In a subsample with complete data ( $n = 50$ ), significantly more patients abstained from cocaine from Monday to Wednesday of the test week (84%) than from Monday to Wednesday of the week before (36%) or after (32%) the test week. Furthermore, while almost all patients (94%) decreased their benzoyllecgonine concentration from Monday to Wednesday of the test week, significantly fewer patients' benzoyllecgonine concentrations decreased from Monday to Wednesday of the week before (56%) or after (48%) the test week. This highly efficacious procedure may have clinical application where reliable abstinence initiation is desired, either on a temporary basis (e.g. sobriety sampling) or at the start of longer-term interventions. It may also be possible to use the brief abstinence test as an experimental model to assess the effects of other therapeutic interventions on abstinence initiation in treatment settings.

### Take-home incentives

Take-home incentives can serve two objectives:

- lower the threshold for entry into and retention in treatment for persons who do not want their methadone maintenance treatment to interfere with their job;
- reinforcement measure: motivation and stimulation for patients that do well (Soyka 1997).

Several studies show that take-home contingencies reinforce abstention from illicit opiates and can help improve treatment outcomes (Chutuape MA; Silverman K, and Stitzer ML 1999) (Chutuape MA; Silverman K, and Stitzer ML 1998a). Whether the conditions for receiving such take-home incentives should be strict or not, is not clear (Chutuape; Silverman, and Stitzer 1999). In several countries, patients can get take-home doses if they comply well with the treatment objectives, while these take-home privileges get withdrawn if the patient fails to comply to the rules (California Society of Addiction Medicine 1998; EMCDDA 2000).

One study reported the use of take-home medications rather than vouchers as reinforcement for desired behaviours. Iguchi, Lamb et al. (1996) compared the effectiveness of 2 types of contingency management interventions on reducing unauthorised substance use among methadone maintenance patients. Take-home medications were used to reinforce either the provision of drug-free urines (UA) or attendance of groups providing training in interpersonal problem solving (TIPS). Newly enrolled patients were randomly assigned to either the TIPS (n=34) or the UA (n=32) condition after a 12-week stabilisation period. During the course of the 24-week intervention period, UA participants showed greater improvement than TIPS participants in rates of abstinence from unauthorised drugs. Further, a significantly greater proportion of UA participants met a priori criteria for clinical improvement, whereas a significantly greater proportion of TIPS participants met a priori criteria for clinical deterioration. Schmitz et al. (1998) also used take-home medication doses as reinforcement for the delivery of opiate-free urines. They hypothesised, that allowing participants to sample the take-home reinforcement condition on a non-contingent basis would increase the likelihood that they would respond for take-home medications under contingent conditions. They tested this by randomly assigning methadone maintenance patients to one of two 8-week baseline take-home (TH) conditions differing in frequency of clinic visits per week (2/week versus 5/week). This was followed by a 12-week contingency management (CM) procedure in which frequent THs were contingent upon the delivery of drug-free urines. Participants receiving more frequent THs during baseline had lower illicit drug use during the first 6 weeks of CM.

### Urine tests

Urine tests serve two objectives at a time: controlling whether methadone maintenance patients have used illicit drugs and in that way stimulating them to refrain from the use of illicit opiates. Many trials use positive urinalysis or clinic attendance as measures for compliance (Iguchi M.Y. 1996; Morral A.R. 1999b). Urinalysis only shows the use of illicit opiates in the past hours or days, depending on the drug. Therefore, announced urinalysis gives patients the opportunity to use illicit opiates in the 'safe periods' of the week, seemingly complying to treatment rules. Thus, one would expect that more illicit drug use would be detected if the urinalysis were to be unannounced. This premise was questioned by Baker et al. (1995), who found that preannounced and unannounced urine testing resulted in an equal rate of detection of illicit opiate use. Baker argues that as there is no difference between preannounced and unannounced

testing anyway, preannounced testing is to be preferred, because it gives patients a feeling of control over their treatment. There have not been any other studies to confirm these results, and the authors do not discuss whether rates of use for drugs other than opiates or the possibility that alternative urinalysis regimes might have different impacts on those rates. These subjects need further study before any conclusions can be drawn.

## **7.2 Interventions Involving Families**

Stanton & Shadish (1997) conducted a meta-analytic review of drug abuse outcome studies that included a family-couples therapy treatment condition. The evidence, across 1,571 cases involving an estimated 3,500 patients and family members, favours family therapy over (a) individual counselling or therapy, (b) peer group therapy, and (c) family psychoeducation. Family therapy is as effective for adults as for adolescents and appears to be a cost-effective adjunct to methadone maintenance. Because family therapy frequently had higher treatment retention rates than did non-family therapy modalities, it was modestly penalised in studies that excluded treatment dropouts from their analyses, as family therapy apparently had retained a higher proportion of poorer prognosis cases. Re-analysis, with dropouts regarded as failures, generally offset this artefact.

