

a reference manual for participants

pharmacotherapies

accreditation course

***Pharmacotherapies Accreditation Course
- A Reference Manual for Participants***

NSW HEALTH DEPARTMENT

This work is copyright. It may be reproduced in whole or in part for study training purposes subject to the inclusion of an acknowledgement of the source and no commercial usage or sale.

© NSW Health Department 2001

SHPN: (DPB) 010051
ISBN: 0 7347 3286 4

For more information and further copies, please contact:

Better Health Centre
Publications Warehouse
Locked Mail Bag 5003
Gladesville NSW 2111
Tel. (02) 9816 0452
Fax. (02) 9816 0492

May 2001

TABLE OF CONTENTS

Introduction

The aim of this manual	1
Regulatory context in management of opioid dependence	2
Competencies	4
Assessment of competence	8

Section 1.

AN OVERVIEW OF OPIOIDS, HEROIN ADDICTION AND TREATMENT APPROACHES

Chapter 1: ***Opioid Drugs***

1.1	Opioids	9
1.2	Tolerance and neuroadaptation	10
1.3	Dependence	12
1.4	Withdrawal	13
1.5	Some specific opioid drugs	14
1.6	Dose-equivalence of opioids	17
1.7	Pharmacology and addiction	18
1.8	The medical use of opioid drugs	18
1.9	Diversion and regulations	20

Chapter 2: ***Heroin Addiction and Associated Problems***

2.1	Heroin addiction	24
2.2	Multiple or polydrug dependence	26
2.3	Medical conditions associated with injecting drug use	27
2.4	Psychiatric comorbidity	31

Chapter 3: ***Treatment of Heroin Addiction***

3.1	Harm Reduction	33
3.2	The public health frame of reference	34
3.3	Attitudes, values and assumptions in the treatment of addiction	35
3.4	The components of effective treatment	36
3.5	Treatment options	40

	Answers to Self-assessment Questions for section 1	42
--	--	----

THE MEDICAL TREATMENT OF OPIOID DEPENDENCE

Chapter 4:	<i>Assessment</i>	
4.1	The objectives of assessment	43
4.2	The content of assessment	44
Chapter 5:	<i>Methadone Maintenance Treatment</i>	
5.1	Pharmacology of methadone	51
5.2	Side effects of methadone	53
5.3	Use of methadone	54
5.4	The effectiveness of methadone maintenance treatment	55
5.5	Consumer perspectives on methadone treatment	58
Chapter 6:	<i>Clinical Issues in Methadone Maintenance Treatment</i>	
6.1	Determining suitability for treatment	60
6.2	Urgent initiation of treatment	64
6.3	Induction into methadone treatment	65
6.4	Stabilization on methadone	67
6.5	Optimizing the benefits of maintenance on methadone	68
6.6	A framework for quality improvement	72
6.7	Safety	75
6.8	Record keeping	76
6.9	The logistics of methadone treatment	76
6.10	Review of treatment	77
6.11	Responding to continuing drug use	79
6.12	When a change in treatment is indicated	82
6.13	Methadone and pain management	86
6.14	Management of pregnant, opioid dependent women	86
Chapter 7:	<i>Buprenorphine Treatment</i>	
7.1	Pharmacology of buprenorphine	91
7.2	Pharmacokinetics	93
7.3	The effectiveness of buprenorphine maintenance treatment	93
7.4	Side effects of buprenorphine	94
7.5	Safety of buprenorphine	95

Chapter 8:	<i>Clinical Issues in Buprenorphine Treatment</i>	
8.1	Buprenorphine maintenance	96
8.2	When a change of treatment is indicated	101
8.3	Buprenorphine in heroin withdrawal	102
Chapter 9:	<i>Naltrexone in the Management of Opioid Dependence</i>	
9.1	Naltrexone pharmacology	106
9.2	Naltrexone treatment for relapse prevention	107
9.3	Naltrexone and rapid detoxification	110
Chapter 10:	<i>Clinical Issues in Naltrexone Treatment</i>	
10.1	Patient selection for naltrexone	112
10.2	Induction onto naltrexone	113
10.3	Maintenance on naltrexone	115
10.4	Responding to continuing heroin use	117
10.5	Other drug use	118
10.6	Depression and suicidal ideation	118
10.7	Duration of treatment	119
10.8	Issues for patients on naltrexone	119
	Answers to Self-assessment Questions for section two	112

Section 3.

REFERENCES AND APPENDICES

	<i>References</i>	122
Appendix 1	<i>Administration of the NSW Methadone Program</i>	125
Appendix 2	<i>Legal Requirements for Prescribing S8 Drugs</i>	127
Appendix 3	<i>Subjective withdrawal scale</i>	128

Section 4.

ACKNOWLEDGMENTS

	Acknowledgements	130
--	-------------------------	-----

INTRODUCTION

The training program

This manual has been prepared as a resource for health professionals, particularly medical practitioners, wishing to increase their skills in treating opioid dependence - particularly, heroin addiction. It is one component of a training program comprising:

- ▶ the training manual
- ▶ a one day workshop
- ▶ an interactive website
- ▶ a clinical placement.

A written exam based on material in the manual may be undertaken during the workshop, or on an interactive website. Performance by trainees at the workshop, the exam and the clinical placement will be formally assessed, with the outcome for trainees being either Satisfactory or Not Satisfactory. Where any performance is judged to be unsatisfactory, the trainee will receive feedback identifying any deficiencies in knowledge or performance which have been identified.

The aim of this manual

This is a training manual, and has two key aims - identifying skills needed in treating addiction, and promoting a deeper understanding of the complexities of practice in this area. It is hoped that the manual will stimulate the reader's curiosity and encourage them to think critically about an interesting and challenging area of medical practice.

The emphasis in all aspects of the training program is on generic skills of value in all areas of medical practice. Opioid-dependent people often pose distinct management difficulties, and practitioners who acquire the skills to treat dependent patients effectively will find the skills of great value in all areas of clinical practice.

There are many regulatory and procedural issues around delivery of treatment, and practitioners involved in delivering treatment should, in addition to this manual, be familiar with several useful documents:

- ▶ NSW Methadone Maintenance Treatment Clinical Guidelines
- ▶ National Guidelines on the use of Buprenorphine
- ▶ National Guidelines on the Use of Methadone
- ▶ National Guidelines on Naltrexone in Relapse Prevention
- ▶ NSW Treatment Agreements
- ▶ Methadone Maintenance Treatment, Essential Information.

This manual contains the information required by practitioners wishing to complete assessment of competence in the training program.

Background — the growth of medical treatment of addiction

There has been an impressive growth in research on addiction, and particularly on pharmacotherapies for opioid dependence, in the last decade. With the registration of naltrexone in Australia in 1999, and the registration of buprenorphine in 2000, doctors and

their patients are confronted with greater choices, and a need for more information on which to base treatment decisions.

Following the National Drug Summit of 1985, there has been a progressive expansion of methadone maintenance in Australia. There are now around 25,000 people in methadone treatment in Australia, and the number is steadily rising. Such a large treatment sector requires a skilled workforce, and over the last 15 years there has been a progressive increase in the number of medical practitioners involved in the treatment of addiction.

The rapid expansion of treatment has not been without problems. There are continuing concerns about the quality and safety of methadone treatment as it is being delivered. Reports of deaths early in treatment, as a result of practitioners prescribing doses of methadone greater than patients' level of tolerance, led to the establishment of the first Australian training program in Victoria in the early 1990s.

Training programs have not solved all the problems, and there are continuing concerns regarding the delivery of methadone treatment — about uneven standards of care, inadequate assessment and inappropriate treatment practices. As in other areas of medical practice, initial training has only a limited role in ensuring that standards of professional practice are maintained. One of the competencies identified in this program relates to the importance of quality improvement — the process of monitoring standards of care to achieve the best outcomes from treatment.

The training course is based on the assumption that the acquisition and maintenance of competence is a process involving continual learning. This manual aims to provide basic information needed to manage opioid-dependent people safely and effectively. However, any treatment manual will require continual revision, and the information in this manual will be dated by the time it is published. Competence requires practitioners to approach treatment in a spirit of curiosity rather than dogmatism, so that we can learn from experience. Competence also requires the discipline and commitment to participate in continuing education.

Regulatory context of treatment of addiction

In most countries, there are restrictions on how doctors prescribe drugs of dependence. **In Australia, it is not legal to prescribe Schedule 8 drugs (drugs of addiction) to anyone who is a known addict, without an individual authority to prescribe from state health departments.**

This regulation governing prescribing, is designed to minimize the harm associated with prescribing opioids. By reducing the likelihood that a patient can receive prescriptions for opioids from multiple doctors simultaneously, it minimizes the likelihood that diversion of prescribed opioids becomes a major source of street drugs. In many parts of the world, particularly where heroin is of limited availability, many opioid dependent people maintain their dependence by obtaining prescribed opioids. In such circumstances, there is also a thriving black market in pharmaceutical opioids. Medical practitioners are often under pressure from patients who become adept at manipulating them to prescribe opioids.

It is not the intention of these regulations to obstruct access to appropriate treatment with prescribed opioids. In all Australian jurisdictions there is increasing access to MMT, and delays in entering treatment are minimized by State authorities.

The medical treatment of addiction is not merely a regulatory exercise, the dispensing of opioids according to policy. Methadone treatment (and buprenorphine and naltrexone treatment) is a clinical issue, requiring skilled assessment, clinical judgement, and thought. It occurs within a regulatory framework, but is not simply a regulatory exercise.

In Australia, methadone may only be used in the treatment of addiction by medical practitioners authorised to deliver this treatment. Authorised methadone doctors may only initiate methadone treatment in patients for whom they have received individual authorisation from state health authorities. An exception to these regulations concerns the management of heroin users hospitalised with serious medical problems, in whom doctors may use methadone as part of management while the patient remains in hospital.

In most Australian states, to become an authorised methadone prescriber involves satisfactory completion of the state-based training program. In NSW, there are two aspects to authorisation of doctors:

1. **Initial training and certification.** Initial training introduces basic concepts, and outlines the skills and assumptions which are likely to be required for effective management of opioid dependence.
2. **Recertification,** based on participation in continuing education, and on demonstration of practice standards, allows practitioners to increase the number of patients for whom they may prescribe, and the flexibility to treat patients in different settings.

In addition to these activities, **accreditation** of clinics, demonstrating an understanding of systemic, organisational aspects of treatment, is required. Practitioners working in large clinics need to participate in this process.

Successful completion of initial training allows authorisation for limited numbers, to be treated in specified contexts (e.g., in a methadone clinic, a correctional facility, a specified private practice).

Practitioners wishing to increase the number of patients whom they can manage need to demonstrate:

1. Competence in practice — through submitting case histories or undergoing a clinical audit.
2. Support — by demonstrating that there is an adequately supported setting in which treatment can be conducted. Practitioners working in clinics supported by multi-disciplinary staff involved in case management, can be authorised for more patients. Practitioners in more isolated practice settings who demonstrate that they make use of mentoring and referral may also be certified to take on greater numbers.

3. Involvement in continuing education and professional activities will also be considered in certification and recertification. One ready way to access such continuing education is through the web-based training program.

All certification is conditional on professional standards being maintained, and may be revoked by the Director-General if substantial concerns regarding safety, competence or impairment are raised in relation to practitioners.

Competencies

The NSW training program is based on the competencies required to manage patients. Competencies are described in terms of identifiable tasks employing specific knowledge and skills. However, professional competence also demands that a practitioner working with drug dependent individuals possess attitudes congruent with their responsibilities towards patients, families, other health professionals and the community. In the following pages, competencies assessed in the training program are outlined.

Competency 1 – Attitudes and professional practice

Patient Focus - A practitioner conveys an accepting, non-judgmental attitude that allows him/her to develop effective therapeutic relationships. Practitioners accept that patient autonomy and choice is the basis of treatment. Working with drug dependent people requires both respect for the individuals autonomy, and a capacity to set limits when people act in ways which are a risk to themselves or others. He/she is aware of and sensitive to issues of ethnicity, culture, gender and sexuality. He/she recognises the importance of the patient's family in supporting the patient, as well as the potential difficulties the family may experience in the care of a drug-using family member.

Professional Role - A practitioner behaves with courtesy, responsibility and accountability towards patients and their families, and towards other health professionals.

A competent practitioner understands the extent and limitations of their competence. He/she recognises and respects the contributions and roles of other medical practitioners in the process of care, and consults where appropriate.

Maintenance of Professional Standards - A practitioner working with opioid-dependent people views competence as a continuing process of education and learning by which he/she ensures that clinical practice is of the highest standard. He/she is willing to review personal competence regularly, and to improve clinical skills as necessary.

Interdisciplinary Management —The practitioner recognises the necessity of interdisciplinary team management, and respects the key role of other professionals — including nurses, pharmacists, and counsellors — in the care of opioid-dependent people. He/she understands the specific skills of each professional involved in patient care, and develops a close professional relationship with these allied disciplines. The practitioner appreciates the synergistic effect of cohesive management, and supports all professionals involved in joint care of patients.

Patient Advocacy — Practitioners involved in the care of opioid-dependent people support their patients in overcoming stigma, and receiving appropriate medical care and psychosocial support, and to pursue their chosen lifestyle with independence and dignity.

Tasks:

- ▶ Maintain patient privacy and confidentiality.
- ▶ Engage patients in a respectful manner.
- ▶ Respond to patients in a non-judgemental, non-punitive way.
- ▶ Provide family members and significant others with appropriate information.
- ▶ Participate in continuing education.
- ▶ Refer patients appropriately according to their need for comprehensive care.
- ▶ Communicate with other health professionals to ensure optimal care and supervision.

Competency 2 – Assessment

The cornerstone of all treatment of dependency problems is assessment. This is the process of clarifying why the patient is being seen, the nature of their problems, their supports and difficulties, and developing a treatment plan. It is based on a comprehensive approach to patients — medical, psychological and social circumstances.

Initial assessment is often best undertaken over several interviews. Throughout treatment, there will be occasions for reassessment, particularly when problems are appearing or a change of treatment is being contemplated.

Assessment is a critical ingredient in establishing a therapeutic alliance.

Documentation is a critical component of assessment.

Tasks:

- ▶ Identify the presenting problem and gauge patient's motivation for treatment.
- ▶ Take a detailed drug use history and make an estimate of the severity of dependence.
- ▶ Take a medical and psychiatric history.
- ▶ Take a psychosocial history.
- ▶ Perform mental state examination.
- ▶ Perform focused physical examination.
- ▶ Undertake appropriate investigations.
- ▶ Make an accurate diagnosis of medical and psychiatric problems.
- ▶ Provide feedback to patients.
- ▶ Inform patient about treatment options.
- ▶ Formulate a management plan.
- ▶ Document assessment and provide appropriate written reports.

Competency 3 – Developing a treatment plan

Description:

Competence in medical management of opioid dependence requires the practitioner to plan, initiate, administer and review appropriate and comprehensive long-term management, utilising and coordinating the skills of an interdisciplinary team, and communicating effectively with the patient, family, medical colleagues and other relevant agencies and professionals. The practitioner demonstrates knowledge of those approaches to treatment which have been demonstrated to improve outcomes.

Tasks:

- ▶ Provide accurate, balanced and well-informed information about treatment options.
- ▶ Plan realistic and appropriate ongoing management in conjunction with the patient (and, where appropriate, the family).
- ▶ Explain treatment with methadone, buprenorphine and naltrexone to patients.
- ▶ Obtain informed consent for treatment.
- ▶ Identify risk factors during induction.
- ▶ Maximize safety during induction into treatment.

Competency 4 – Management of comorbidity

Description:

The practitioner monitors patients regularly, identifying and responding appropriately coexisting medical and psychiatric conditions.

Tasks:

- ▶ Identify and initiate management of medical and psychiatric conditions.
- ▶ Diagnose and respond appropriately to intoxication and withdrawal states from alcohol, benzodiazepines, opioids, and other psychoactive drugs.
- ▶ Provides accurate information and appropriately manages drug use in pregnancy.
- ▶ Integrates drug and alcohol rehabilitation into the wider framework of the patient's medical care by liaison and consultation with other medical practitioners and health services.
- ▶ Identify, and refer or manage psychiatric factors affecting rehabilitation management, including adjustment disorders, depression, anxiety and psychosis.

Competency 5 – Patient management

Description:

The practitioner reviews patients regularly, seeks to maintain an effective therapeutic relationship, and in discussion with patients, updates a treatment plan in the light of evidence regarding factors associated with better outcomes of treatment. The practitioner manages (or advises on management) problems (including intoxication, dosing errors, non-compliance and disruptive behaviour), so as to minimize the harm to patient and to others.