Catalano et al. (1999) examined whether intensive family-focused interventions with methadone treated parents can reduce parents' drug use and prevent children's initiation of drug use. Parents were assigned randomly into either a 33 session family training intervention followed by 9-months of home-based case management or a control condition that received no supplemental services. Assessments of parents and children occurred at baseline, post-test, and 6 and 12 months following the intervention. In all, one hundred and forty-four methadone-treated parents, and their children ( $n = 178$ ) ranging in age from 3 to 14 years old were enrolled in the study. One year after the family skills training, results indicate significant positive changes among parents, especially in the areas of parent skills, parent drug use, deviant peers and family management. Few changes were noted in children's behaviour or attitudes.

Related to this, Kidorf, Brooner & King (1997) report on a unique intervention applied to seventy-five chronically drug using patients. Patients were enrolled in high-intensity psychosocial treatment due to chronic drug use, and were given 3 weeks to identify a drug-free 'significant other' that would be willing to participate in their treatment. Patients noncompliant with this intervention were started on a methadone dose taper that was stopped when significant other support was identified. Patients and their significant others were required to attend a significant other group one time per week for a minimum of 6 weeks. Eighty-five percent of the patients brought a drug-free significant other into treatment. Significant others included family members, partners, and friends. Patients who identified significant other support complied with 77% of their scheduled sessions. The results demonstrated that most methadone patients have drug-free support people who are willing to participate in their treatment.

### 7.3 Other Adjunctive Treatments

Saunders et al. (1995) conducted a randomised controlled trial with 122 persons in methadone maintenance treatment, who were randomly assigned to either motivational interviewing or an educational procedure (control group). The subjects in motivational interviewing showed more commitment to abstention from illicit drugs, they expected more positive outcomes from this abstention, they reported fewer opiate-related problems, thought more often of changing their behaviour, had higher retention in the methadone programme and relapsed less quickly than the group of patients that got the educational procedure. However, the opiate dependence in both groups remained the same, and the educational group reported more self-efficacy.

Woody et al. (1995) tested the efficacy of individual psychotherapy in the rehabilitation counselling of psychiatrically symptomatic opiate-dependent patients during methadone maintenance treatment in community programs. Eighty-four subjects were recruited from three community programs and randomly assigned to 24 weeks of counselling plus supplemental drug counselling or to counselling plus supportive-expressive psychotherapy. Patients receiving supportive-expressive psychotherapy and those receiving drug counselling had similar proportions of opiate-positive urine samples, but the patients receiving supportive-expressive psychotherapy had less cocaine-positive urine samples and required lower doses of methadone. One month after the extra therapy ended both groups had made significant gains, but there were no significant differences between groups. By 6-month follow-up many of the gains made by the drug counselling patients had diminished, whereas most of the gains made by the patients who received supportive-expressive psychotherapy remained or were still evident; many significant differences emerged, all favouring supportive-expressive psychotherapy.

Kidorf, Hollander, King & Brooner (1998) also evaluated the impact of a mandatory employment requirement in a community-based methadone treatment program. All unemployed patients who had been in the methadone substitution program for at least 1 year ( $n = 36$ ) were required to enhance their treatment with 20 h of employment (paid or volunteer). Patients with significant psychiatric or medical disabilities were excluded from the routine treatment requirement. Patients were informed by counselling staff that they had 2 months to secure employment. Those who did not accomplish the goal within that time period were transferred to more intensive weekly counselling (i.e. up to 8 h/week) for 10 weeks, with the enhanced counselling focusing primarily on resistance to the employment goal. Patients who remained resistant to the treatment plan were eventually started on a 21-day methadone taper until employment was verified. Seventy-five percent of the patients secured employment and maintained the position for at least one month. Positions were found in an average of 60 days. Most patients (78%) continued working throughout the 6-month follow-up. Those who failed to find work or maintain employment engaged in more illicit drug use. The authors maintain that their results demonstrate that behavioural contingencies can

motivate many methadone maintenance patients to obtain verified employment in the community.

Abbott, Weller, Delaney & Moore (1998) compared a community reinforcement approach (CRA) to standard counselling for opiate-dependent patients on methadone maintenance. The CRA intervention was described as a comprehensive package of behavioural skills/intervention sessions, intended to reinforce abstinence. Initial sessions involved a functional analysis of drug use and the identification of environmental cues that trigger drug use as well as the availability of reinforcement available in the person's environment. Participants were trained to avoid drug cues while building a social environment that would reinforce abstinence. Reinforcement may be found in the person's family, social, recreational, or vocational environments. Groups include problem solving skills, communication skills, drug refusal training, social/recreational counselling, marital/partner reciprocity training, and a Job Finding Club. One hundred eighty subjects were randomised to three treatment conditions: standard, CRA, and CRA with relapse prevention (CRA/RP). Of these, 151 subjects were followed up 6 months after intake. Since few of the RP sessions had been concluded at the 6-month follow-up, the two CRA groups were combined for analyses. The combined CRA groups did significantly better than the standard group in consecutive opiate-negative urinalysis (3 weeks), and the 6-month ASI drug composite score. Abbott, Moore, Weller & Delaney (1998) also examined the effectiveness of CRA effect on AIDS risk behaviours and the relationship between comorbid psychiatric disorders and with respect to AIDS-related risk behaviours. Subjects (N = 227) were drawn from the larger clinical trial cited above. Both CRA and standard treatment demonstrated a significant effect on reduction of AIDS risk behaviours.