Tasks:

- ▶ Regular review and documentation of the patient's progress including, as necessary, the use of standardized outcome measures.
- ▶ Revision of treatment plans and goals.
- ▶ Monitoring the adequacy of the patient's dose of methadone or other drug.
- ▶ Determining and reviewing the appropriate setting for treatment.
- ▶ Appropriate use of urine testing.
- ▶ Utilises assessments and therapies of the interdisciplinary team.
- ▶ Appropriate use of take-home medication .
- ▶ Deliver treatment in ways supported by research findings.
- ▶ Identifies legal and professional responsibilities including the Mental Health Act and child protection concerns.
- ▶ Three monthly clinical review with other members of the treatment team.

Competency 6 – Quality improvement

Description:

Quality improvement is based upon measuring and monitoring the processes and outcomes of treatment, and making use of the information to improve the delivery of care. The practitioner works within a treatment system, and implements quality improvement approaches to ensure that the system delivers care in ways which are effective and accountable.

Tasks:

- ▶ Maintenance of adequate documentation of treatment processes.
 - ▶ Maintenance of clear lines of responsibility and communication between professionals involved in the delivery of care.
 - ▶ Patient details and records are stored securely, only accessible to those who need the information.
- a Participate in accreditation programs, if required.

Assessment of competence

There is a range of ways in which competence in these aspects of practice can be demonstrated. Factual material will be assessed in a written examination, which will also include scenarios for discussion. This will also be available on the interactive website. Clinical skills and interaction with patients will be assessed in the clinical placement.

All aspects of competence can be assessed through a review of clinical records.

Further reading

There has been a great deal written about methadone maintenance treatment. In particular, professionals are directed to three important resources:

1. A comprehensive review of the scientific literature on methadone — Ward, J., Mattick, RP, & Hall, W., *Methadone Maintenance and Other Opioid Replacement Therapies* (Harwood Academic Publishing, Amsterdam, 1998).
2. For a summary of operational issues in delivering methadone treatment — *NSW Methadone Maintenance Treatment Clinical Practice Guidelines* (NSW Health, 1999).
3. *National Guidelines* are being prepared to assist practitioners in using methadone, buprenorphine and naltrexone in the treatment of opioid dependence.
4. *Drugs Dilemmas and Choices by a Working Party of Royal College of Psychiatrists and the Royal College of Physicians*. Gaskell, London 2000.

AN OVERVIEW OF OPIOIDS, HEROIN ADDICTION AND TREATMENT APPROACHES

CHAPTER 1: **OPIOID DRUGS**

1.1 Opioids

Opiates is the name given to compounds extracted from the juices of the poppy *Papaver Somniferum*. Morphine and heroin are an example of opiates. These drugs act on receptors in the brain, the opiate receptors. Methadone and pethidine are examples of drugs which also act on the opiate receptor, but which are synthesized in the laboratory rather than derived from opium. In general, **Opioids** are the labels given to include both opiates, and synthetic compounds which bind to opiate receptors.

Opioids which bind to receptors and activate them are referred to as **agonist** drugs (such as morphine), while those which bind to receptors but do not activate them are called **antagonists** (such as naloxone).

Mu (morphine) opiate receptor agonist drugs have a range of pharmacological actions:

- ▶ analgesia
- ▶ a sense of well being (euphoria)
- ▶ sedation
- ▶ CNS depression, particularly respiratory depression (in high doses)
- ▶ pupil constriction
- ▶ reduced pulse and blood pressure.

Opioids are the most powerful analgesics in the pharmacopoeia, and are particularly valuable in relieving the affective component of pain.

The administration of opioids produces a number of side effects:

- nausea and vomiting
- constipation
- increased sweating
- decreased sexual function- impotence.

Toxicity from overdose of opioids is characterised by:

- unconsciousness with difficulty in being aroused
- respiratory depression (hypoventilation)
- pinpoint pupils
- hypotension
- bradycardia
- heavy snoring.

The toxicity of opioid drugs is greatly increased in the presence of other respiratory depressant drugs, particularly alcohol and benzodiazepines. Post-mortem toxicological analysis indicates that in most opioid overdose deaths there are other drugs present. Overdose can also produce pulmonary oedema, which is almost invariably present in fatal cases.

1.2 Tolerance and neuroadaptation

The repeated administration of opioids can produce two important observable responses — tolerance and withdrawal.

Tolerance is the phenomenon whereby repeated administration of the drug produces a diminished effect, as the body adapts to the presence of the drug.

Tolerance to opioids can be dramatic; with repeated exposure to increasing doses of opioids, an individual can appear and function normally, despite having taken doses which would be fatal in a non-tolerant individual.

Withdrawal is the phenomenon whereby after a period of prolonged exposure to opioid drugs, stopping the administration of the drug leads to physiological and psychological changes — an abstinence syndrome .

Tolerance and withdrawal are manifestations of the same process by which the body adapts to the presence of administered opioids. The term **neuroadaptation** is used to describe the changes inferred from observing tolerance and withdrawal. Neuroadaptation assumes adaptive changes occur in the CNS as a result of exposure to opioids; however, the mechanisms of neuroadaptation to opioids are not well understood.

Neuroadaptation begins immediately following the administration of an opioid agonist. Four hours after the administration of a single dose of morphine to a non-dependent subject, a mild withdrawal reaction can be precipitated by the administration of large doses of naloxone, indicating that a degree of neuroadaptation has already occurred.

With repeated administration of an opioid, so long as the interval between doses is sufficiently short to ensure that there is no time for neuroadaptation to completely reverse between doses, neuroadaptation and tolerance quickly become established. It is possible to progressively raise the administered dose of an opioid until within weeks, tolerance is such that the patient can receive very large doses without evidence of toxicity.

However, tolerance to all opioid effects is partial. When a patient has been stabilized on methadone at 80mg/day (a dose which would be fatal in a non-tolerant person) for many months, blood levels fluctuate within fairly narrow range and the patient appears and functions normally. From about 30 minutes after the daily ingestion of the dose, blood levels are rising, and the patient generally feels a sense of well being, and increased energy. Although largely tolerant, some patients experience slight opioid effects as the blood level is rising, and slight symptoms of withdrawal when the blood level is falling.

The reversal of neuroadaptation begins quite rapidly when the level of opioid agonist drugs in the CNS begins to decline. Reversal of neuroadaptation is associated with the emergence of an abstinence syndrome — signs and symptoms of withdrawal. After about three weeks

of regular opioid use, discontinuation is associated with the spontaneous emergence of symptoms and signs of withdrawal.

The severity of opioid withdrawal is determined by two major factors:

- ▶ firstly, the greater the dose of opioid being administered regularly, the more severe the withdrawal syndrome on discontinuing
- ▶ secondly, the more rapid the rate at which the opioid is withdrawn, the more severe the withdrawal syndrome.

Since the more rapidly the drug is cleared from the body, the more pronounced is the abstinence syndrome, withdrawal from short-acting drugs tends to be more severe than withdrawal from long-acting drugs. Morphine has a half-life of about two to three hours, which means that morphine blood levels decline fairly rapidly, from a peak following intravenous administration. Abrupt cessation of regular morphine leads to quite a severe withdrawal syndrome. Long acting drugs such as methadone or buprenorphine have much more mild (but more prolonged) withdrawal syndromes on cessation. Even with these drugs, it is recommended that they be tapered over a period to allow more gradual and less symptomatically distressing reversal of neuroadaptation.

The most severe withdrawal reactions occur when an opioid antagonist is administered to a dependent patient who at the time has a high level of circulating opioid agonist. By competitively inhibiting the agonist, the administration of naloxone or naltrexone abruptly blocks agonist effects — instead of declining over many hours, drug effects are reversed in minutes. The result is a very severe withdrawal reaction, with profound physiological and psychological effects.

From this discussion, it will be apparent that in any given individual, the degree of tolerance fluctuates over time, depending on recent level of exposure to opioid agonists.

Neuroadaptation is more likely to develop after regular exposure to long-acting opioids than short-acting ones, because long-acting opioids ensure more continuous exposure of the CNS to the drug, and less time when there is no drug present for the CNS to readapt.

For example, the opioid pethidine has a very short half-life, and it is extremely uncommon for someone having even two or three injections per day to become neuroadapted. This is because for most of each 24 hour period there is almost no pethidine in the CNS, so neuroadaptation does not become established. This means that there is no physiological withdrawal syndrome on stopping pethidine, even after prolonged, daily exposure. In contrast, repeated exposure to a long-acting opioid such as methadone ensures a significant degree of neuroadaptation, due to constant exposure to the drug. After about three to four weeks of daily dosing with methadone, a withdrawal syndrome occurs on discontinuing the drug.

1.3 Dependence

The most important concept relevant to opioid drugs is dependence. The key element in drug dependence is that drug use and drug seeking become self-perpetuating, dominant behaviour, displacing other activities, and producing harm to the individual.

Operational criteria have been developed to standardize the diagnosis of dependence.

Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following occurring at any time in the same 12-month period:

- (1) *Tolerance, as defined by either of the following:*
 - (a) *a need for markedly increased amounts of the substance to achieve intoxication or desired effect*
 - (b) *markedly diminished effect with continued use of the same amount of the substance.*
- (2) *Withdrawal, as manifested by either of the following:*
 - (a) *the characteristic withdrawal syndrome for the substance*
 - (b) *the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.*
- (3) *The substance is often taken in larger amounts or over a longer period than was intended.*
- (4) *There is a persistent desire or unsuccessful efforts to cut down or control substance use.*
- (5) *A great deal of time is spent in activities necessary to:*
 - (a) *obtain the substance (e.g., visiting multiple doctors or driving long distances)*
 - (b) *use the substance (e.g., chain-smoking)*
 - (c) *recover from its effects.*
- (6) *Important social, occupational, or recreational activities are given up or reduced because of substance use.*
- (7) *The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).*

Specify if:

With Physiological Dependence: *evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present).*

Without Physiological Dependence: *no evidence of tolerance or withdrawal (i.e., neither Item 1 nor 2 is present).*

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

Drug dependence is not an all-or-nothing phenomenon, but varies in severity between individuals, and over time. The presence of tolerance and withdrawal are the most reliable diagnostic features of opioid dependence. However, dependence is not equivalent to neuroadaptation. Some people are highly dependent on opioid drugs, preoccupied with drug seeking and focussed on when their next dose will be available, yet do not use opioids frequently enough to become neuroadapted. In contrast, some cancer patients taking high doses of morphine for pain are significantly neuroadapted, but have no other features of dependence.

1.4 Withdrawal

Symptoms of opioid withdrawal include:

Anorexia and nausea, abdominal pain, hot and cold flushes, bone, joint and muscle pain, insomnia and disturbed sleeping, cramps, intense craving for opioids.

Signs of opioid withdrawal include:

Restlessness, yawning, perspiration, rhinorrhoea, dilated pupils, piloerection, muscle twitching (particularly restless legs while lying down), vomiting, diarrhoea.

Spontaneous withdrawal has been described as objectively mild but subjectively severe. The physical signs of withdrawal are easy to overlook, but patients are often very distressed, and in severe withdrawal may lie curled in the foetal position. Their intense craving for opioids is related to the knowledge that a dose of opioid will alleviate distress, and is one reason why many subjects fail to complete withdrawal.

The onset and duration of withdrawal from opioids depends on the half-life of the drug being taken. For heroin, which is a relatively short acting drug, the onset of subjective symptoms of withdrawal is usually 8-24 hours after the last dose of heroin, reaches a peak at 24-48 hours, then resolves after five to seven days.

Withdrawal from a long-acting opioid such as methadone has a slower onset, usually 24-48 hours after the last dose. The peak severity of withdrawal tends to be considerably lower than for heroin withdrawal, but the withdrawal syndrome is more prolonged, with a debilitating low-grade withdrawal syndrome lasting three to six weeks.

Following the resolution of acute withdrawal, there appears to be a protracted, low-grade withdrawal syndrome lasting many months. These more chronic symptoms include anxiety, dysphoria, anhedonia, insomnia, and drug craving. It is probable that protracted withdrawal is one factor contributing to the high rate of relapse after detoxification from opioids.

Diagnostic Criteria for Opioid Withdrawal

A. Either:

- ▶ Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer).
- ▶ Administration of an opioid antagonist after a period of opioid use.

B. Three (or more) of the following, developing within minutes to several days after A:

- ▶ dysphoric mood
- ▶ nausea or vomiting
- ▶ muscle aches
- ▶ lacrimation or rhinorrhoea
- ▶ pupillary dilation, piloerection, or sweating
- ▶ diarrhoea
- ▶ yawning
- ▶ fever
- ▶ insomnia.

1.4.1 *Assessing the severity of dependence and withdrawal*

In clinical situations, it is often more useful to assess the severity of opioid withdrawal rather than simply to diagnose it.

Several questionnaires have been developed to provide standardized assessments of the severity of opioid dependence, and of the severity of opioid withdrawal. In general, these have primarily been used in research. However, rating scales can be of considerable value in clinical practice, particularly scales for rating the severity of withdrawal. There are three situations in which rating the severity of withdrawal is clinically useful:

- ▶ Assessing the need for symptomatic treatment in the management of withdrawal.
- ▶ Assessing the adequacy of doses of methadone or buprenorphine during induction.
- ▶ Assessing the response to a naloxone challenge test.

Withdrawal scales which assess both subjective and objective features of withdrawal are most useful. An approach which has been used by some practitioners in Australia, and which is simple and easy to use, has been the Subjective and Objective Withdrawal Scales (Handelsman). Copies of these scales are included in the appendices.

1.5 *Some specific opioid drugs*

Morphine is the prototypical mu (morphine) receptor agonist. Administered parenterally the onset of action is within minutes depending on whether it is administered intravenously, intramuscularly or subcutaneously. The half-life is 2-3 hours, but the duration of analgesia from a dose of morphine is 4-6 hours. With single dosing, the potency of oral morphine is about 1/6 that of parenteral morphine; with regular dosing, oral morphine is about 1/2 - 1/3 the potency of parenteral morphine. Morphine is primarily metabolized by conjugation. One metabolite, morphine-6-glucuronide, is an active metabolite. This compound is excreted via the kidneys, and can accumulate in renal failure, meaning that the dose of morphine needs to be reduced in renal impairment.

Naloxone is a pure mu-receptor antagonist, meaning it binds to the mu receptor but has no intrinsic activity. Naloxone antagonises the effect of opioid agonists. When an opioid antagonist is administered to an opioid dependent patient, the antagonist competitively inhibits any circulating opioids, reversing intoxication and causing a severe precipitated withdrawal syndrome. This is the basis of the use of naloxone in practice:

- ▶ Naloxone is used in emergency situations to reverse the effects of opioid overdose.
- ▶ Naloxone challenge test (Narcan test) may be used to establish the presence of opioid dependence.
- ▶ Naloxone may be used in the procedure rapid detoxification .

Due to high first-pass metabolism, naloxone is unsatisfactory for oral administration, and it is used either intravenously or intramuscularly. Naloxone has a short half-life (about 45 minutes). The short half-life has important implications in practice. If a patient overdoses on a long half-life drug such as methadone, a single injection of naloxone will rapidly reverse sedation and respiratory depression. However, within about one hour, the naloxone will be metabolized, while the long-acting methadone will still be present, and the patient is likely to lapse back into stupor and hypoventilation. The management of overdose on long-acting opioids is to establish a naloxone infusion, and observe people for a sufficient duration to ensure that the risk of respiratory depression is over before the patient is discharged. In the case of an overdose involving methadone, the patient should possibly be observed for a period of 24 hours and a naloxone infusion should be used to reverse respiratory depression.

Naltrexone is also a mu-receptor antagonist, devoid of agonist activity. (Although, for unclear reasons, naltrexone produces a degree of pupil constriction). Naltrexone is orally active, and has a prolonged half-life. The oral administration of 25mg of naltrexone will block the subjective and physiological effects of 30mg IM morphine, a blockade lasting more than 24 hours.

The capacity to antagonize opioids is the basis of naltrexone in relapse prevention. Administered to users who have been detoxified from opiates (either heroin, methadone or other) a daily dose of naltrexone will block (or at least markedly attenuate) the effects of administered heroin and will protect against re-establishment of tolerance.

Heroin (diacetyl morphine) is a potent mu receptor agonist. Administered intravenously, it is approximately 2.5 times the potency of morphine. Because it is highly lipophilic, it crosses the blood-brain barrier rapidly, producing very rapid onset of action after intravenous administration. The half-life of heroin is measured in minutes. It is rapidly metabolized to morphine, and after the initial action, has persisting morphine-like actions and duration of action. It appears in the urine as morphine and metabolites.