Avants et al. (1999) examined the efficacy and relative costs of two intensities of adjunctive psychosocial services--a day treatment program (DTP) and enhanced standard care (STD)--for the treatment of opioid-dependent patients maintained on methadone. A 12-week randomised clinical trial with 6-month follow-up was conducted in a community-based methadone maintenance program. Of the 308 patients who met inclusion criteria, 291 began treatment (DTP: N=145; STD: N=146), and 237 completed treatment (82% of those assigned to the DTP and 81% of those receiving STD). Two hundred twenty of the patients participated in the 6-month follow-up (75% of those in the DTP and 73% of those in STD provided a follow-up urine sample for screening). Both interventions were 12 weeks in duration, manual-guided, and provided by master's-level clinicians. The DTP was an intensive, 25-hour-per-week program. The STD was standard methadone maintenance plus a weekly skills training group and referral to on- and off-site services. Although the cost of the DTP was significantly higher, there was no significant difference in the two groups' use of either opiates or cocaine. Over the course of treatment, drug use, drug-related problems, and HIV risk behaviours decreased significantly for patients assigned to both treatment intensities. Improvements were maintained at follow-up. Providing an intensive DTP to unemployed, inner-city methadone patients was not cost-effective relative to a program of enhanced methadone maintenance services, which

produced comparable outcomes at less than half the cost. In a related study, Avants, Margolin et al. (1998) hypothesised that socially anxious methadone-maintained patients would attain greater benefit from coping skills training provided in the context of a lower-intensity STD methadone maintenance intervention than in the context of the high-intensity, socially demanding DTP. Their hypothesis was supported: Socially anxious patients were drug free longer during treatment, were more likely to be abstinent at treatment completion, and had greater reductions in HIV risk behaviours if assigned to the STD intervention, which was provided at 1/3 the cost of the DTP.

Dees, Dansereau & Simpson (1997) randomly assigned 155 patients enrolled in methadone treatment to receive either "node-link mapping" (n = 82) or "standard" (n = 73) counselling treatment. Node-link mapping is a strategy for visually representing interrelationships between client's ideas, feelings, and experiences. These multirelational maps are developed (usually by counsellors) during individual and group counselling sessions to clarify client's issues and problems. A review of urinalysis results revealed that mapping clients had significantly fewer opiate-positive urines during months 2-6 of treatment and that session attendance was a significant predictor of cocaine-positive urines over months 2-12 for mapping clients. Pitre, Dansereau & Joe (1996) examined the effectiveness of mapping-enhanced counselling with less educated methadone clients (i.e., clients with no high school diploma or GED). Their results indicated that less educated clients exposed to node-link maps during treatment showed better 12-month follow-up outcomes than similar clients exposed to standard methods of counselling. Less educated mapping clients were less likely than their standard counterparts to have used drugs and to have engaged in criminal activities in the 6 months before the follow-up interview. Pitre, Dansereau & Simpson (1997) also suggest that mapping enhances the efficiency of counselling sessions by increasing "on task" attention and by reducing communication problems. Mapping counselling was associated with greater coverage of collateral issues (i.e., issues indirectly related to drug use) than standard counselling and lower during-treatment use as indicated by urinalysis results.

### Acupuncture

Acupuncture does not appear to be a useful adjunct to methadone maintenance. In a study with 60 methadone maintenance patients, Wells et al. found that the patients who received acupuncture experienced significantly more craving for heroin than did patients that received non-specific (placebo) acupuncture (Wells 1995).

### Yoga

Shaffer, LaSalvia & Stein (1997) investigated whether clients in outpatient methadone maintenance treatment who practice weekly Hatha yoga in a group setting experience more favourable treatment outcomes than those who receive conventional group therapy. After a 5-day assessment period, 61 patients were randomly assigned to conventional methadone treatment or methadone enhanced by Hatha yoga therapy. Patients were followed for



6 months and evaluated on a variety of psychological, sociological, and biological measures. The evidence revealed that there were no meaningful differences between traditional group therapy and Hatha yoga presented in a group setting. Both treatments contributed to a treatment regimen that significantly reduced drug use and criminal activities. Psychopathology at admission was significantly related to program participation regardless of treatment group.

#### **7.4 Treatment intensity**

It is not yet clear how intensive the treatment should be. In a controlled clinical trial, Brooner et al. (1998) compared two reinforcement treatments for methadone-maintained antisocial drug abusers. In the experimental group, patients with good compliance received methadone take-home doses, could influence their methadone dose and dosing time, and could schedule their counselling sessions themselves, while patients that did not comply well, lost control of these aspects. This way, the experimental group had a possibility to gain control over their own treatment. The control group had a more fixed schedule of doses and counselling sessions; they could not gain control this easily. All patients started on a stable dose of 55 mg/day. The authors found that antisocial drug abusers respond quite well to methadone treatment along with behavioural treatment, but that the experimental group did not respond better or worse than the control group. Rosenblum et al. (1995) examined the impact of treatment intensity on cocaine use. Seventy-seven cocaine-using methadone patients were enrolled in a six-month, structured, manual-driven, cognitive-behavioural treatment program. Sessions consisted of five individual and/or group sessions per week. At intake subjects showed extensive polydrug abuse, psychiatric comorbidity, criminal histories, and HIV risk behaviours. Treatment intensity was measured by dividing number of sessions attended into quartiles. Paired comparisons, within treatment quartiles, were made between subjects' intake and six-month self-reports of cocaine use. Subjects in quartiles two through four showed significant reductions in frequency of cocaine use at follow-up, with subjects who received the most treatment showing the greatest reductions in cocaine use. Bivariate and multivariate analyses showed that treatment sessions attended remained a strong predictor of reduction in cocaine use at follow-up, even after controlling for drug use at intake and background variables. The results indicate that there is a substantial treatment dose-response relationship. In a later experimental trial examining this observation, the same group (Rosenblum; Magura; Palij; Foote; Handelsman, and Stimmel 1999) randomly assigned cocaine dependent methadone patients to 6 months of high intensity cognitive-behavioural therapy or low intensity therapy. Both treatment groups showed significant and equivalent reductions in cocaine use during the post-treatment period. Completing either therapy and lower cocaine severity at baseline were associated with lower proportion of cocaine-positive urines across a 48-week post-treatment period. Examination of the treatment x cocaine severity interaction provided some evidence that high-severity patients improved more if exposed to high intensity treatment than to low intensity treatment. Positive outcomes for therapy completers relative to non-completers increased over time. The results are consistent with several

clinical trials showing that: (1) participation in treatment is associated with reductions in cocaine use; and (2) the relationship between treatment intensity and outcome is not linear and may better be explained by an interaction between patient and treatment factors.

## **7.5 Conclusion**

Numerous studies continue to support the use of treatment vouchers to reinforce abstinence and other appropriate behaviours. An area where not much knowledge has been generated is that of take-home incentives and urine tests. Take-home incentives can be used both to lower the threshold for treatment and to reinforce good treatment participation. Evidence exists that take-home incentives can help improve treatment outcomes and stimulate patients to refrain from using illicit opiates. One weak study by Baker et al. describes urinalysis, leaving this controversial issue open to further discussions.

Several studies appear to support the use of family interventions in the treatment of those enrolled in methadone treatment. Furthermore, multiple studies demonstrate that numerous psychosocial interventions may significantly improve treatment outcomes including psychotherapy, inclusion of non-drug using significant others in treatment, the community reinforcement approach, or node-linked mapping. Not much research has been done on non-traditional interventions and no support for acupuncture or yoga was noted. Finally, several studies have focused on treatment intensity. These studies provide support for the proposition that more intensive treatments will improve treatment outcome when compared to lower intensity interventions.



## **8 Perceptions of addicts of methadone maintenance treatment**

Some studies have focused on the way addicts perceive methadone treatment. Although perception studies give highly subjective outcomes, they might give some clues about the incentives for starting and - hopefully - staying in treatment. Knowledge of the perceptions of addicts of physiological and psychological effects of drug use and its treatment may be useful when structuring a treatment programme or treating an individual patient. Every addict experiences both the addiction and its treatment differently. Therefore, the main finding of the study of Hughes (2000) was that people had diverse experiences of substitute prescribing. His study population consisted of 24 persons who were or had been in methadone maintenance treatment in prison who had difficulties getting treatment in prison - some study participants could not get treatment in prison or their treatment was stopped all of a sudden - and with the treatment itself. Persons who have experienced methadone maintenance treatment themselves, are generally more positive about this than persons who have not (Zule and Desmond 1998b).

Addicts may use methadone maintenance treatment for a number of reasons (Koester 1999):

- as self-prescribed attempts of harm reduction — to stop or reduce the use of heroin and to use drugs in a safer environment;
- in order to have some rest and be away from the life of searching for heroin all day;
- to test methadone maintenance treatment, because they anticipate entering treatment later.

### **8.1 Favourable perceptions**

According to Fischer, most users are generally positive about methadone maintenance treatment. It can help them to stop the use of heroin (Delile 2000; Fischer B in press).

Being on treatment reduces the need to commit crimes for money for drugs. Also, methadone is cheaper and its quality is more reliable than that of street-bought heroin. For this reason, some addicts even consider it an easy way to get drug satisfaction without the hassle to obtain the drug. Therefore, prescription should be controlled well (Fischer B in press). This control, often through enforcement rules, can be a useful aid to patients in controlling their addiction (Neale 1999).

Patients generally prefer take-home doses as reinforcement measures over dose increases and counselling sessions as compliance reinforcement measures (Chutuape MA and others 1998a).

## **8.2 Unfavourable perceptions**

Negative perceptions of methadone can be based on a number of phenomena. For example, addicts do not experience a 'high' on methadone. Methadone only takes care of the physical dependence, but not of the psychological dependence. Therefore, in addition to the prescribed methadone, addicts may use other drugs such as cocaine or heroin itself in order to experience a 'high'. Furthermore, they might experience side-effects of methadone or symptoms of withdrawal from heroin (Fischer B in press). Methadone is, of course, supposed to counter these withdrawal effects, but in the early phase of treatment it is hard to set the correct dose immediately and withdrawal effects might occur.

The argument heard first when discussing the negative aspects of methadone maintenance is that it might become 'just another dependence' and that it is harder to withdraw from methadone than from heroin (Fischer, in press) (Hughes 2000). This might have to do with the fact that the results of methadone treatment on psychological and social aspects are not always satisfactory (Delile 2000).