Like most highly lipophilic drugs, heroin is unsatisfactory for oral administration, as it undergoes extensive first-pass metabolism in the liver after absorption from the gut. It is used either by intravenous injection, by smoking, or by inhaling fumes from heating heroin on foil (chasing the dragon).

There is an intense initial flash following intravenous administration of heroin. Concomitant with this, inexperienced users almost invariably vomit, and even long-term users often do so. Following this initial euphoria, there is a prolonged (several hours) period of calm, contentment, often with sedation (on the nod). As an addict's tolerance increases, it requires higher doses to achieve the same initial intensity, and the duration and magnitude of pleasurable effects diminishes. It is not uncommon for an addict after a period of out-of-control heroin use to report that they find themselves using heroin just to feel normal. This experience indicates a high level of neuroadaptation. Between 8-12 hours after the last injection, the dependent user begins to experience withdrawal symptoms. Signs of withdrawal (pupil dilatation) appear about 12 hours after the last shot in highly tolerant users. Signs and symptoms of withdrawal increase in intensity over the following 48 hours, then diminish in intensity, resolving after about 5-7 days.

The commonest cause of death among heroin addicts is drug overdose. This is particularly a risk in heroin addicts who have undergone detoxification, as their tolerance is reduced. The mechanism of death in heroin overdose has recently been elucidated in several Australian studies. The most common finding is that heroin overdose usually occurs in the setting of use of other drugs, particularly alcohol and benzodiazepines. Having injected, patients lapse into a stupor, with marked hypoventilation. Patients are often rousable at this point, but are frequently noted to be snoring heavily. Even large doses of opioids by themselves do not produce motor incoordination or slurred speech. Some patients vomit, with aspiration of this vomitus common due to depressed gag reflex. Over a period of hours, sometimes several hours, patients develop pulmonary oedema (this is invariably present in fatal cases). While still alive many patients have been noted to be producing frothy sputum. In the presence of ongoing hypoventilation and pulmonary oedema, patients die of hypoxia.

Methadone parenterally is approximately equal in potency to morphine, and very similar in actions. Oral methadone is only marginally less potent than intramuscular methadone. Oral bioavailability is 80-95%. Oral methadone is slowly absorbed, with effects beginning about 30 minutes after administration, and peak effects being observed two to four hours after administration. The half-life of methadone with repeated dosing appears to be about 22 hours, but there is significant individual variation.

Administered to ex-addicts, methadone in a dose-dependent fashion reduces craving for opioids and attenuates the effects of injected opioids. The pharmacology of methadone is discussed in detail in later chapters.

Buprenorphine is described as a partial mu receptor agonist. 1mg subcutaneous (s.c.) buprenorphine produces similar subjective effects as 30mg s.c. morphine, or 30mg s.c. methadone. The duration of subjective effects (euphoria, sedation) of the 3 drugs is similar, but buprenorphine and methadone produce more prolonged pupil constriction than morphine.

Like methadone, buprenorphine in a dose-dependent fashion reduces opioid craving, and attenuates the effect of injected opioids. It has a prolonged terminal half-life, due to enterohepatic recycling. Like methadone, it is an effective drug in both detoxification and maintenance treatment. There are important pharmacological differences between methadone and buprenorphine which will be discussed in later chapters.

1.6 Dose - equivalence of opioid drugs

Practitioners need to be able to estimate approximately equipotent doses of different opioid drugs. A table of single dose analgesic equivalence is shown below.

<i>Single-dose analgesic equivalence</i>		
	Subcutaneous (mg)	oral (mg)
Morphine	10	60
Heroin	4	-
Methadone	10	20
Buprenorphine	0.3	1 (sublingual tablet)
Codeine	120	200

The analgesic dose equivalence table primarily reflects the peak activity of a single dose. However, in maintenance treatment, what is probably more important is not the peak effect, but the trough level achieved at the end of the inter-dosing interval. Because the opioids listed have very different half-lives, the total daily dose equivalents required for maintenance treatment differ considerably from single-dose equivalents.

<i>Maintenance dose equivalence (total daily dose)</i>		
	Subcutaneous (mg)	oral (mg)
Morphine	40	100
Heroin	16	-
Methadone	10	20
Buprenorphine	1	2 (sublingual tablet)
Codeine	-	600

<i>Assessment of intoxication with opioids</i>			
Moderate Intoxication		Marked Intoxication	
Drowsiness	Pupil constriction	Drowsiness	Shallow breathing
Conjunctival injection	Drooling	Poor circulation	Lowered temperature
Dizziness	Itching/scratching	Slow Pulse	Nausea & Vomiting
		Headache	Heavy snoring

Signs such as slurred speech and unsteady gait are more likely to reflect intoxication with alcohol or benzodiazepines than with opioids alone.

1.7 Pharmacology and addiction

Heroin is a short-acting drug, which when taken intravenously produces very high blood levels which rapidly subside. The majority of people using heroin regularly fluctuate between intoxication and withdrawal states. Several studies have demonstrated that current heroin users report high levels of dysphoria and background withdrawal symptoms. The rationale for maintenance with methadone or buprenorphine is that the long half-life and relatively stable blood levels of these drugs produce a steady state which allows the patient to function normally. Freed from the cycle of symptoms, the heroin user can develop normal interests and pursue a more healthy and productive lifestyle.

This process of stabilization has been elegantly demonstrated in research studies. Active heroin users were recruited to a research study in which they received either methadone or buprenorphine. On the initial day of treatment, at different times, subjects reported high withdrawal scores and high intoxication scores. These scores, reflecting the cycle between intoxication and withdrawal, fell progressively throughout the first week, to reach quite low levels by day 7. At that point, having reached reasonably stable blood levels, both intoxication and withdrawal symptoms were markedly diminished.

The analgesic action of opioid drugs involves more than abolishing pain. Opioid drugs are particularly effective in relieving the affective accompaniments of pain, such as fear and anxiety. This is why opioid drugs have traditionally been used as premedication before surgery, as they reduce apprehension and produce a state of calm. It is likely that in addition to abolishing the cycle of intoxication and withdrawal experienced by heroin users, opioid agonist drugs have an important effect in attenuating dysphoric moods.

Understanding pharmacology is critical in the treatment of addiction. However, the limitations of pharmacological solutions to addiction need to be borne in mind. It seems probable that even with maximum availability, with diversity in the programs and with flexibility in how it is delivered, treatment will only succeed in attracting, retaining and rehabilitating a limited proportion of heroin-addicted people. Many heroin users crave for elements of illicit drug use and its related life-style that treatment cannot provide. These include psychoactively exciting drugs (heroin, cocaine, etc.) injection mechanics and sensations, the social aspects and rituals of illicit drug use, and the routine and challenges of life as an illicit drug user. In particular, self-identification with the drug-using lifestyle is important for many people.

1.8 The medical use of opioid drugs

An early possibly the first published finding on medical use of opioids is a reference in the Ebers papyrus (approximately 1500BC) to the efficacy of opium to prevent the excessive crying of children. A millennium later, Galen, one of the seminal figures in the evolution of medicine, noted many more uses for opium, including the cure of such diverse ills as snakebite, deafness, epilepsy, asthma and jaundice.

It is hardly surprising that early in medical history, opium was identified as a virtual panacea, since there were few effective remedies. The capacity of opioids to relieve distress and promote a sense of well being remains unequalled to this day.

The capacity to produce this sense of well being — euphoria — is the basis of the recreational use of opioids, and presumably of their addictive potential. Although the phenomena of tolerance and withdrawal had been noted by some practitioners (and recreational users), it was not until the 1870s in the USA that the addictive properties of opioids began to attract widespread concern. Opioids were widely prescribed by medical practitioners during the latter half of the nineteenth century, and reports of iatrogenic addiction became increasingly common.

An epidemic of iatrogenic addiction in the late nineteenth century (USA)

The constant prescription of opiates by certain physicians .has rendered the habitual use of that drug very prevalent
(Dean of Harvard Medical School)

The habit in a vast majority of cases is first formed by the unpardonable carelessness of physicians, who are fond of using the little syringe, or relieving every ache and pain by the administration of an opiate
(Report to the Iowa Board of Health, 1885)

Quoted in Conrad and Schneider, 1992

In 1898, a major pharmaceutical company began marketing a synthetic opioid, heroin. It was presented as a non-addictive alternative to morphine, and was available for injection without prescription. Within a few years it became clear that heroin was addictive. Unlike morphine, which was used in the treatment of pain, heroin had been marketed solely as a treatment for addiction, and when this indication proved flawed, the drug fell from favour in the USA. (The spectacular failure of heroin as a cure for addiction has not deterred generations of researchers from continuing the hunt for the non-addicting opioid.)

It seems that at the turn of the twentieth century, the majority of people addicted to opioids in the USA were white, middle-class, middle-aged females, the majority of whom had been initially prescribed opiates by medical practitioners. However, attitudes to prescribing opioids hardened, and for complex reasons an increasing stigma grew around opioid use. These were the decades leading up to the Prohibition of alcohol in the USA, and moral and religious views of the harms of drug use were dominant. By the 1920s, the number of people using opioids had dropped dramatically, and the characteristics of the users had also changed — to marginalised, urban, young men. Addiction came to be seen as a social menace, strongly associated with deviance and criminality.

Medical practitioners' views of opioids also underwent a corresponding change. After decades of liberal prescribing, by the beginning of the twentieth century, medical textbooks were beginning to carry warnings of the addictive properties of opiates. Practitioners may have been slow to realize the problems caused by opioid dependence, but once it was recognised, the reaction against the medical use of opioids was profound. Prevailing medical attitude to opioid prescribing throughout most of the twentieth century has been labeled *opiophobia*. Opioids — which remain the major drugs for control of severe pain — were regarded as dangerously addictive, and were prescribed very sparingly. The consequence was undertreatment of severe pain, and considerable needless suffering.

Back to the future?

Interestingly, there is some suggestion that at the close of the 20th century, the medical profession was in the process of travelling full circle in relation to opioid prescribing. A century that began with an epidemic of iatrogenic addiction, then passed through 75 years of parsimonious prescribing and needless suffering, ended with an explosion of opioid prescribing. Opioid consumption increased dramatically in Australia during the 1990s, a trend noted internationally (Bell, 1998).

The impact of this upsurge in the medical use of opioids remains to be seen. However, the surge in opioid prescribing strongly suggests that all medical practitioners need the skills to use opioids effectively. It seems highly likely that the diagnosis and management of opioid dependence will be an increasingly common problem in medical practice.

1.9 Diversion and regulations

There is a thriving black market in pharmaceutical opioids in many parts of the world. Because the non-medical use of opioids is prohibited, and yet there is a substantial street demand for opioids, every doctor prescribing opioids must be aware that there is a risk that the drugs may be diverted to the black market. Many consumers become adept at manipulating medical practitioners to issue prescriptions. Even where heroin is readily available, there is a proportion of people who identify themselves as addicts and who maintain their habit on prescribed opioids. In some parts of the world, particularly where heroin is relatively unavailable, most addicts maintain their opioid habit by obtaining prescribed pharmaceutical opioids. For example, in New Zealand, during the 1980s, morphine and buprenorphine were the major drugs used by people presenting to detoxification units (Robinson, 1993).

There is therefore a valid public health basis for concern over inappropriate prescribing, and a need to differentiate between patients who are likely to divert drugs to the black market and those who obtain prescribed opioids for their own use. Towards this end, all Australian jurisdictions have similar regulations governing the prescribing of S8 drugs (drugs of dependence).

The aim of these regulations is to minimize the risk of diversion and uncontrolled use of S8 drugs. Unfortunately, a degree of confusion surrounds the terminology used in these regulations, which require practitioners to identify whether a patient is an addict. A medical practitioner can prescribe an S8 drug to anyone who is not an addict, at least for a period of two months. A doctor requires an individual patient authority to prescribe opioids continuously to any patient for a period of greater than two months.

If a patient is identified as an addict, an individual patient approval is required before a schedule 8 drug can be prescribed. In general, only authorized practitioners will be granted approval to prescribe methadone or buprenorphine in the treatment of addiction. In most jurisdictions, in order to become authorized prescribers, doctors have to satisfactorily complete a training program.

Clearly, the important clinical issue in determining whether a patient is an addict is trying to judge whether there is a risk of diversion, and/or whether the patient is

simultaneously obtaining prescriptions from multiple doctors. Such patients are probably best managed in a highly structured, dispensing program (supervised dosing). Indications for supervised dosing include:

- ▶ patients who are using street heroin
 - ▶ patients with evidence of current injecting drug use
 - ▶ patients with continuously escalating dosage requirements
 - ▶ patients who appear highly unstable — polydrug use, overdoses
 - ▶ patients over whom the practitioner has concerns — even if these are non-specific
- The prescribing doctor must always err on the side of caution.

In treating both pain and addiction:

The aim of prescribing opioids is to improve people's well being and functioning and to minimise harm to the individual.

The critical issue is whether prescribing opioids improves the experience and functioning of the patient, or whether it contributes to making them worse.

In those circumstances where there is a perceived risk that prescribed opioids will not be taken as directed, it is appropriate to dispense the drugs to be taken under supervision:

- in patients with recent or current use of street drugs
- in patients who are unable to regulate their use of opioids, and regularly take in excess of prescribed amounts (even though they have never bought or sold drugs illicitly).

Some of the hazards of opioid prescribing are illustrated in the following case history.

A case history

HM was a 31 year old woman who was referred for an assessment of her opioid use. She had a history of migraine from late adolescence. She had suffered a severe migraine approximately once a month for many years, until the age of 27. During those years, her health was good apart from problems of infertility, for which she was treated with the range of infertility treatment, culminating in several unsuccessful attempts at in-vitro fertilization. At the age of 27, she and her husband moved into a new suburb, and she came under the care of a new general practitioner. The general practitioner had a particular interest in migraine, as his own wife suffered from this condition. He made home visits to provide parenteral pethidine to several of his migraine-suffering patients. Within a few months of coming under his care, HM was experiencing an increasing frequency of severe headaches, which were now requiring pethidine at least once or twice per week. Over the next two years, she was referred to neurologists, but antimigraine treatment was ineffective. By the age of 30, she was experiencing daily severe headaches, receiving pethidine on most days, and taking large doses of oxycodone in an attempt to control her pain. By the age of 31 she lived the life of an invalid, lying in a darkened room most of the day, unable to perform any domestic duties. She reported that the only thing that gave her any relief was pethidine, and without it her life would not be worth living.

While it may be hypothesized that the patient's headaches became worse as a result of a change in underlying disease, it seems more credible to suggest that ready access to pethidine from a sympathetic, caring practitioner contributed to an escalating cycle of pain and dependence on opioids.

This case history illustrates the key difficulty associated with use of opioids — unlike adverse reactions due to other treatments, the development of dependence as a result of prescribing opioids is not likely to be brought to the doctor's attention.

For those interested in what happened to HM, the treatment agreed to — after prolonged discussions with her and her husband — was that she would undergo a rapid detoxification. Two previous attempts at conventional detoxification had been unsuccessful due to severe headaches. She was hospitalised, successfully detoxified using naloxone, and kept in hospital for several days to observe what would happen. During this time she was well, bright and optimistic — and headache free. Her husband commented that it was the best she had been in several years. However, on the day following discharge she presented to her general practitioner, who provided her with a prescription for oxycodone. She did not return for further specialist follow-up.

Doctors make most clinical decisions without access to large amounts of relevant information. Indeed, often all a doctor has to go on is what the patient in front of us chooses to present. If the patient has become dependent on opioids, and are fearful of losing access to these drugs, they may feel very reluctant to supply any information to reveal how bad things have become.

Many doctors respond to this situation by having a blanket policy of never prescribing opioids, for fear they may be being tricked or may inadvertently be doing harm. While this may avoid problems, it removes powerful and useful treatment from a practitioner's therapeutic armamentarium, and denies some patients access to appropriate care. **The aim of this manual is to help doctors use opioids in ways which minimize harm and maximize the benefits.** The skills and knowledge gained in treating opioid dependent people are an asset in all areas of clinical medicine.

Summary - prescribing opioids

Opioids are invaluable drugs in relieving pain and promoting a sense of well being.

Dependence on opioids (either illicit or prescribed) can contribute to a cycle of escalating distress, disability, and drug use.

It is unhelpful to distinguish between prescribing opioids long-term for treating chronic pain and for treating dependence. In both situations, the aim of prescribing is to contribute to rehabilitation by improving patients functioning and well being.

To minimize the risks and maximize the benefits of using opioids, they should only be prescribed in the context of a comprehensive assessment and treatment plan, with regular reviews of whether treatment is being beneficial.

Chapter 1 Self-assessment questions

Q1 Opioid withdrawal is characterised by which of the following?