Fischer et al. (in press) report that the use of the needle is an important part of the addiction to some addicts even though it has nothing to do with physical dependence. Methadone, which is administered orally, does not offer this option; on the contrary, one of the advantages of methadone is believed to be this avoidance of the use of needles, because needles can lead to tissue damage and possibly transmission of HIV. However, for some addicts that have been injecting for all their lives, use of the needle may be the only alternative to get and retain them in treatment (Metrebian N. 1998a).

The knowledge and attitudes of staff in methadone maintenance clinics were sometimes called insufficient and without respect. Also, drug users consider reinforcement regulations as an infringement on civil liberties or a patronising way of treating them (Fischer B in press)(Neale 1999). Patients that are given more control over their methadone use and dose enter treatment more easily, stay in treatment longer and use higher doses of methadone (White 1996). This is not confirmed in scientific literature (Brunner R.K 1998). Methadone treatment in a clinic is often associated with the stigma of being addicted and the lack of privacy. Furthermore, staying in a clinic precludes all possibilities for regular daily activities, such as work or education (Ling W and others 1996b).

## **8.3 Conclusion**

Research in the past five years has not led to any definitive conclusions on how to cope with the perceptions addicts may have of treatment. Experience still seems to be the best advertisement, because addicts who have been in treatment tend to be more positive about it than those who have not. The studies about perceptions of addicts have merely shown that addicts can have different opinions about take-home doses, injectable prescribing, and so on, but they cannot relate this to recommendations for clinical practice.

## **9 Methadone maintenance treatment as compared to other substitution treatments**

The debate on the efficacy of methadone as compared to newer substitution drugs is heated and shows no sign of ending. This chapter briefly discusses studies on the efficacy of other substitution treatments. While some state that methadone works better than buprenorphine and LAAM (Zule and Desmond 1998a)<sup>3</sup>(Glanz M. 1997;Ling W and others 1996a)<sup>4</sup>, others state that buprenorphine is equally effective (Johnson R E 2000)(Ling W and others 1996)(Weber 1998) and that LAAM is even better, because it has advantages in terms of practical and operational benefits (Glanz M. 1997). Weber states that buprenorphine might have this advantage as well, because the interval between prescriptions can be longer (Weber 1998b).

### **9.1 Buprenorphine**

In a recent randomised clinical trial using buprenorphine (2 and 6 mg) and methadone (35 and 65 mg), Kosten & Rayford (1995) compared low-level opiate withdrawal symptoms among: Whites (n = 84), Hispanics (n = 20), and African Americans (n = 21). During the first 2 months of opiate stabilisation, persistent low-level opiate withdrawal symptoms were significantly lower in African-Americans and Hispanics than in the white patients. As expected pharmacologically, this relative underreporting of low-level withdrawal by minority patients was greater for the low opiate doses (buprenorphine 2 mg and methadone 35 mg). This underreporting may reflect sociocultural as well as biological differences, because subjective, but not objective, withdrawal symptoms showed this ethnic difference.

Levin, Fischman, Connerney & Foltin (1997) demonstrated the feasibility of switching methadone maintained individuals over to buprenorphine. Eighteen participants maintained on methadone for 1-19 years were recruited for a residential cocaine self-administration study. All subjects were maintained on 60 mg methadone for up to 1 1/2 weeks before the 7-day changeover (60, 40, 30, 30, 0 mg methadone; 4, 8 mg buprenorphine). Fifteen participants successfully completed the transfer from methadone to buprenorphine, experiencing moderate withdrawal symptoms. Withdrawal symptoms were the highest during the first assessment of the day, at the time of buprenorphine administration. Withdrawal scores returned to baseline 4 days after the switchover, demonstrating that within a supportive inpatient setting, research

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<sup>3</sup> Although the authors conclude that methadone is more effective, they do this on the basis of study retention and compliance to treatment rules; there was no difference between methadone- and buprenorphine-patients in the consumption of opiates, benzodiazepines and cocaine.

<sup>4</sup> Ling et.al. (Ling W and others 1996a) found that high-dose methadone was more effective than either low-dose methadone or buprenorphine; the effects of low-dose methadone and buprenorphine were equal.

volunteers can be rapidly switched from high-maintenance doses of methadone to buprenorphine.

Pani et al. (2000) point out that comparisons of methadone and buprenorphine in the treatment of opioid dependence have generally employed an alcoholic solution of buprenorphine, which has a bioavailability superior to that of the tablets. Since the product available for large-scale use is in tablet form, their study sought to verify the efficacy of this formulation. In a multicentre randomised controlled double blind study, 72 opioid dependent patients were assigned to treatment with buprenorphine (8 mg/day) or methadone (60 mg/day) for a period of 6 months. The two compounds did not show any significant difference with regard to urinalyses: the average percentage of analyses proving negative was 60.4% for patients assigned to buprenorphine, and 65.5% for those assigned to methadone. With regard to retention, a non-significant trend in favour of methadone was observed. Patients completing the trial improved significantly in terms of psychosocial adjustment and global functioning, as ascertained by the DSM-IV-GAF and symptom checklist-90 (SCL-90) scales, and this was independent of the treatment group. Finally, in the case of buprenorphine, patients who dropped out differed significantly from those who stayed, in terms of a higher level of psychopathological symptoms, and a lower level of psychosocial functioning. The authors state that their results further support the utility of buprenorphine for the treatment of opioid dependence.