1. Nausea and vomiting
2. Tremor
3. Dilated pupils
4. Hypertension
5. Restlessness

Q2 Opioid toxicity characteristically includes which of the following?

1. Ataxia
2. Drooling
3. Nausea and vomiting
4. Slurred speech
5. Snoring

See answers on page 42

2.1 Heroin addiction

From the time of prohibition of opioids, up until relatively recently, non-medical opioid use has tended to be mainly restricted to the young, socially excluded and disadvantaged individual. Though the preferred drug of use alters according to fashion, in recent years, heroin has been the drug of choice for most opioid addicts. Though there is a pharmacological basis to which drug is prone to misuse and dependence, addiction is also a socially determined phenomenon, and requires both a supply of, and demand for, the drug. Attempts at controlling supply through criminal sanctions have been confounded because the demand for opioids is sufficient to ensure that there are large profits to be made by those prepared to risk the legal consequences of supplying the drug.

Demand for heroin has social determinants. Impulsive and alienated young people lacking social supports and interpersonal skills are often drawn to drugs and to the addict subculture. High-risk behaviour, and involvement in delinquency and crime, is common in this population, often preceding opioid use. These adjustment problems are intensified, and their resolution made more difficult, by the development of addiction to heroin.

Involvement in the heroin-using lifestyle provides an unhappy and unskilled young person with more than merely pharmacological relief. It can provide a sense of identity, and it most certainly provides meaning and purpose. Life can become very focussed on cycling between intoxication and withdrawal, and the constant need to obtain money to buy drugs.

However, in recent years a new phenomenon has emerged in Australia and in the USA — the rise of what has been dubbed the middle-class addict. Whereas up to the 1980s, most heroin users presenting for treatment had poor education, few social skills and often disrupted relationships, increasingly people from seemingly stable, affluent backgrounds, with education and vocational skills, are presenting with heroin dependence. Whether this is a change in patterns of seeking help, or a genuine change in the patterns of heroin use in the community, is uncertain. However, there is also distinctive evidence that heroin use is increasing in prevalence in Australia (McKetin et al, 1999), making it more likely that we are witnessing a change in pattern of heroin use. Recent estimates are that there are around 30 - 50,000 dependent heroin users in NSW.

Dependence on heroin can have a range of adverse consequences, including:

Risks associated with the pharmacological effects of heroin

- fatal overdose
- drug dependence, and its associated psychological and social dysfunction.

Risks associated with intravenous injection and needle sharing

- blood-borne viruses
- infection due to non-sterile injection
- thrombophlebitis.

Risks associated with lifestyle

- diminished quality of life and well-being
- breakdown in personal and family relationships
- serious financial disadvantage
- involvement in crime and imprisonment.

It is not known what proportion of people who ever use heroin become dependent upon it. Some people apparently use heroin intermittently for many years without becoming dependent on the drug or experiencing serious problems in relation to its use. What is known is that **once established, dependence on heroin tends to be a chronic relapsing problem, with significant morbidity and mortality.** In any population of heroin dependent people, it is estimated that:

- 3-5% per annum will permanently discontinue heroin use
- 1-2% per annum will die, usually of drug overdose (Lynskey, 1998).

This mortality rate is about 17 — 35 times higher than the expected mortality rate for a population of young people. For most people, dependence is a long-term problem, characterised by multiple episodes of remission and relapse. Particularly during periods of physiological dependence on heroin, people are often highly dysfunctional, with disrupted personal relationships, increasing marginalisation, involvement in crime, and risk of disease and death.

The public health implications of heroin addiction are significant. The death rate from heroin overdose is rising alarmingly. Injecting drug use is the commonest cause of HCV transmission in the Australian community.

To date, there is no evidence that an episode of detoxification (or any other form of treatment) improves upon the rate of spontaneous remission from addiction and achievement of a stable, drug-free state. Although participation in treatment has not been demonstrated to increase the likelihood of eventual abstinence from drugs, this may reflect the difficulty of reaching rigorous research conclusions. What is clearly demonstrated is that treatment has many potential benefits — particularly, reducing mortality and improving quality of life.

Summary – heroin addiction

Heroin use and fatal heroin overdose are currently increasing in Australia.

The natural history of heroin addiction is that each year:

- ▶ 1-2% die (mostly of overdose).
- ▶ 3-5% achieve stable abstinence.

For the remainder, heroin addiction is a chronic, relapsing predicament with significant morbidity and risk:

- ▶ HIV, Hepatitis B and C transmission.
- ▶ Reduced quality of life.
- ▶ Disrupted family and personal relationships.

2.2 Multiple or polydrug dependence

Among dependent heroin users, multiple or polydrug drug use is common. An important part of managing injecting drug users is the identification and management of dependence on a range of drugs. The effects of the commonly abused types of drugs are summarised in the tables below.

<i>Acute intoxication states from commonly used drugs</i>		
Class of Drug	Intoxication	Overdose
Opioids (eg., methadone, heroin, morphine)	Constriction of pupils Itching/scratching Sedation/somnolence Lowered blood pressure Slowed pulse Hypoventilation	Loss of consciousness Respiratory depression Pinpoint pupils Hypotension Bradycardia Pulmonary oedema.
Alcohol	Relaxation Disinhibition Impaired coordination Impaired judgement Decreased concentration Slurred speech Ataxia Vomiting	Disorientation/confusion Respiratory depression Loss of consciousness Loss of bladder control
Benzodiazepines (e.g., diazepam, oxazepam, flunitrazepam)	Disinhibition Sedation Drooling Incoordination Slurred Speech Lowered blood pressure Dizziness	Stupor/coma Ataxia Confusion Respiratory depression
Stimulants (eg amphetamines, cocaine)	Hyperactivity Restlessness Agitation Anxiety/nervousness Great dilation of pupils Elevated blood pressure Increased pulse Raised temperature Sweating Tremor	Panic Acute paranoid psychosis Seizures Cardiac arrhythmia s Myocardial ischaemia Hypertensive crisis Cerebrovascular accidents Hyperpyrexia Dehydration
Cannabis	Relaxation Decreased concentration Decreased psychomotor Performance Impaired balance Conjunctival injection	Paranoid psychosis Confusion Agitation Anxiety/panic Hallucinations

<i>Withdrawal states from commonly used drugs</i>			
Drug class	Onset	Duration	Symptoms
Opioids	8-12 hours	Peaks 2-4 days Ceases 7-10 days	Anxiety, Muscle tension, Muscle and bone ache, Muscle cramps, Sleep disturbance, Sweating, Hot and cold flushes, Piloerection (goosebumps), Yawning, Lacrimation, Rhinorrhoea, Abdominal cramps, Nausea, Vomiting, Diarrhoea, Palpitations, Elevated blood pressure, Elevated pulse, Dilated pupils
Alcohol	As blood alcohol level falls:- depends on rate of fall and hours after last drink.	5-7 days	Anxiety, Agitation, Sweating, Tremor, Nausea, Vomiting, Abdominal cramps, Diarrhoea, Anorexia, Craving, Insomnia, Elevated blood pressure, Elevated pulse, Temperature, Headache, Seizures, Confusion, Perceptual distortions, Disorientation, Hallucinations, Hyperpyrexia.
Benzodiazepines	1-10 days depending on half-life	3-6 days	Anxiety, Insomnia, Muscle aching and twitching, Perceptual changes, Feelings of unreality, Depersonalisation, Seizures.
Stimulants	8-36 hours	Several days, occasionally 2-3 weeks	Lethargy, Depression, Irritability, Hyperphagia, Anhedonia, Dysphoria, Desire for sleep increased.
Cannabis	Usually days	Weeks	Irritability, Anxiety, Insomnia, Anorexia, Sweating, Muscle spasms, Headaches.

The onset and duration of withdrawal depends on the half-life of the drug. In general, drugs with short half-lives induce earlier onset, shorter duration, and often more severe withdrawal than long half-life drugs.

2.3 Medical conditions associated with injecting drug use

The major adverse consequences of heroin use are the risk of developing dependence, with loss of individual potential and disruption of social and emotional development and functioning. There is also a significant risk of death by overdose. Aside from these major health risks, most of the adverse medical consequences of heroin addiction relate to the **route of administration** of heroin. Intravenous injection of street drugs, particularly if it involves the sharing of injecting equipment, carries with it the risk of serious disease.

There are many consequences of intravenous injection of foreign material:

- ▶ Injection of pyrogenic material can lead to an acute febrile reaction lasting 24-72 hours, sometimes associated with rigours and jaundice. This is referred to as a dirty hit .
- ▶ More seriously systemic fungal and bacterial infections (including endocarditis) can result for non-sterile injection.
- ▶ The injection of crushed pharmaceutical tablets (many of which contain talc) can contribute to the development of talcosis — extensive deposits of talc in the pulmonary microcirculation, with granuloma formation and fibrosis.

However, the most common medical consequences of injecting drug use result from the sharing of injecting equipment — the transmission of blood-borne viruses.

2.3.1 *Human Immunodeficiency Virus*

The human immunodeficiency virus, the causative agent of AIDS, can be spread by needle sharing, sexual intercourse, and can be spread from mother to child in utero. In some cities around the world intravenous drug use is the major route of spread of this infection. Risk factors for injecting drug users to acquire HIV include frequency of injecting use, polydrug abuse, and involvement in high risk sexual practices.

Australia has been reasonably successful to date in containing the spread of HIV due to needle sharing. Seroprevalence for HIV is less than 5% among injecting drug users. The widespread availability of clean needles and syringes, the expansion of methadone programs, and a campaign to educate drug users, have probably all contributed to keeping the problem contained. Most injecting drug users are aware of the risks, and endeavour to avoid sharing needles, particularly with strangers. It is important that this success to date not be compromised by a relaxation of efforts to encourage people to avoid needle sharing to be aware of high risk behaviour - both sexual and drug use - which can lead to exposure to HIV.

Patients who are HIV positive should be referred for specialist assessment and management. Treatment of HIV infection is clearly effective in prolonging life.

2.3.2 *Hepatitis B (HBV)*

Hepatitis B can be transmitted by all body fluids from a person who is a carrier. In particular it is efficiently spread by blood to blood contact, such as occurs with needle and syringe sharing, but may also be spread by sexual contact and by household contacts. It can also be transmitted by breast feeding and is often transmitted perinatally.

Infection with the hepatitis B virus most commonly causes an acute hepatitis, usually two to six months after initial exposure to the virus. This disease is characterised by malaise, lethargy and jaundice, and patients may be quite unwell. Sometimes the infection is mild and subclinical.

Most HBV infections resolve within a few months. Between 1 and 10% of adults exposed to hepatitis B become chronic carriers (defined as hepatitis B surface antigen positive for greater than six months). About 4% of injecting drug users are chronic carriers: most other IDUs are immune to this virus, having been exposed but successfully clearing the infection.

The small proportion of IDUs who are not immune to hepatitis B should be offered vaccination. Injecting drug users who are chronic carriers of hepatitis B should be cautioned that they are potentially infectious, and their partners and household contacts should be offered vaccination.

Patients who are chronic HBV carriers are at risk of progression to cirrhosis and hepatocellular carcinoma. Patients with chronic HBV who have abnormal liver function tests should be referred for assessment at a specialist liver unit. Most liver units will offer treatment with alpha interferon to those injecting drug users who are abstinent from drugs, or stable on a methadone program and not continuing to use intravenously.

2.3.3 *Hepatitis C (HCV)*

Hepatitis C virus (HCV) is mainly transmitted by blood-blood contact, and by far the commonest mode of transmission in Australia is the sharing of needles by injecting drug users. Transmission by homosexual or heterosexual intercourse has been reported but appears to be unusual. Within 2 years of habitual injecting, a majority of drug users will have antibodies against HCV.

Infection with HCV occasionally leads to an acute hepatitis similar to hepatitis B. Much more commonly, however, it leads to a subclinical chronic infection. It is currently thought that of 100 people exposed to hepatitis C:

- ▶ 15-20 will clear the virus within about six months, but will have persisting antibodies to the virus for several months
- ▶ 80-85 subjects will go on to have long-term infection.

However, it appears that in a large proportion of those with chronic infection, particularly those who have contracted the virus through injecting drug use, the infection may not have serious consequences.

- ▶ Up to 60% of infected IDUs will have a positive antibody test but little or no evidence of liver damage after 20 years, suggesting a very indolent course of infection.
- ▶ About 20% of people infected will go on to develop cirrhosis of the liver, of whom about half will develop liver failure or hepatocellular carcinoma.

These figures are best estimates on available data, which seems to indicate that the course of HCV infection in IDUs is less adverse than in people who contract HCV through blood transfusion. Furthermore, the outcome after a further 20 years may show progressively more symptomatic liver disease.

HCV is the most common cause of liver disease in injecting drug users. It is usually asymptomatic, and infection is typically associated with fluctuating levels of transaminases, which may periodically be normal and then flare again. The severity of HCV infection is best determined by liver biopsy. While the outcome in most infected individuals appears reasonably benign, the public health implications of HCV are terrible. Given the very large number of people contracting HCV through injecting drug use, even if only 20% develop liver disease in the long term, this will be a major increase in serious liver disease.

A positive antibody test for HCV is generally an indicator of infection, rather than a marker of previous exposure and/or immunity.

While all factors influencing the severity of HCV have not been fully identified, alcohol abuse accelerates the liver damage associated with this disease. Alcoholic liver disease (often in conjunction with HCV infection) is the commonest cause of symptomatic liver disease in injecting drug users.

Treatment with interferon, sometimes with other anti-viral agents added, appears to be moderately effective, and three months of treatment induces remission of abnormal liver function in 60% of patients. Virological cure, however, is less common, and is probably achieved in less than 30% of cases. It is uncertain whether liver biopsy and interferon treatment should be recommended for people with hepatitis C and abnormal liver function tests. If they are still actively injecting drugs, it may be most appropriate to stabilize patients drug use and provide advice about how to protect their health — particularly:

- ▶ drink <20g alcohol per day
- ▶ immunize for Hepatitis A & B if patient is not immune
- ▶ eat a balanced diet.

In stable patients who are HCV positive and have discontinued drug use, and in any patient who expresses high levels of concern about being HCV positive, referral for assessment at a liver clinic may be appropriate.

2.3.4 Testing for blood-borne viruses

Which tests should you perform?

There needs to be a clear rationale for investigating for blood-borne viruses, rather than performing routine screening. Probably the best rationale for such testing is that it is performed in the context of a general health assessment, as part of comprehensive assessment, and as part of providing patients with important information about how to reduce health risks.

In patients who have not been previously tested, or not tested within the last 12 months and actively engaged in risk-taking behaviour, it is reasonable to offer testing for LFTs, HCV, HBV, and HIV.

Pre-test counselling

Testing for blood-borne virus infection should always be conducted with the patients informed consent. Informed consent requires basic pre-test counselling. In addition, counselling makes testing a more constructive intervention.

- ▶ Assess the patient s understanding of the disease(s) to be tested for.
- ▶ Assess the patient s knowledge of risk factors.
- ▶ Explore the patient s personal risk factors.
- ▶ Explain the implication of a negative test (particularly, that recent infection may remain seronegative for up to six months in HCV and three months in HIV).
- ▶ Explain the implications of a positive test.
- ▶ Ask whether the patient has any questions.

Post-test counselling

The interpretation of test results depends on the history of recent potential exposure, signs and symptoms of disease (such as a seroconversion illness, symptoms of liver disease such as fatigue, malaise, nausea, or signs such as enlarged liver or spleen). If there is uncertainty about the meaning of tests, if patients are highly anxious, or if patients have unexplained symptoms, referral for specialist assessment may be appropriate.

2.4 Psychiatric comorbidity

Psychiatric comorbidity or Dual diagnosis are labels referring to the situation in which a drug user has a psychiatric diagnosis additional to a diagnosis relating to substance abuse.

This is an important and difficult area of medicine, for two reasons:

- ▶ firstly, the diagnosis of a range of psychiatric disorders can be difficult in the presence of drug dependence
- ▶ more importantly, there are often problems in service delivery due to poor coordination between Mental Health Services and AOD services.

Most drug users who seek entry to methadone programs are leading dysfunctional lives, with disrupted relationships and disturbances of mood. Often, such disturbances appear to be a consequence of drug dependence and the drug-using lifestyle, and improve after a period of stabilisation on methadone. However, in some patients there are persistent deviations in mood and cognition which warrant a further psychiatric diagnosis. Such patients require further assessment and treatment if they are to derive the full benefit from methadone maintenance or other forms of treatment for drug abuse.

Psychiatric services tend to see the patients as having primarily a drug abuse problem, and are reluctant to accept them for treatment. Drug abuse treatment agencies tend to assume, not always correctly, that the problems will improve with treatment for drug abuse. It is therefore important for practitioners to be aware that there is a high incidence of psychiatric comorbidity among methadone patients, that for certain diagnoses it is important to recognise and to treat these problems. It is necessary to identify treatment resources or referral lines able to assist in the management of these patients.

In the circumstance where a patient with a major mental illness seeks entry to methadone treatment, such a person may not be in a position to provide informed consent, and requires prompt psychiatric treatment before re-evaluation of the appropriateness of methadone.

Major co-existing psychiatric syndromes

A range of psychiatric diagnoses is common in patients using illegal drugs. This population has about seven times the incidence of a psychiatric disorder than the general population. Where there is an effective treatment, treatment for the associated psychiatric diagnosis often leads to markedly improved functioning and less relapse to illegal drug use. Perhaps most importantly, accurate psychiatric diagnosis can identify patients who need and are likely to benefit from psychotherapy as an adjunct to methadone maintenance.

Opioid-dependent individuals are approximately:

- ▶ 24 times more likely than the general population to have antisocial personality disorder
- ▶ 13 times more likely to have an alcohol dependence or abuse problem
- ▶ 9 times more likely to have schizophrenia
- ▶ 5 times more likely to have a diagnosis of depression
- ▶ 3 times more likely to have a diagnosis of anxiety.

Diagnosis of all forms of personality disorder is difficult, and much of the behaviour associated with illegal drug use is antisocial behaviour. Much of this antisocial behaviour disappears when drug use stops. Nonetheless, taking into account the lifetime history of behaviour and using careful diagnostic criteria, a high proportion of male opioid users meet the diagnostic criteria for antisocial personality disorder (ASPD). This is not a particularly helpful diagnosis to make, as there is no specific treatment. The hallmarks of this diagnosis - difficulty in forming sustained and meaningful relationships, impulsiveness, and lack of empathy as reflected in little remorse over harming others — mean that establishing a relationship with these patients can be challenging. Given the intense dysphoric moods and impulsiveness of patients with ASPD, it is possible that medication with methadone is in itself helpful in stabilizing patients with the disorder.

Depression may contribute to, may be caused by, or may exacerbate problems of opioid dependence. It may be quite independent of opioid dependence. Some cases of depression resolve with methadone maintenance. However, there is reasonable evidence that methadone maintenance patients with a diagnosis of depression respond well to psychotherapy, and improve in overall functioning compared to untreated patients.

One major health benefit of engaging patients in maintenance pharmacotherapy is the opportunity this presents to provide patients with health information, and to address specific co-morbid medical and psychiatric conditions.

Assessment of psychiatric conditions should generally follow a period of stabilization in treatment, and attention to concomitant drug use.

Chapter 2 Self-assessment questions

Q1 Concerning heroin addiction, which of the following is/are true?

1. The commonest cause of death among heroin users is HIV infection.
2. In a cohort of heroin users, 3-5% will achieve stable abstinence in any given year.
3. Between 30-50% of dependent heroin users in Australia are HCV antibody positive.
4. Treatment of psychiatric comorbidity can improve the outcomes of MMT.
5. The prevalence of heroin addiction is declining in Australia.

Q2 Withdrawal from which of the following drugs can cause seizures?

1. Alcohol
2. Heroin
3. Benzodiazepines
4. Amphetamines
5. Cannabis

See answers on page 42

3.1 Harm reduction

For complex historical reasons, abstinence from all drugs has historically been the principal goal of treating heroin dependence. Doctors (and the community) often assume that anyone using heroin must want to stop. However, many people prefer to continue using drugs, even despite problems resulting from their drug use. For many drug users there is a fine balance between the appeal of continuing to use drugs and the advantages offered by entering treatment. One of the most difficult lessons for practitioners and for the community is that drugs work for addicts .

It is a lesson reinforced by the chronic, relapsing nature of addiction, and the low rate at which people with established dependence problems achieve abstinence. On the basis of this, rather than aiming solely for abstinence, treatment should aim to reduce the harmful consequences of drug use, and improve people's social functioning and well-being. These are important and achievable goals of treatment which do not require abstinence from all drugs. This approach to treatment has been labelled harm reduction.

The goal of any health intervention is to improve the quality of life. As with other health problems, there are a number of means to this goal, which include, but are not restricted to, abstinence oriented therapies. Unfortunately, the means is often confused as the goal.

Some people have difficulty with harm reduction. For people with a moral or religious commitment to abstinence, any evidence that addicts have difficulty in stopping drug use is seen as providing the heroin user with excuses, and undermining the likelihood of recovery. Individuals with this belief argue that it is more important to send the right message (that abstinence can and should be achieved) than to acknowledge the research evidence regarding the natural history of dependence. This evidence indicates that most heroin-dependent individuals will have a prolonged period of time using heroin, perhaps interspersed with episodes of abstinence, some periods of sporadic heroin use, and periods of heavy, dependent use. For most, addiction is a chronic relapsing condition, with periods of remission followed by relapse. The practitioner's role is to increase the periods of remission and to reduce the harm during the periods of relapse.

Drug misuse fractures a person's social integration. Often drug users are friendless and jobless, increasing their social exclusion. This compounded with a history of profound childhood deprivation (even amongst the wealthier addicts) leads to the picture of an isolated, bored person with very low self-esteem. Treatment aims to address and for some to redress these and to enable the patient gain some control over their lives. For many, it is not even to reinstate a previous high functioning state, as most drug users began their habit before they were able to set up the networks and develop the lifeskills that would carry them forth. Therefore, treatment must teach these people basic social, educational and life skills necessary to integrate them into their society.

There are many ways short of abstinence which reduce the harm associated with drug use. Indeed, as in many areas of medicine, the aim in treating addiction is not to achieve cure but to prevent disease progression and to promote rehabilitation and social reintegration.

Medical Rehabilitation

The maintenance of health, the restoration of function, and the palliation of symptoms are the major challenges in dealing with all chronic diseases and disabilities. Maintenance treatment with methadone (and other drugs such as buprenorphine) are examples of medical rehabilitation. Such treatment aims to restore well-being and social functioning to individuals disabled by addiction.

Many patients are not ready or able to take advantage of the respite and stability offered by treatment, continuing psychoactive drug use, and making limited lifestyle changes. It is important to take a long perspective. The critical issue is judging whether the unstable patient is better off remaining in treatment, finding another form of treatment, or returning to street heroin addiction.

3.2 The public health frame of reference

Traditionally, treatment services have focused on the well-being of those in treatment. Since the advent of the HIV epidemic among injecting drug users, and the realization that injecting drug use is the primary mode of transmission of HCV, much of the support for methadone treatment has come from the perception that it is one crucial component of the public health response to transmission of blood-borne viruses.

Methadone treatment has another public health contribution to make, in that by stabilizing injecting drug use, and bringing patients into contact with health services, it allows for provision of a range of health care interventions for a marginalised population. Health issues include such diverse issues as antenatal care of pregnant women, management of chronic psychiatric disorders, and treatment of injecting site infections.

Public Health Function

The medical treatment of addiction has a public health role:

- ▶ reduction in transmission of blood-borne viruses
- ▶ improved access to health care for a marginalised population.

The public health frame of reference challenges some of the traditional assumptions made in treatment programs. Programs which seek cure for the small number of motivated individuals may compromise treatment of the much larger number of patients who find — often to their own frustration — that abstinence is difficult to achieve, and even harder to sustain. The many patients who drop out or fail in abstinence-oriented treatment have been labelled unmotivated or not ready for change. Their failure to benefit was seen as the patient's failure, rather than a failure of the treatment. A public health perspective shifts the focus away from individual addicts and onto the overall effectiveness of programs. If there is a high drop-out rate from treatment, there is little point blaming those who drop out for being unmotivated — this simply avoids admitting that the treatment is not being very effective. A program which retains more patients and reduces the risks and harms associated with continuing drug use, can have a greater public health benefit.

3.3 Attitudes, values and assumptions in the treatment of addiction

Within methadone programs, the paradoxical consequence of focusing on cure has been that those programs least tolerant of heroin use in treatment, and most oriented to abstinence, actually achieve worse individual treatment outcomes.

This finding is a reflection of the impact which practitioners attitudes and beliefs can have on the outcomes of treatment. The challenge in treatment is to promote rehabilitation and improved functioning, by working with the patients and their aspirations rather than trying to manage them or control their behaviour. This approach requires establishing a therapeutic, non-judgmental relationship with patients.

This can be difficult for many practitioners, as there is profound community fear and disapproval of drugs and drug addiction. It is difficult to provide support and encouragement to patients who evoke dislike and disapproval. The temptation to challenge patients, to insist that they must change, permeates treatment services. Illegal drug use is conceived in a moral or legal framework. The promotion of zero tolerance of drug use makes it difficult to sustain tolerant, accepting, non-judgmental treatment of addiction. Health professionals are far from immune to community attitudes — indeed, one reason for becoming a medical practitioner is the wish to have a respected role in the community. It is difficult for practitioners to integrate their personal disapproval of addicts and addiction, while working therapeutically with addicted individuals. One result is that there is an uneasy amalgam of punishment and treatment in many programs.

Attitudes to drug use are not something which can be adopted for therapeutic convenience. Many health professionals wisely avoid becoming involved in the treatment of drug dependence precisely because they recognise that their disapproval of drugs makes it difficult for them to work therapeutically with addicted individuals. What is less easy to understand, and far more problematic, is the occasional practitioner who elects to treat heroin addicts with methadone despite disapproving of this form of treatment and disliking the patients. **Such an approach is a recipe for an unhappy practitioner and less than optimal treatment outcomes.**

And for practitioners who sometimes have bad days, and periods when treatment seems frustrating, in short, for everyone involved in treatment of dependence, it can be helpful to remember that there is an impressive evidence base for the effectiveness of methadone treatment (which will be briefly reviewed in coming chapters). Sticking to the evidence and avoiding unrealistic expectations is essential for anyone seeking to practice good medicine.

The attitudes and beliefs of practitioners have a major impact on treatment outcomes. Practitioners with an orientation to abstinence alone rather than other treatment goals, particularly those who do not tolerate any heroin use, are likely to have:

- ▶ poor retention in treatment
- ▶ paradoxically, more heroin use in treatment, than practitioners who are oriented to providing care for patients over the longer term, and have non-judgmental attitudes towards drug use.

3.3.1 *Stigma*

The difficulties which most health professionals experience in relation to methadone treatment is an example of the powerful stigma associated with drugs and addiction.

Stigma impacts on treatment at every point.

- ▶ Many heroin users themselves share community attitudes, and keep striving for the acceptable outcome of abstinence rather than entering methadone treatment
- ▶ Practitioners involved in delivering treatment may express their negativity to drug users through punitive and exploitative approaches to treatment
- ▶ Communities and administrators feel more comfortable with highly regulated treatment, expressing punitive attitudes through restrictive and inflexible program rules
- ▶ Political and community support for methadone treatment is inconsistent.

The stigma associated with addiction is a powerful indication that those in the community who are anxious to send the right message about drugs have in fact been devastatingly successful:

- ▶ Heroin is feared.
- ▶ Those who use it are disliked.
- ▶ Those who treat heroin addiction tend to find themselves professionally marginalised.

Stigma probably deters many people from experimenting with opioids, and may therefore be seen as having a public health role (although this is difficult to assess).

The downside of stigma is that those who do succumb to heroin addiction find their plight intensified, and rehabilitation more difficult, as a result of being stigmatised and marginalised.

3.4 **The components of effective treatment**

Treatment of addiction is an example of behavioural medicine — medicine which addresses a person's medical problems in the context of their relationship to society and their personal aspirations. Conceptually, it is helpful to divide behavioural medicine into 4 components.

3.4.1 *Provision of information*

The simplest component of treatment is to provide patients with information.

Providing information seems so simple that it is often overlooked. Furthermore, it is not a straightforward activity, but is an acquired clinical skill. It is important to keep information clear and simple, and to reiterate important issues. Often, it is useful to provide written information to back up explanations.

Information is one cognitive component of treatment. Some examples of basic information which all prospective patients (and current patients) should receive are:

- ▶ treatment options and alternatives
- ▶ risk factors for transmission of HIV and other infectious diseases, and how those risks can be minimized
- ▶ side-effects of methadone and other drugs used in treatment
- ▶ the importance of an adequate dose
- ▶ information for family members (important in view of stigma associated with MMT).

The above examples are relatively straightforward factual information. However, provision of information can be much more sophisticated. Every time a competent and diligent practitioner takes a comprehensive history from a patient, they are not only gathering information — they are also providing it, by reflecting it back to the patient. Many individuals come to treatment after a prolonged period of chaos, and seem unwilling or unable to see what is happening to them and their lives (hence the oft-repeated statement that addiction is a disease of denial). By taking a detailed psychosocial and drug use history, it is possible to reflect back to the individual what has been happening to them over a period of months or years. This is a valuable therapeutic activity if handled sensitively. Information about drug use and the effect it is having on a person's life appears to be a far more powerful a therapeutic tool than insight into why a patient is using drugs.

During assessment, and in reviews during treatment, the doctor aims to get to know the patient, and the patient sees him/herself from the clinical perspective. This process is facilitated by relevant, empathic history taking by the practitioner.

Sometimes, provision of information involves assisting patients and their families to see and understand addiction and its treatment better. Information is one valuable way to address stigma. By reframing addiction and treatment, using explanations that avoid guilt and blame, by refuting the idea that willpower is all that is required, practitioners can enhance treatment effectiveness.

3.4.2 *Relief of symptoms*

Forms of treatment which provide symptomatic relief are more likely to attract and retain patients than treatment which provides little or no symptomatic benefit. Inpatient detoxification provides sanctuary from the rigours and uncertainty of life on the street, and relief from withdrawal distress. Methadone maintenance provides relief from cycle of intoxication and withdrawal, and relief from the insecurity of dependence on illegal and expensive drugs. It probably also provides attenuation of intense dysphoric moods, particularly anger and frustration, often experienced by heroin users. The large numbers of former heroin addicts continuing to take methadone for prolonged periods is a strong indication that the drug is valued by patients, who endure stigma, expense, and irksome treatment requirements, to continue to have access to a daily dose of methadone.

The importance of symptom relief is clearly demonstrated in the powerful effect of methadone dose in improving treatment outcomes. Doses far higher than are needed to block withdrawal are required for effective maintenance in most patients.

3.4.3 *Therapeutic relationship*

An important component of effective methadone treatment, and of many other interventions for dependency problems, is the establishment of a therapeutic relationship. The basis of a therapeutic relationship is for clinicians to be experienced as working with the patient, rather than on them, or, even worse, against them. The patient needs to experience acceptance and validation, rather than objectification or rejection. For many trained in primary care medicine this therapeutic relationship is central to their work. Establishing a longitudinal relationship, which is broad based (involving the social, psychological and physical) and involving the family, is the bed rock of primary care

practice. The more chaotic or damaged the individual, the more important it is to develop this relationship.

While it is not possible to completely spell out the nature of a therapeutic relationship, it can be characterised in the following terms:

Empathic	not	Judgmental
Accepting	not	Punitive
Validating	not	Objectifying
Clear and explicit	not	Vague and implied
Consistent	not	Inconsistent
Collaborative	not	Controlling

Despite aiming for collaborative relationships with patients, there are frequently circumstances where it is essential for safe and effective treatment to set clear limits on what is acceptable, limits which may lead to conflict with patients. The basis for a good therapeutic relationship is to have set clear limits on what constitutes acceptable behaviour, ensure patients are informed of the limits, and to enforce the limits when they are transgressed. Such clarity and consistency is just as important in fostering a therapeutic relationship as empathic and accepting attitudes.

The common assumption in treatment services that the goal of treatment is abstinence from all drugs is one factor which can compromise the therapeutic relationship. While this is a valuable goal, there are many worthwhile goals, notably, reduction in drug use, reduced risk-taking behaviour, improvements in quality of life, which can be compromised by insisting on the optimal treatment outcome of abstinence.

Most heroin users have long histories of experiencing rejection, and punishment. This experience entrenches their alienation and sense of antagonism. Treatment is an opportunity to provide them with a different experience - of safety and containment instead of confrontation and rejection.

It is often said that many drug users are manipulative. This label reflects the extent to which doctor and patient have different goals; when the patient wants something different from what the doctor is willing to offer, the patient is perceived as manipulative. Doctors need to become sensitive to such interactions, and to use the clinical interview to spell out what the patient is seeking, and what the doctor is willing or able to provide.

Many drug users are challenging to work with, as they do overturn the normal doctor-patient relationship, built on trust and respect. Drug users may lie, be manipulative, push boundaries, and test relationships. The skill of the practitioners is to acknowledge these and to work with the patient in spite of them, in fact to use these assumptions in the consultation.