## **9.2 Heroin**

In the United Kingdom, methadone and heroin were compared. Both substitution therapies were prescribed at liberal doses; patients could negotiate higher or lower doses. Results were measured using interviews with the patients. By the time of the second interview, heroin prescribed patients had negotiated a higher dose, while methadone prescribed patients had negotiated a lower dose. Illicit cocaine use was reported more frequently among heroin prescribed patients than among methadone maintained patients (Stohler 1998). A survey of general practitioners prescribing heroin in the United Kingdom revealed that variations were mainly due to differences in prescribing habits of individual doctors (Strang 1997). Cancrini (2001) doubts the quality of both this trial and the Swiss heroin trial and expects 'longer and finer studies' to study the effectiveness of prescribed heroin. One study that might live up to these expectations is the trial currently being conducted in Amsterdam. Van den Brink et al. (2000) are conducting two multi-center randomised clinical trials, one with inhalable heroin and one with injectable heroin. A total of 625 (375 inhaling, 250 injecting) chronic treatment resistant heroin addicts are offered heroin (in combination with methadone) for a period of six to twelve months. No results have been reported as yet.

### **9.3 Dihydrocodeine**

Dihydrocodeine seems to help patients from becoming depressed because of a lack of heroin during methadone treatment, and could therefore be administered together with methadone. A small dose of dihydrocodeine can already help (Ulmer 1998). Few health professionals would offer an opiate such as dihydrocodeine to opiate dependent persons, as long as other anti-depressants without addicting characteristics exist.

### **9.4 Conclusion**

While the effectiveness of buprenorphine and LAAM has been established by now (although, as with methadone, the dosing remains subject of discussion), studies about prescribed heroin are just starting to show results.





## **10 Conclusions: Recommendations for guideline development**

This report has summarised the literature on methadone maintenance that has appeared between 1995 and 2000. It has shown a wide variation in studies, both concerning their content and their quality. The purpose of this review is to provide a knowledge base for the development of clinical guidelines in Switzerland. Therefore, we started with a description of guidelines for methadone maintenance treatment in a large number of countries, followed by a description of literature reviews that have already been done in this field. Consequently, the most recent clinical evidence was summarised. Articles on methadone maintenance treatment and concurring treatment modalities were discussed in detail, as well as existing knowledge about specific populations. Prognostic factors to patients' responses to treatment and perceptions of opiate dependent persons, although not essential for the construction of guidelines, may be a useful source of information to practitioners in managing their methadone maintenance treatment and in assessing the best possible treatment. A small chapter finally described other substitution treatments in comparison to methadone maintenance. As the focus of this review is on methadone maintenance, these treatments were only briefly mentioned.

This final chapter aims to synthesise the information of the review into a structured information source for thinking about guideline development. It summarises the findings of the review according to general quality measures for treatment and according to the main phases of methadone treatment: initiation, maintenance and stabilisation, and, for some patients, cessation of methadone maintenance treatment. Within these phase descriptions, important elements for inclusion in guidelines are discussed. The way these elements are filled in is left to the determination of the experts in Switzerland. It will depend on their own medical expertise, but also on their perceptions of drug addicts and addiction treatment and on the current policy in a country.

### **10.1 General characteristics of methadone maintenance treatment**

Most authors agree that methadone maintenance will be most successful if

- a) The treatment is provided by a well trained, motivated staff;
- b) The treatment is provided in the appropriate treatment environment;
- c) The treatment aims at maintenance rather than abstinence; abstinence may be a long-term goal.
- d) The treatment is given in a multidisciplinary environment, where general practitioners, pharmacists, specialised drug treatment doctors and nurses co-ordinate their actions
- e) The treatment is multidisciplinary in itself; this means that methadone maintenance is not the only treatment, but that other needs of the patient, be they medical, social, legal, psychiatric or something else are addressed at the same moment. After all, these factors may include the reason for using illicit opiates;
- f) Treatment is matched to the patient's individual needs; each patient has his personal history and individual characteristics. Some authors also state

that it is important to give the patient a feeling of control over his own treatment.

g) The patient stays in treatment as long as necessary. This may be a period of one or two years, but it may also imply life-long methadone treatment. Research has consistently demonstrated a significant correlation between effectiveness of treatment and treatment retention (Grella 1996).

Many patients fail to become abstinent from licit and illicit opiates over the long term (Des Jarlais and Hubbard 1999). However, the quality of life of opiate dependent persons can be greatly improved and harm reduction can be achieved (Soyka 1997).

## **10.2 Initiation**

Access to treatment for any opioid dependent person who is eligible and motivated for treatment should be facilitated (Verster A. 2000). Lack of treatment capacity could lead to a loss of motivated persons. In order to encourage participation in substitution therapy, a range of treatment options and venues might be considered. Low threshold treatment programs, full service clinics, GP prescriptions, pharmacy dispensing, or even methadone dispensed in residential settings might all play a useful role in attracting opiate abusers into treatment, while other clinics with higher thresholds might be better suited for better motivated patients. Clinic rules should not turn away patients and since each patient is different, different treatment environments will be best able to provide service to all patients.

Guidelines on the first phase of treatment could include the following elements:

### **a) Eligibility criteria**

The physician should assess whether a patient is eligible for treatment entry. Many countries use the (modified) criteria for opioid dependence as defined in the DSM-IV as the basic eligibility measure and add their own criteria, such as a minimum number of years of opioid use, or proof of opioid use in the past few weeks. At treatment entry, patients should have a clear idea of what they can expect and what is expected of them. This latter point is important, as patients should participate in treatment actively (Post 1997).

Patients may want to enter methadone maintenance treatment for different reasons. They may consider methadone prescription as a temporary method to get some rest from the hectic life of drug seeking and craving for heroin. They may also want to stop using (illicit) drug altogether. Chapter 8 discussed the perceptions patients may have of treatment with methadone. The treating physician should try to find out with what goal somebody wants to enter methadone maintenance, as this influences the treatment objectives and the treatment plan.

Some countries have applied stricter regulations for treatment entry as a consequence of a shortage of capacity; by setting the threshold higher, fewer addicts are eligible for treatment.

b) Criteria of possible effectiveness

Guidelines should assess the patient's specific treatment needs. Specific guidelines might be usefully developed for the treatment of:

- Pregnant patients
- Patients with HIV-infection or AIDS
- Antisocial patients (Broome 1999a)
- Polydrug users, especially cocaine and alcohol users (Grella 1995);(Seivewright 2000)
- Patients with psychosocial or psychiatric comorbid disorders (e.g. Avants 1998)

These factors may lead doctors to provide priority entry into treatment services (e.g. for pregnant and HIV-infected persons) or to pay extra attention to the provision of additional or tailored psychosocial treatment (e.g. for polydrug users, or those demonstrating antisocial behaviours). If more knowledge about prognostic factors becomes available, this might also help in establishing the optimal treatment options individual patients.

Many patients have psychiatric comorbidities. Co-operation with doctors in internal medicine, psychiatry and other medical specialisations is recommended to complement social reintegration therapy (Soyka 1997).

All authors agree that the patient should start at a low dose of methadone in order to prevent overdose. There has not been any research on starting doses, but guidelines state starting doses of 10 to 40 mg, depending on the quantity and quality (i.e. purity) of heroin the patient is used to; a dose higher than 40 mg/day may be very dangerous (Department of Health 1999). The patient should be monitored closely. If the patient experiences withdrawal symptoms, the dose should be increased slowly and carefully, while it may be decreased if the patient seems to experience adverse effects from the methadone. These adverse effects might also occur as a consequence of interactions with other licit and illicit drugs.

Authors state that, in the early phase of treatment, the patient had better not receive take-home doses, except for exceptional personal circumstances. Daily administration in a treatment setting is the preferred method of treatment in the phase that the patient is not yet on a stable dose of methadone (Department of Health 1999). Furthermore, the patient may have used heroin to suppress depressed feelings or a comorbid psychiatric disorder. Stopping the use of heroin could well initiate the re-emergence of such problems. This is another reason for doctors to monitor their methadone patients carefully in the early phases of treatment, as such psychiatric problems may cause patients to relapse to heroin use (American Psychiatric Association 1995).

### **10.3 Stabilisation and maintenance**

Once the patient has stabilised on a certain dose of methadone, he or she can start to concentrate on the problems which might have been the underlying factors for starting to use heroin or which are the consequences of the heroin dependence. These problems, along with patient characteristics, should lead the doctor to decide on the most appropriate treatment for this patient.

Basically, the treatment is composed of two components that are closely related: the medical component of methadone prescription and the psychosocial element of therapy and treatment environment.

### Methadone prescription

The medical component exists of the assessment of the appropriate dose of methadone and of the clinical monitoring of the patient. The following aspects should be taken into account:

- **Stabilisation dose:** this dose may vary between 20 mg/day and 300 mg/day, depending on the needs and desires of the patient. A higher dose (>60 mg/day) has proven effectiveness, because it blocks the euphoric effects of heroin. This way, the patient has no incentive to use heroin. Over the years, the dose may change as patients indicate their preferences or when they have to use other medications which influence the metabolism of methadone. Chapter 5 contains a section on drug interactions. There is, however, no agreement about the extent to which the patient may become addicted to methadone or about the desirability of such possible methadone addiction.
- **Administration of methadone:** administration of methadone in a liquid oral form is the preferred one in most literature, closely followed by methadone pills. Pills could be crushed and thus used for injection, which would increase the harms associated with drug use again. Adding naloxone to the methadone solution can prevent injection. Naloxone blocks the euphoric effects of methadone when it is injected, while it does allow methadone to do its work when it is taken orally.
- **The position on injectable methadone** is still ambiguous in many countries. Some state that injectable methadone can be a good solution for patients who have been using injected heroin for long periods of their lives (see chapter 8). Administering methadone with needles may be a good option to get patients to enter treatment and to remain in treatment (Metrebian N. 1998). Others consider that one of the objectives of methadone maintenance should be that patients stop using the needle.
- **Time of day of methadone consumption:** a small number of studies discuss the time of day methadone could best be administered. As methadone reaches its peak two to four hours after administration and the effect then slowly decreases in the following 20 to 30 hours, it is argued that the dose should be administered in the morning, so that the patient is asleep when the effect is decreasing, while the peak effects of methadone are at the moment when the patient craves most for heroin (Best D 1997).
- **Compliance:** The literature has discussed several enforcement strategies. Urinalysis is the best known. Urinalysis can be used just to assess whether a patient has used other drugs than methadone. A treatment centre could also decide to enforce sanctions when urine samples are opioid positive or it could reward a number of consecutive negative samples or it could do both. While rewards have proven effectiveness, the use of sanctions is still disputed. Patients prefer announced urine tests because then they know what they can expect and because they feel taken more seriously and have a feeling of