The provision of a daily dose of methadone in itself is an important validation. Instead of negating the addict's subjective awareness that drugs are very difficult to give up, methadone treatment affirms the validity of their need for drugs. This is a liberating experience for people who have found that drugs work for them, but have been told repeatedly that they are expected to do without them.

The concepts of **transference** and **countertransference** can be useful in understanding what takes place in interactions between doctor and patient. Transference refers to the feelings a patient has towards the practitioner, and the assumption that the patient brings issues from their previous experience — such as anger and conflict with authority figures — and transfers them to the therapeutic relationship. Such patients often appear to seek out conflict, and can be difficult to work with. Countertransference refers to the feelings which the practitioner has about the patient. For example, some patients make us angry or arouse feelings of antipathy. It is important to recognise and acknowledge countertransference, otherwise we are likely to act on these feelings by behaving in ways which are not helpful.

3.4.4 *Structure*

Structure refers to the behavioural component of treatment - the way treatment is organised. In all approaches to treatment, this fundamental aspect is easily overlooked. Such issues as frequency of attendance, the use of appointments, dealing with people who present late, payment of fees - all these policy and procedural issues, and the way in which they are handled, are important aspects of treatment, which can influence treatment outcomes.

In methadone treatment, one important structural issue is daily attendance for dosing. During the early phases of treatment, the requirement to attend daily for dosing under supervision is probably important for many people. It provides an alternate structure to the daily routine of drug dealing, and provides the basis for a relationship between the patient and the person dispensing methadone. By minimizing the risk of diversion, injection, and taking erratic quantities of drug, it makes treatment safer. Although some patients find daily attendance irksome, others acknowledge that safety from the temptation to sell or inject doses is appreciated. It needs to be remembered that for people with little sense of control over their lives, externally imposed controls such as daily attendance for dosing can be a valuable component of treatment.

However, while it is important early in treatment, daily attendance for dosing is unnecessary for people who are stable and functional; for these patients, daily attendance for dosing can become an obstacle to social reintegration. Therefore, as with all aspects of treatment, it is important to individualize the structure of treatment.

Summary - the components of treatment

- ▶ Provision of information
- ▶ Symptom relief
- ▶ Therapeutic relationship
- ▶ Structure

A case history

MP was a 36 year-old man who had been on methadone maintenance for 12 months. He was quiet, compliant, and never complained. He was on 40mg/day of methadone. His was submitting one urine test per week, on a day chosen at random by the clinic, and for the previous 6 months all his urine tests had been positive for methadone only. He attended a review interview with his methadone doctor, who at the time was inexperienced. Noting that he seemed to be doing well in treatment, the doctor asked MP how he occupied his time. MP replied that most days, after picking up his methadone, he caught a train to the local harbour, and spent the day fishing. The doctor (who, like most doctors, worked a 60-hour week), became irritated, and suggested forcefully to the patient that he should look for a job, as it was no life for anyone to sit around doing nothing. The patient was visibly distressed by the interview, which ended with the doctor rationalizing the tension between himself and the patient with the thought that the patient needed to be confronted.

From that week onwards, for the next 10 weeks, every urine sample submitted by MP tested positive for morphine. The doctor noted this with mounting dismay, but although he felt sure that his confrontation had triggered the relapse to heroin use, he was unsure what to do. Then, abruptly, the urine tests became consistently negative for morphine again.

At a further review interview about a month later, the doctor indicated to MP that he felt bad about the previous interview, and apologised. He went on to ask MP why, having relapsed to regular heroin use for 10 weeks, he had stopped using heroin again. MP replied that he had been seen by a research assistant, who was conducting a survey of patients at the clinic, and had interviewed him about his use of heroin. As he reported how much he was spending on heroin to the researcher, he thought to himself This is ridiculous , and resolved to stop using — which he did.

This case history (which, like all the case histories in this manual, is a real case), illustrates a crucial lesson — trying to push people to change is much less effective than providing them with information which can be a basis for their own decision to change.

This is a painful lesson which everyone involved in treatment of drug problems must learn. Indeed, it is helpful to paraphrase the AA slogan - the first step in becoming an effective practitioner in Addiction Medicine is to admit that we are powerless over our patients.

3.5 Treatment options

A range of options exists for treating opioid dependence. These include detoxification, outpatient and day patient programs, therapeutic communities, and self-help groups. Maintenance approaches to treatment will be considered in the following chapters.

3.5.1 Detoxification

Spontaneous withdrawal from opioids is not life threatening. Occasionally subjects with severe vomiting and diarrhoea may become dehydrated. Episodes of acute psychosis in patients with a history of schizophrenia have been reported. Some people harm themselves during withdrawal distress. However, serious adverse events are uncommon, and the majority of dependent heroin users have been through multiple episodes of withdrawal, without any symptomatic treatment.

Detoxification is the process of providing symptomatic relief to assist patients to complete withdrawal and avoid adverse events associated with withdrawal.

Withdrawal is often seen as the major barrier to discontinuing drug use. However, contrary to the hopes of patients, families, and health professionals, assisting people to complete withdrawal is not usually followed by long-term abstinence from opioids. The great majority of subjects who undergo detoxification will return to heroin use within the next 12 months (usually, within the next month).

There has always been considerable consumer demand for detoxification. Patients are fearful of withdrawal, particularly after periods of heavy heroin use. Most commonly, patients present to detoxification services in times of crisis. Almost all people in this situation report wanting to become long-term abstinent. However, many detoxified patients, having reduced their neuroadaptation, resume at much lower levels of heroin use. Often, for many months after an episode of detoxification, heroin use remains substantially lower than before entry to treatment. Thus, while initially aiming for abstinence, a good outcome for some patients is that detoxification interrupts a heavy period of heroin use, allowing them to reduce their level of tolerance and regain — at least for a time — a degree of control.

Those patients who after an episode of detoxification continue in some form of treatment — counselling, naltrexone, or maintenance with methadone — appear to do better than those who do not.

The goals of an episode of detoxification may be summarized as:

- ▶ reversing (or at least reducing) neuroadaptation to opioids
- ▶ promoting patient's involvement in post-detoxification treatment.

To promote these objectives, detoxification services:

- ▶ provide symptomatic relief during withdrawal
- ▶ prevent the occurrence of adverse events (such as dehydration, psychotic decompensation, and minimizing the risk of overdose post-detoxification).

Even an unsuccessful episode of detoxification, in which a patient continues to use heroin, can be the basis for an effective longer-term intervention if the patient takes up methadone or buprenorphine maintenance treatment rather than simply dropping out and continuing heroin use.

3.5.2 *Outpatient and day patient programs*

Outpatient and day patient treatment is offered in several settings - by private and state practitioners, public hospitals and community services. The interventions provided vary widely. Counselling services may be a useful adjunct to methadone maintenance for some patients, and the availability of counselling and support services has been shown to improve treatment outcomes in some studies.

3.5.3 *Therapeutic communities*

These are generally long-term residential programs which are highly structured. They are often based around principles of self-help although many of these programs are now using other interventions such as relapse prevention, motivational interviewing and cognitive-behavioural approaches to drug dependence. Therapeutic communities are often staffed by program graduates although many also employ academically qualified clinicians.

Therapeutic communities attract and retain a relatively small proportion of heroin users. Those who remain longer in treatment have improved post-treatment outcomes compared to those not receiving treatment.

3.5.4 *Self-help groups*

Narcotics Anonymous (NA) is a self-help group for people who identify themselves as being addicted to drugs. It is based on the same principles, of recovery through the development of spiritual awareness, as Alcoholics Anonymous (AA). It has similar approach to meetings, and principles, as AA. Self-help groups are generally highly accessible, continuous over time and confidential.

Answers to self-assessment questions for section 1

Chapter 1	Q1. 1, 3, & 5 Q2. 2, 3 & 5
Chapter 2	Q1. 2 & 4 Q2. 1 & 3

THE MEDICAL TREATMENT OF OPIOID DEPENDENCE

Previous sections of this manual have provided the background information — about opioid drugs, heroin addiction, and treatment approaches — which underpins clinical practice. The remainder of this manual deals with how to put this information together in clinical management of opioid-dependent individuals.

CHAPTER 4: **ASSESSMENT**

Assessment is the basis of treatment of people with drug-related problems.

4.1 The objectives of assessment

There are three objectives in performing an assessment:

1. Clarification of the nature and severity of the patient's problems (for both clinician and patient).
2. Formulation of problems and, if appropriate, development of an initial treatment plan.
3. Establishment of a therapeutic relationship.

Clarification of the nature and severity of a patient's problems can be surprisingly complex and subtle. Particularly at the first interview, prospective patients are often wary and give little information away. This is one reason why, although often referred to as the assessment interview, assessment is an ongoing process which may take several interviews to be completed.

The critical issues which need clarification are:

What is the patient requesting or wanting?

- ▶ Is the patient opioid-dependent?
- ▶ What is the current level of neuroadaptation?
- ▶ Is the patient dependent on or using other drugs?
- ▶ What is the motivation for seeking treatment or a change in circumstances?
- ▶ Is there significant coexisting medical or psychiatric comorbidity?
- ▶ What are the patient's social and emotional supports?
- ▶ What are the patient's social and interpersonal difficulties?
- ▶ Are there significant others in the patient's environment who are relevant to treatment?
- ▶ What is the patient's understanding of his/her condition?
- ▶ The nature of treatment alternatives, and patient's understanding of them.

Formulation of problems is the process of taking a focused history from the patient, and reflecting the information back, summarizing the salient features. In addition, at this stage it may be appropriate to propose a treatment plan.

Throughout the interview, by listening courteously and empathically, by relating respectfully to the patient, the practitioner can begin the process of **establishing a therapeutic relationship with the patient**. The best way to do this is to focus on the relevant, concrete concerns the patient has, and provide the information they need to understand and participate in the treatment process. In doing so, it is important for the doctor to demonstrate an accepting, non-judgmental approach to patients, being neither authoritarian nor overly intrusive.

For the prospective patient, the assessment interview is often a time of great vulnerability and expectation. The decision to seek treatment is frequently taken at a time of crisis. In the case of people seeking entry to methadone treatment, this problem is confounded because many patients feel ambivalent about maintenance treatment, and entering treatment may be marked by a sense of failure and guilt. Despite this ambivalence, patients usually appear preoccupied with whether and when they will be allowed to receive methadone or buprenorphine. **Such focussing on access to the drug is characteristic of drug dependence**. Unless this issue is dealt with fairly early in the interview, it is difficult to establish any rapport. Once opioid dependence is confirmed, the patient can be reassured about their eligibility for methadone and issues such as treatment alternatives, program rules and procedures, side-effects of methadone, can be discussed more meaningfully.

At the initial interview, in order to ensure their access to treatment, some patients will (probably not unreasonably) say whatever they think their doctor wants to hear. For this reason, it is not often appropriate to set specific treatment goals at the initial interview, as patients tend to nominate unrealistic expectations of what they will achieve from treatment.

The initial interview should not normally aim to complete a comprehensive assessment, but should focus on the issues relevant to initiating treatment, leaving detailed assessment to subsequent interviews.

4.2 The content of assessment

Most practitioners use a fairly structured approach to assessment, (just as most practitioners use a structured approach to a medical history). The standard approach to assessment in Addiction Medicine is set out below.

- Assessment comprises six domains:
1. Presenting problem and motivation for treatment
 2. Drug use history and severity of dependence
 3. Medical and psychiatric history
 4. Psychosocial history
 5. Examination
 6. Formulation and development of an initial treatment plan

4.2.1 *Presenting problem and motivation for treatment*

Generally the patient will express a reason for attending — a request for methadone treatment, a request for detoxification, perhaps a request for benzodiazepines to help get through withdrawal, or perhaps just a non-specific request for assistance. However, not uncommonly, a patient will be brought in by parents or partner, and express no reason for coming. On other occasions, a patient may attend on the advice of his/her solicitor, and is seeking treatment in order to present this information to a magistrate at an upcoming hearing. All these may be valid reasons for initiating treatment. However, it is helpful, in order to establish an open, collaborative basis for treatment, to clarify such issues.

Having established at the outset of the interview why the patient is attending, it is generally helpful to go into a history, drug use, psychosocial history, medical and psychiatric history, and then towards the conclusion of the interview, to return to the issue of motivation for treatment. Many practitioners find the technique of motivational interviewing helpful. Armed with a fresh history of drug use and attendant problems, it is useful to ask the patient what are the good things about using drugs, and what are the bad things. By balancing the advantages and disadvantages of drug use, the interviewer encourages the patient to reach his own judgment as to whether treatment may offer advantages over continued drug use. It is also useful to identify two separate dimensions related to change: How important is it for the person to change and how confident are they about changing. For example, some people are very confident that if they wanted to change they could, but they do not see it as important to change. For others, change is very important but they are not confident about their ability to initiate and maintain change. Clearly, the focus of intervention may be influenced by these dimensions. There is little to be gained by convincing a patient that change is important when the major barrier is their confidence about change.

4.2.2 *Drug use history*

- ▶ Primary drug of concern:
 - current average daily use
 - route of administration
 - duration current pattern of use
 - age of initiation, episodes of abstinence, overdoses
 - diagnosis and severity of current dependence
 - history of previous treatment.
- ▶ Other drugs used
 - currently
 - other current drug dependence
 - previous drug use.
- ▶ History of treatment for drug problems.
- ▶ All drugs used in last 3 days
 - hours since last drug use.
- ▶ A urine test may be useful to corroborate history.

4.2.3 *Medical and psychiatric history*

Comprehensive medical and psychiatric assessment is best left until a patient has been stabilized in treatment, by which time many psychiatric symptoms may be resolving, and patients are in a better position to benefit from counselling regarding blood-borne viruses.

At the initial interview, the critical issue is to focus on medical and psychiatric issues which may impact on the choice of treatment, or on the patients capacity to give informed consent to treatment. These include:

- ▶ pregnancy
- ▶ HIV, hepatitis B and C infection
- ▶ major or unstable medical conditions (eg decompensated liver disease, heart disease)
- ▶ unstable psychiatric conditions (eg active psychosis, severe depression with suicidality, mentally disordered)
 - psychiatric history, current and previous treatment
 - symptoms of depression (depressed mood, sleep disturbance, suicidal ideation, suicide attempts, anhedonia)
 - symptoms of anxiety (panic attacks, social phobia).

Once a patient is stabilized in treatment, attention to medical issues and psychiatric issues should be more detailed. This should include counselling with or without testing for blood-borne viruses, advice re smoking and diet. It should include advice about dental care, as methadone has anti-cholinergic side-effects and can reduce salivary flow, dry mouth, increasing the risk of caries.

4.2.4 *Psychosocial history*

The psychosocial history is an attempt to understand the patient s experience of their life and their social interactions. It covers the patients report of their:

- ▶ family of origin — relationship with parents and siblings, early experience, schooling, age of onset of problems
- ▶ relationships (partners) — current relationship, length of previous significant relationships
- ▶ education
- ▶ employment record, current employment, sources of income
- ▶ involvement with the criminal justice system
- ▶ living circumstances.

The psychosocial history provides a context by which to understand the patient. Otherwise, it is terribly easy to fall into the usual medical assumption that the outcome of treatment depends on three factors:

- ▶ the diagnosis (and severity of the condition)
- ▶ skill of the practitioner
- ▶ the effectiveness of available treatment.

The outcome of treatment of drug dependence is more likely to be determined by the patient s social circumstances — in particular, whether they are in a stable relationship, have employment, or have a supportive family.

4.2.5 **Examination**

Mental state examination and focused physical examination are valuable components of assessment.

Physical assessment, at this stage, should focus on the issues relevant to opioid dependence.

- ▶ Inspection of injecting sites, to document the presence and severity of vein damage.
- ▶ Documentation of signs of intoxication and withdrawal.
- ▶ Inspection for jaundice and other stigmata of chronic liver disease.
- ▶ Nutritional status, especially a record of weight.

Occasionally, further examination may be indicated if suggested by medical history.

Mental state examination is performed by the experienced clinician throughout the assessment interview, although in some cases formal examination may be indicated. At assessment, the practitioner should document:

- ▶ mood (eg depressed, elated, reactive, euthymic)
- ▶ affect (eg appropriate, hostile, seductive, bizarre)
- ▶ cognition (clouded, paranoid, thought disordered).

Testing attention, concentration and memory may be indicated.

4.2.6 **Formulation**

The most crucial aspect of assessment is putting together the information obtained. This is a highly skilled activity, requiring clinical judgment and sensitivity on the part of the interviewer.

Sometimes, formulation is relatively straightforward, and leads without difficulty into a treatment plan acceptable to both patient and practitioner. At other times, formulation is confusing, and no clear treatment option seems acceptable. Some brief sketches will help to illustrate how putting information together can be more or less straightforward.

Case 1.

PT is a 34 year old male who presents requesting to be placed on methadone treatment. He reports using heroin since age 18, and a pattern of use on most days since age 20. He has had 3 admissions for in-patient heroin detoxification, and spent 2 months in a residential rehab when he was 27. He has supported his habit through property crime, and has served 3 prison terms. He was last released from prison 5 months ago, at which time he was abstinent from drugs. However, he resumed heroin use 2 months after release, and has been using 1-2 shots daily for the last month. He reports he wants to go on methadone because he can see he will end up back in gaol soon if he does not do something. He has no charges pending. He lives alone, and has never been in a long term relationship. He has no contact with his parents. He is employed on a casual basis loading trucks at the Fruit Markets. Apart from heroin, his only other drug use is cannabis and tobacco.

He reports that his last use of drugs was 4 hours before the interview, when he injected \$25 worth of heroin. On examination, he has pinpoint pupils, evidence of long-term and recent vein damage in his left cubital fossa, but no other findings.

This brief sketch suggests a long history of opioid dependence, with a (verifiable) history of long-term problems associated with heroin use (previous episodes of detoxification, evidence of injecting sites), evidence of harm associated with heroin use (forensic history), and evidence of recent opioid use (signs of intoxication). However, the history also suggests that the patients current level of tolerance is not high, as 4 hours after injecting \$25 of heroin he continues to have pronounced signs of intoxication. This would be consistent with the patients stated use of 1-2 shots of heroin daily over the last month.

In developing a treatment plan for this patient, there is a strong argument that methadone maintenance is the treatment most likely to be of assistance. He has few social supports (other than his employment, which is tenuous), and despite several attempts at abstinence has always relapsed to heroin use. Therefore, his request for methadone treatment seems very appropriate, and the next step in formulation is to convey this to the patient. The program philosophy and objectives, and policies and procedures, need to be briefly explained (preferably, written material being provided for him to take home). If he consents to treatment as explained, the appropriate state registration needs to be completed, dosing arrangements finalised, and a starting dose of methadone determined. (This will be discussed in the section Induction onto MMT).

Case 2.

PH, 26 year old man, presented with his mother, requesting to be placed on naltrexone. He stated that having used heroin and been in trouble with the law for some years, he had been on methadone for 14 months, and was currently on 120mg/day. On this dose he felt well, and was not using heroin or other drugs. He was not troubled by side-effects. He was not working, was in no relationship, and lived at home with his mother.

He explained that his reason for wanting a change was that, although he found methadone helpful, and felt he had a good relationship with his doctor, he felt it was not really curing his addiction. A couple of months earlier, he had started to reduce his methadone dose with a view to coming off. But when his dose got down to 80mg/day, he began using heroin again, and began stealing. With the same bad luck that had always dogged his criminal career, he was arrested, charged, and was currently serving a period of home detention. (This news briefly perturbed the doctor, but PH explained that he had permission to attend the clinic for a medical appointment). He went back up to 120mg/day of methadone, had again stopped heroin use, but he felt the whole incident demonstrated clearly that being on methadone had not fixed his problem. He thought he should try naltrexone.

This history perplexed the doctor, who explained that as he understood it, methadone seemed to have worked very well, abolishing heroin use and leaving PH feeling well and, indeed, untroubled by side-effects. Methadone only began to fail when the patient started to withdraw.

This brief discussion at first appeared helpful. PH looked mightily relieved, and began to relax. He agreed that remaining on methadone was the best course of action. He smiled, stood up, extended his hand and said Thanks very much, doctor — at which point his mother, who had been sitting in the room throughout the interview without saying a word, also stood up and said bitterly Thanks for nothing and strode out of the room. Embarrassed, her son hurried after her.

Only at the end of the interview did the critical issue emerge — it was in fact the young man's mother who wanted a change of treatment. Indeed, it may well have been her who originally pressured him to reduce his dose from 120mg/day. This history is quoted here to illustrate the importance of not always taking a request at face value.

This was a particularly sad case, as there was a sequel to it.

Nearly 18 months later, PH was admitted to hospital with endocarditis. He reported that he had remained on methadone without problems for some months after the interview above. Then, abruptly, his mother had died of a heart attack. PH lost the plot, dropped out of methadone, and returned to full on heroin use. Within a few months was back in gaol. He did not use heroin during his 6 months in gaol, but on release resumed heroin use, and within a couple of months fell ill — with, as it turned out, bacterial endocarditis. He was recommenced on methadone in hospital.

4.2.7 **Child protection in methadone treatment**

One factor which must be borne in mind during assessment of the drug-dependent patient, and throughout treatment, is the clinical and statutory obligations in relation to the abuse and neglect of children.

Child protection is one of the most difficult issues to address in treatment of drug dependence.

The NSW Child Death Review Team 1998-1999 Report estimated that drugs and/or alcohol directly or indirectly contributed to nearly 25% of all child deaths notified to the coroner in the period January 1996 to June, 1999 (p75).

An earlier Victorian report also noted that a significant proportion of child deaths were deaths of young infants from parental neglect in the context of parental drug dependence. The Victorian report commented (The pattern) was of a very young child, born prematurely and/or drug dependent, discharged home, sometimes on a court order, sometimes not. The custodian was in a number of cases drug dependent or otherwise led a chaotic lifestyle and was objectively incapable...of adequately looking after a vulnerable young child.

The NSW report identifies some of the reasons for the association between parental drug use and abuse and neglect of children.

Risk factors for abuse and neglect of children:

social isolation	poverty
domestic violence	parental mental illness
parental personality disorder	involvement in drug-using networks
single parenthood with serial partners	criminal activity
inadequate support networks	

NSW Child Death Review Team 1998-1999 Report (p85).

The report also points out that substance-dependent parents are more likely to use medication to alleviate discomfort or distress in their children, and that the rate of overdosing of children in these families is higher than expected.

All readers should be cautioned against assuming that all drug-dependent parents are incapable parents. However, there is a responsibility on all practitioners treating drug-dependent patients to be alert for the possibility of abuse and neglect of children. There is a statutory obligation to notify children at risk.

Chapter 4 - Self-assessment questions

Q1 A 26-year-old man presents with a small, non-fluctuant area of redness and induration in his left antecubital fossa. On questioning, he tells you that he is a regular heroin user, and has been using for four years. He is a self-employed carpenter, has had no trouble with the law, and uses about \$50 per day of heroin in one or two injections. He says that the heroin use is ruining him financially, but he has not been able to cut down. He has never previously sought treatment, but has tried to stop for himself. His longest period of abstinence in the last four years is about 6 weeks. His wife knows that he used to use drugs, but thinks he is currently clean. He is very anxious that she may leave him if she finds out he is using.

Which of the following statements is/are correct?

- This man is opioid dependent.
- He should be advised about treatment options.
- He should be advised of the risks of injecting drug use.
- He should be referred for marital counselling.
- He should be advised to undertake detoxification.

See answers on page 121

Methadone is available in Australia in three formulations:

- ▶ 5mg and 10mg tablets, for use in pain management
- ▶ two formulations of methadone syrup, each 5mg methadone per ml of syrup — which are the only forms of methadone available for treatment of addiction.

Only medical practitioners authorised to use methadone in the treatment of addiction can prescribe methadone for this purpose, and then only to patients for whom they have an individual patient authority.

An exception to this blanket regulation is made in NSW and some other states, such that opioid-dependent individuals who are admitted to hospital for acute medical or psychiatric treatment may be treated with methadone prescribed by hospital medical staff. This allowance is made in recognition of the fact that opioid withdrawal can seriously compromise management of hospitalised patients, and that it is inhumane to withhold treatment. In these circumstances, it is suggested that an experienced clinician be consulted over the use of methadone and the appropriate dose (which may need adjustment in the light of coexisting medical conditions).

5.1 Pharmacology of methadone

Oral methadone is slowly absorbed, with effects beginning about 30 minutes after administration, and peak effects being observed 2-4 hours after administration. Methadone is metabolized in the liver, to inactive metabolites. A proportion of methadone is excreted in the urine, and acidification of the urine can marginally increase methadone clearance. However, most reports indicate that the dose of methadone does not need to be adjusted in renal impairment.

Methadone is stored in fat and in the liver. The first dose is significantly sequestered in adipose tissue, meaning that the blood level achieved after the initial dose is significantly lower than achieved after the second dose. The half-life of methadone with repeated dosing appears to be about 22 hours. This means that the administration of a stable dose of methadone leads to progressively higher peak blood levels for the first 5-6 days of treatment. After approximately 5 half-lives, steady state is reached, and a single daily dose maintains a reasonably stable blood level in most patients.

The important clinical implication is that the first dose of methadone achieves considerably lower blood levels than subsequent doses. In palliative care practice, some practitioners recommend titrating the initial dose of methadone against the patients response (analgesia), then administering half the dose on the following days, to avoid producing toxicity. All practitioners prescribing methadone must be aware that if toxicity is going to occur, it is most readily observed 2-3 hours after the first, second or third dose.

There is considerable variation in methadone metabolism:

- ▶ If a patient metabolizes methadone slowly, with repeated dosing the level of methadone in the blood (and tissues) rises progressively and much more steeply than in a patient with more rapid metabolism. Such a patient receiving his first dose of methadone may appear fine, but after the second dose becomes more intoxicated, and after the third dose even more so. It is possible that slow metabolism, and resultant progressive accumulation, may contribute to fatal toxicity during induction into treatment.
- ▶ If a patient metabolizes methadone rapidly, the variation between peak and trough level is wider, and this may be the basis for therapeutic failure. Instead of pharmacological stability, such patients may fluctuate between symptoms of intoxication and withdrawal.

However, despite many years of research into methadone treatment, the role of therapeutic drug monitoring in optimizing the benefits of treatment has not been established. It has been suggested that for successful methadone maintenance, trough methadone levels (the blood level 24 hours after the last dose) should be greater than 150 or 200ng/ml. However, research on this is very limited. In practice, it is seldom helpful to measure blood levels, and more useful to raise patients' doses when they appear to be doing poorly. Despite reports from a few practitioners that some patients require very high daily doses of methadone (in excess of 200mg/day), there is no systematic research to support doses greater than 100mg/day.

Long term use of methadone leads to partial tolerance to all effects. Symptomatically, constipation and increased sweating often continue to be troubling, and some patients are troubled by sexual dysfunction with higher doses. Methadone has slight anti-cholinergic side-effects, producing a reduction in salivary flow, and this may contribute to accelerated caries in patients with poor dental hygiene.

Methadone reduces craving for opioids and attenuates the effects of injected opioids. These effects are dose-dependent, with higher dose producing greater reduction in craving. The regular administration of methadone for greater than 3-6 weeks produces neuroadaptation and physical dependence. Thereafter, abrupt discontinuation of methadone is followed by an objectively mild but prolonged and symptomatically troubling withdrawal syndrome.

Patients on a stable dose of methadone develop sufficient tolerance that cognitive skills and attention are not impaired. They are able to drive cars safely. However, during the initiation of treatment, when the dose is being raised, patients should be warned of possible impairment of concentration, and hence reduced driving skills.

5.1.1 Drug interactions with methadone

Methadone is primarily metabolized to an inactive metabolite via the P-450 isozyme 3A4. Other isozymes involved in methadone metabolism are 1A2 and 2D6. Some drugs which inhibit the relevant enzymes can inhibit methadone metabolism, resulting in significantly higher blood levels of methadone. Enzyme-inducing drugs can convert methadone to a relatively short half-life drug, compromising the effectiveness of treatment.

Drugs causing higher methadone levels include:

- ▶ SSRIs (especially fluvoxamine).
- ▶ Ketoconazole.

Drugs causing enhanced methadone metabolism (may precipitate withdrawal):

- ▶ Anticonvulsants (phenytoin, carbamazepine, and barbiturates induce metabolism; Valproate is the anticonvulsant of choice for patient on methadone).
- ▶ Rifampicin.

Many psychotropic drugs potentiate the actions of methadone:

- ▶ Benzodiazepines and other CNS depressants potentiate the sedating and respiratory depressant effects of methadone. The commonest finding in cases of methadone toxicity is that a combination of benzodiazepines and methadone is involved.
- ▶ Tricyclic antidepressants can also potentiate the effects of methadone.

5.2 Side-effects of methadone

Most patients on methadone are troubled by two common side effects:

- ▶ sweating
- ▶ constipation.

Patients need advice on diet and fluid intake to deal with these side effects, which are generally more of a nuisance than a barrier to remaining in treatment. Other side effects include:

Sexual dysfunction

Many patients on methadone experience reduced libido. Males may experience impotence and difficulty ejaculating.

Withdrawal symptoms

About 1/3 of patients on methadone experience symptoms which are similar to withdrawal — generalised aches and pains, restlessness and lack of energy, dysphoria. These symptoms are difficult to interpret, as they may coexist with signs and symptoms of opioid intoxication, such as constricted pupils and constipation. Patients with signs of withdrawal need dose increases. However, the optimal way to respond to these symptoms in the presence of signs of opioid effects is unclear. Some patients may respond to dose increases.

Sleep disturbance

Some patients report sleep disturbances while on methadone. This is difficult to interpret, in view of the prevalence of sleeping difficulties and the multiple factors which can contribute. There are some reports of disturbed sleep architecture on methadone.

It is unclear how to respond to this. As it is the sedating property of methadone which disrupts sleep architecture, benzodiazepines may well exacerbate this problem. Some patients report that if they take methadone late in the day, they have difficulty sleeping.

A small proportion of predisposed subjects may develop a degree of obstructive sleep apnea, a rare but important and treatable cause of morbidity.

Dental caries

Methadone has anti-cholinergic side-effects, which lead to a slightly dry mouth. This is one factor which may contribute to accelerated caries. Patients should be advised on measure to promote oral hygiene. Those with symptoms of dry mouth can be advised to chew sugar-free gum.

5.3 Use of methadone

Short term courses of decreasing doses of methadone may be used to manage withdrawal from heroin. However, the use of methadone in withdrawal has largely been abandoned in Australia, for a variety of complex historical reasons which have little to do with the efficacy of the drug. Essentially, practitioners working in detoxification often have a strong commitment to abstinence as the goal of treatment, and have regarded methadone with suspicion, believing (probably correctly) that people offered methadone for detoxification will frequently decide that they would prefer to remain on it as a maintenance treatment. Practitioners working in methadone maintenance treatment have discouraged patients from using methadone in detoxification, believing (probably correctly) that patients were far better going into long-term maintenance. Thus, primarily for reasons of service orientation, methadone has not usually been used in detoxification.

Methadone maintenance treatment involves the daily administration of an oral dose of methadone for an indefinite period.

There are two approaches to providing methadone:

- ▶ dispensing programs, in which patients are required to attend a clinic or pharmacy and take their dose under supervision
- ▶ prescribing programs, in which patients receive a prescription from their doctor, have it made up by a pharmacist, and take the drug home to use without supervision.

Dispensing programs have less risk of patients taking methadone while intoxicated with other drugs, less risk of injecting methadone, and less risk of diversion to the black market. They are the appropriate structure for heroin addicts new to treatment, and for those who remain unstable — injecting drugs, continued links to drug markets, abusing other types of drugs, not achieving improvements in social functioning and social reintegration.

However, for patients who have been in treatment for prolonged periods, particularly those who have made significant improvements in social functioning, the continued requirement to attend daily for dosing becomes a barrier to rehabilitation rather than a factor contributing to it. For such patients, a more relaxed structure such as a prescribing program may be more appropriate. However, at present in Australia the only alternative to daily supervised dosing is the provision of limited take-home doses for patients judged to be at low risk of diverting their medication.

5.3.1 *Objectives of methadone treatment*

In his early experiments in which heroin users were regularly administered a variety of opioid drugs, Vincent Dole described how addicts maintained on morphine appeared apathetic, preoccupied with when their next dose of morphine was due, and constantly requested increasing doses. In contrast, those maintained on methadone ceased being focussed on when their next dose was due, or how much drug they would receive, and became interested in other, everyday activities. What Dole was describing was a lessening in the level of dependence in individuals maintained on high dose methadone - paradoxically, while highly neuroadapted to opioids, patients on methadone treatment exhibit less severe dependence. The most important aim of treating dependent patients is to return to them a greater degree of autonomy and flexibility in their lives.

With any treatment, it is important to identify objectives against which the effectiveness of treatment can be measured.

Some of the objectives of methadone treatment are:

- ▶ to reduce heroin use by patients
- ▶ to improve the health and well being of patients
- ▶ to reduce patients risk of blood-borne viruses (HIV, HBV and HCV)
- ▶ to reduce deaths associated with heroin addiction
- ▶ to facilitate normal social functioning of patients.