control over their own treatment (Baker JG and others 1995). A disadvantage of urinalysis is that it cannot show at what dose a drug has been used, so it cannot show a gradual decrease in illicit opiate use. Other compliance measures are attendance to counselling sessions, Addiction Severity Index and compliance to individual treatment objectives. Possible means of enforcement are take-home doses and vouchers.

- Take-home doses: take-home doses can be an integrated part of treatment for stabilised patients, but it can also be part of an enforcement strategy. For example, patients could get a take-home dose for each three consecutive illicit opiate-negative urine samples, or they could merit the privilege of three take-home doses per week as long as they keep on showing negative results in the urine tests. A sanction could be to stop this privilege if a test shows positive results.

### Complementary treatment

Complementary treatments are elements of treatment that take care of the non-medical part of the addiction. We also discuss the treatment environment as such an element.

- Most methadone prescription programmes offer at least some personal counselling sessions. During these sessions, treatment goals are set with the patient and problems associated with the drug addiction can be discussed. The counselling sessions are a good way to establish a relationship of confidence between the physician and the patient.
- With treatment environment we mean the setting in which treatment is given. This may be in-patient treatment or outpatient or both. In-patient treatment has the advantage that the patient can be monitored very closely, but the disadvantage that it precludes the possibility of normal daily activities, such as work and education (Ling W and others 1996b). Outpatient treatment may facilitate success in voluntary residential treatment and post-treatment drug-free status, but is less useful for patients with a high risk of relapse (Cheung 1999). Furthermore, the orientation of the treatment can be seen as a treatment environment. Research has found that an abstinence-oriented environment is less likely to be successful than an environment in which healthy behaviour is encouraged without the objective of stopping the use of methadone (Coplehorn 1998).
- Psychosocial treatments and psychiatric treatments address the psychological, social, legal and psychiatric problems of the patient. These problems have probably come up during the assessment, but might also occur during the first weeks of treatment. Special attention needs to be paid to the specific groups of patients that were mentioned earlier: anti-social and depressed patients, and so on. Most guidelines stress the importance of co-operation between the methadone-prescribing doctors and the therapists in order to establish a good relationship with the patient and to enhance retention in treatment.
- Vouchers: vouchers are a way to reward treatment compliance without using money. Just like take-home doses, they can be given for each compliant action, after a number of consecutive compliant actions and they can be withdrawn in some cases. Vouchers have proven effectiveness for longer abstinence from illicit drugs (Bell James

1995)(Saxon AJ and others 1996). The advantage is that patients get a reward in a manner that does engender craving and drug use, as is the case with monetary rewards.

#### **10.4 Reduction of methadone dose**

Over the years, the physician and the patient can decide that a dose reduction or even a total stop of methadone use is appropriate. A patient can have several reasons for stopping the use of methadone. The best reason is when both physician and patient believe that the patient has reached abstinence from illicit drugs and has stabilised his life sufficiently to continue on his own. Stopping the use of methadone does not necessarily mean that concurrent therapies are stopped. It might also be that the patient has to use other drugs for medical reasons that interfere with methadone consumption.

A reduction of the dose of methadone will very probably lead to withdrawal symptoms. Therefore, most authors recommend that such reduction be done very slowly. This is called 'tapering off'. Depending on the patient and his stabilisation dose, the dose can be reduced by 1 mg per fortnight up to 10 mg per day. In the final phase of reduction (one study states: when the patient is at 30 mg/day), the rate of reduction should be slowed down. Tapering off can take a few months for some patients, but a number of years for other patients (Poehlke 1999). As in the early phase of treatment, close monitoring of the patient is recommended.

#### **10.5 Final thoughts**

If the Swiss government is to disseminate methadone on a broad basis, it should consider the possibilities of monitoring this dissemination, for example through the canton registrations. The monitoring system could try to gain information about morbidity and mortality associated with methadone use.

Furthermore, the guidelines might have to leave some room to future developments. For example, research is being done on methadone dispensers that allow take-home doses, without posing a risk to the environment of the addict. In chapter 6, the death of an infant as a consequence of the use of a baby-bottle for measuring methadone dose is described. A baby-bottle is such a risky measuring device, but this risk of inappropriate use could be easily avoided if doses are provided on a day-to-day basis or in childproof containers with measuring device or both. These options are currently being studied. The results of these experiments might influence the way take-home doses are perceived.







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