Treatment can contribute to these objectives in many ways. The pharmacological stability offered by substituting an oral, long-acting opioid for an injectable short-acting one is not the only beneficial change on entering treatment. In recent years clinical trials have demonstrated that for some heroin addicts, the medical supply of heroin can also be an effective therapeutic intervention. This outcome is a reminder that there is more to treatment than pharmacology. Supplying a drug in a treatment context is a dramatically different activity from supplying the same drug in an illegal street drug market: the setting is safer, the drug cheaper, the supply more controlled. The role of the consumer changes, from being an autonomous agent to being a participant in treatment. All these changes can contribute to rehabilitation and social reintegration.

For some heroin users, simply substituting a less expensive, reliable source of supply will resolve many of the problems associated with heroin use. For many, the greater stability from a long-acting, oral preparation is an essential therapeutic ingredient. And for many people seeking treatment for heroin addiction, substantially more intervention — involving psychosocial, medical and welfare assistance - may also be required.

Summary —pharmacological advantages of methadone.

- ▶ Orally active.
- ▶ Long half-life with slow changes in blood level.
- ▶ Reduces craving and withdrawal.

5.4 The effectiveness of methadone maintenance treatment

5.4.1 *Methadone-assisted rehabilitation*

Convincing evidence of the efficacy of any treatment relies on randomized, controlled trials (RCT).

The first RCT of methadone treatment involved 32 prisoners who, prior to release, were randomized to methadone or to a no-treatment group (Dole, 1969). Four subjects randomized to MMT did not enter treatment, leaving a treatment group of 12. At 12 months, none of the MMT patients had returned to daily heroin use, where all 16 in the no treatment group had done so. Only 3 of the MMT patients had returned to gaol; all 16 in the control group had done so. Even on an intention-to-treat analysis (that is, including the 4 who did not enter treatment), the dramatic reduction in heroin use and crime witnessed in the treatment group was statistically significantly better than results in the no-treatment group.

A placebo-controlled, RCT of MMT in Hong Kong recruited 100 consecutive subjects eligible for MMT (Newman, 1979). All subjects were stabilized on 60mg/day for 2 weeks, then randomized to either placebo or continued methadone. Over the next 3 years, four times as many people were discharged for persisting heroin use in the placebo group. At 3 years, 56% of MMT subjects were retained in treatment, compared with 2% in the placebo group. Thus this study confirms the better retention and reduced heroin use in people treated with methadone.

The third controlled trial of MMT was performed in Sweden, and involved subjects being randomized to MMT or to drug-free treatment (Gunne, 1981). In effect, the control group received no treatment, as none accepted drug free treatment. MMT patients received intensive psychosocial support as well as methadone, and could remain in residential treatment for up to 6 months. Sequential patients were randomized to the two groups until significant differences in outcomes became detectable. This occurred after 36 subjects, 17 of whom received MMT. Thereafter, those who had entered the trial were followed for 2 years. The differences between treated and control groups were dramatic. At the end of that time, 12 out of 17 MMT subjects were not using heroin regularly, and were employed or undertaking education. The remaining 5 subjects had been discharged from the program for continuing drug abuse. Two subjects were excluded from the control group as they entered MMT in another program. Of the remaining 17, 1 was drug free, 12 were abusing opioids, 2 were in gaol and 2 were dead.

The importance of this small trial is that it demonstrates that when coupled with intensive psychosocial rehabilitation, MMT can dramatically improve social reintegration.

These studies are now dated, and took place in settings rather different to the 1990 s. However, more recent studies continue to replicate these results. A randomized trial of interim methadone demonstrated significantly lower heroin use in the group receiving methadone, compared to a wait-list control group (Yancovitz, 1992).

Evidence from a large scale observational study in the USA supports and extends the findings from these randomized trials. The Treatment Outcome Prospective Study (TOPS) followed more than 11,000 illicit drug users who commenced treatment between 1979 and 1981 (Hubbard, 1989). The three major modalities of treatment for heroin addiction were studied - MMT, residential therapeutic communities, and drug-free outpatient counselling.

The key findings from this massive study were that patients in all modalities reduced their drug use during treatment, and reduced their involvement in acquisitive crime. Outcomes were expressed relative to the group of patients who left treatment after less than 1 week — essentially, a no-treatment reference group. At follow-up interviews, patients remaining in long term MMT had about 1/4 the prevalence of regular heroin use, and about 1/3 the prevalence of acquisitive crime, compared to this reference group.

The TOPS study was also able to demonstrate that the longer people remained in treatment (of any modality), the less likelihood of regular heroin use or involvement in acquisitive crime after discharge. Relative to those who left treatment within a week, regular heroin use post discharge was significantly lower only in patients who had remained in treatment

for at least 12 months. Given the importance of retention in treatment, a key finding of the TOPS study was that MMT had the best retention of all treatment modalities.

5.4.2 *Long-term medical sequelae*

Extensive follow-up of methadone patients has confirmed that long term administration of methadone does not produce adverse health consequences (Kreek, 1991).

5.4.3 *Methadone is a maintenance intervention*

The protective effect of MMT on mortality among heroin users only persists while people remain in treatment, and, indeed, mortality is increased in the 12 months after leaving treatment (Zanis, 1999). The explanation for the increased risk is that a large proportion of patients who leave methadone treatment relapse to opioid dependence. For example, in John Ball's large observational study from North America, 82% of subjects who left treatment had relapsed by 12 months (Ball and Ross, 1991). A reasonable proportion of subjects who leave treatment in a planned fashion, with the support of clinic staff (who judge the patient is appropriately leaving treatment), are able to remain abstinent from opioids after leaving treatment. However, most patients who drop out of treatment relapse to heroin use.

5.4.4 *Death*

Several studies have demonstrated that a heroin addict's risk of death is reduced by entering MMT (and, indeed, rises again after leaving treatment). However, studies have also clearly demonstrated that the first week of MMT is a period of increased risk of fatal overdose. The common factor in such deaths is patients receiving doses of methadone greater than their level of existing opioid tolerance. In most cases, drugs other than methadone have also contributed to toxicity.

Measures to minimize this risk involve:

- ▶ careful assessment to ascertain level of dependence and identify risks of multiple drug use
- ▶ supervised induction into treatment, with assessment of the patient's response to methadone
- ▶ provision of information about the effects of methadone, and the risks of multiple drug use
- ▶ judicious dose increases early in treatment.

These measures are discussed in detail in the clinical section of this manual.

In addition to the risk of deaths of patients in treatment, one adverse consequence of methadone treatment is risk of deaths related to diversion of methadone. Up to 2/3 of deaths associated with MMT occur as a consequence of diversion of methadone to persons not in treatment. The presumed source is takeaway doses; a study in Sydney found that black-market methadone was almost entirely (88%) diverted takeaway doses.

SUMMARY

Methadone retains people in treatment, reduces use of heroin, reduces risk of death and disease, and reduces involvement in crime.

Repeated randomized trials have demonstrated that methadone is more effective than either placebo or no-treatment.

Observational studies confirm that methadone maintenance has the best retention in treatment of all modalities of treatment of heroin addiction.

Methadone is a maintenance intervention, with lasting benefits only observed after a minimum of 12 months treatment, and greatest benefits observed so long as people remain in treatment.

The long-term administration of methadone does not have adverse health consequences.

5.5 Consumer perspectives on methadone treatment

Consumers and potential consumers are often the most stringent critics of methadone treatment. A guide to the concerns patients have about treatment comes from a UK survey of patients on methadone, who identified the following concerns:

- ▶ methadone is addictive, and that being on it increases or prolongs their dependency on drugs
- ▶ methadone detracted from their quality of life
- ▶ poor quality of treatment delivered in some methadone clinics.

Surveys of heroin addicts not in treatment revealed the perception of the methadone patient as locked into a drug using, static lifestyle. This is the essence of criticism of MMT that while taking methadone, patients are still addicted, both in still taking a drug, and, more broadly, in still living a lifestyle revolving around drug use.

There are two important questions which need to be asked about MMT, and which are relevant to concerns that MMT may prolong addiction. Firstly, does MMT impede patients from achieving a drug-free state? Secondly, does MMT reduce the long-term likelihood of meaningful social rehabilitation?

These questions were investigated in a paper which reviewed several long-term follow-up studies to assess whether MMT impedes eventual attainment of abstinence from opioids (Maddux and Desmond, 1992). From 5 follow-up studies of patients entering MMT, they found the percentage of patients voluntarily abstinent from opioids ranged from 9-21%. From 6 follow-up studies of patients treated in drug-free treatment, the percentage voluntarily abstinent ranged from 10-19%. These figures are remarkably similar, and provide little evidence for the hypothesis that MMT reduces the likelihood of eventual abstinence from opioids. More importantly, they also emphasize the low proportion of treated heroin addicts achieving abstinence.

On the available evidence, the perception that MMT contributes to stasis and the perpetuation of a drug-centred lifestyle is not well founded. Rather, what follow-up studies repeatedly demonstrate is the chronicity of heroin dependence, and the multiple associated problems which heroin-addicted people experience.

One particularly interesting follow-up study provided important information about one of the perceived risks of MMT - the reluctance of many patients to take high doses of methadone, fearing it will make them more addicted, and less able to eventually withdraw from methadone. Ample research has indicated that higher doses of methadone are associated with better retention and less drug use in treatment so reluctance to take adequate doses is a serious clinical problem. There is one study which allowed investigation of the hypothesis that greater neuroadaptation to opioids would make it more difficult to achieve eventual abstinence from opioids. This was a follow-up study of subjects treated at 3 clinics with different policies (McGlothlin, 1981). Two were high-dose clinics (mean doses 95mg and 82mg), and the third a low dose clinic (mean 43mg). Retention in treatment was significantly better in the high dose clinics. The researchers traced and interviewed 86% of a sample of 347 patients, 6-7 years after entry to treatment. At interview, 17% and 20% of the high dose patients, and 11% of the low dose patients, were abstinent from all opioids and not incarcerated. This important study demonstrates that higher doses are not associated with a reduced likelihood of eventual voluntary abstinence. Indeed, if anything the reverse is true — the more effective clinics used higher doses, retained people in treatment longer, and people from these programs were more likely to achieve eventual abstinence.

Chapter 5 - Self-assessment questions

Q1 Which of the following statements is/are true

Oral methadone:

1. Reaches a steady state concentration with two days.
2. Does not cause abnormalities in liver function tests.
3. The dose should be decreased in patients with renal disease.
4. Increases the risk of dental caries.
5. Often causes increased sweating.

Q2 Which of the following statements is/are true

1. Peak effects of a dose of methadone are observed about 2-4 hours after ingestion.
2. Methadone is primarily metabolized by the liver.
3. Methadone metabolism is accelerated by administration of phenytoin.
4. Higher doses of methadone during maintenance make it more likely that people will not be able to withdraw from methadone without relapse.
5. Over 20 years, methadone treatment leads to abstinence in most patients.

See answers on page 121

Assessment for MMT

Prospective patients do not always have a clear idea of what sort of treatment (if any) they want, and detailed assessment and discussion of treatment options is important in developing a treatment plan.

However, more often than not, patients will present requesting a particular treatment.

If a patient presents with a clear request for methadone treatment, the appropriate, empathic response is to address this request by:

- ▶ determining the patient's suitability for that treatment
- ▶ ensuring he or she is adequately informed about treatment
- ▶ the patient consents to treatment as outlined.

More comprehensive assessment usually should be undertaken during the course of treatment. After a few weeks of treatment, the doctor should ensure that physical health and psychological functioning have been assessed, if necessary by referral. Specific screening for blood-borne viruses and for psychiatric illness can be undertaken, along with an assessment of the patient's counselling needs. **None of these issues can be satisfactorily dealt with at initial interview, when the patient is mainly concerned with whether they will be accepted into treatment.**

The fact that a prospective patient requests a particular treatment does not always mean that treatment is appropriate.

While in general terms it is important to develop a collaborative approach to treatment with patients, practitioners still have to exercise diligence and judgment in determining whether a particular treatment is indicated. There are some situations where a patient's request for a particular treatment is problematic, and practitioners should be alert to feeling uneasy or uncertain about how to respond to individual patients. While treatment is more likely to be effective and attractive to patients when they can commence treatment promptly and not have to jump through hoops, this needs to be balanced against the need to avoid making important treatment decisions hastily or with inadequate information. **If in doubt about what treatment is appropriate, the optimal response is to do what would happen in any other area of medicine obtain a second, specialist opinion.**

6.1 Determining suitability for treatment

At the initial interview, the patient is often expecting rejection - this is the pattern in their life. So the practitioner should start as he/she would with other patients — i.e., introduces themselves, thanks them for coming (or acknowledge if this is the first presentation) asks what their problem is, listens politely, formulates at the end and then feeds back and suggests a way forward (which may not be entering them in a MMT program or giving them what they have asked for). If one does this with every one, included drug users, then it will surprise them and start things on a good footing.

The best way to initiate a therapeutic relationship is to focus on the relevant, concrete concerns the patient has, and provide the information they need to understand and

participate in the treatment process. In doing so, it is important for the doctor to demonstrate an accepting, non-judgmental approach to patients, being neither authoritarian nor overly intrusive.

For the prospective patient who has requested methadone treatment, the assessment interview is often a time of great vulnerability and expectation. The decision to seek methadone treatment is frequently taken at a time of crisis. Many patients feel ambivalent about methadone maintenance, and entering treatment may be marked by a sense of failure and guilt. Despite this ambivalence, patients usually appear preoccupied with whether and when they will be allowed to receive methadone. **Such focussing on access to the drug is characteristic of drug dependence.** Unless this issue is dealt with fairly early in the interview, it is difficult to establish any rapport. Once opioid dependence is confirmed, the patient can be reassured about their eligibility for methadone and issues such as treatment alternatives, program rules and procedures, side effects of methadone, can be discussed more meaningfully.

At the initial interview, in order to ensure their access to methadone, some patients will say whatever they think their doctor wants to hear. For this reason, it is not often appropriate to set specific treatment goals at the initial interview, as patients tend to nominate unrealistic expectations of what they will achieve from treatment. **The initial interview is not a time for getting to know people well - it is the time for setting the ground rules.**

If the patient is requesting maintenance treatment, the critical issue to determine is:

- ▶ diagnosis and duration of opioid dependence
- ▶ multiple drug use
- ▶ current level of neuroadaptation
- ▶ informed consent to treatment.

6.1.1 *Diagnosis and duration of opioid dependence*

Methadone treatment is contra-indicated in the absence of opioid dependence.

In most Australian states, regulations stipulate a history of 12 months dependence before a person can be considered for MMT.

The diagnosis of dependence requires history of drug use, of previous episodes of treatment, of withdrawal symptoms, and of an adverse impact on their life of opioid use. This is usually straightforward from the patient's drug use history and psychosocial history, but may be supplemented by the use of questionnaires.

In some cases an individual with little history of opioid use requests methadone treatment. **The diagnosis of opioid dependence, based on patient self-report, always needs corroborative information.** Corroborative information may include needle tracks, signs of withdrawal, or a verifiable history of previous treatment episodes. Avoid an adversarial approach in seeking information. It is common for people seeking treatment to exaggerate their current level of drug use, as they may be highly anxious about getting access to medication. There is little to be gained by aggressive confrontation.

The naloxone test was originally proposed for the minority of patients requesting methadone who had no documented history of detoxification and no signs of withdrawal. Where someone claims to be currently neuroadapted, but has no signs or corroborating history, a dose assessment or naloxone test may provide evidence of dependence.

The most useful approach in circumstances where suitability for maintenance treatment is in doubt is to obtain a second opinion from a specialist practitioner.

6.1.2 *Multiple drug use and current level of neuroadaptation*

Abuse of, or dependence on, drugs other than opioids makes induction onto methadone treatment more hazardous and complex.

- ▶ Use of *nicotine* and *cannabis* are common, but are not a risk factor during induction. They need to be addressed once a patient has been stabilized in treatment.
- ▶ **Alcohol abuse** is a risk factor. A patient who frequently drinks to intoxication needs to be warned of risks during induction. This warning can be reinforced by breath testing for alcohol prior to dosing on the first 3 days of treatment.
- ▶ **Alcohol dependence** is risk factor during induction, and a management problem during treatment. Alcohol dependent patients may require detoxification prior to commencement on methadone. Specialist consultation is recommended.
- ▶ **Psychostimulant use** (amphetamines and cocaine) are not risk factors during induction, but can be significant problems during treatment. The critical issues at assessment is to establish clearly that stimulant users are indeed opioid dependent, and therefore that methadone treatment is potentially helpful. Stimulant use should then be addressed once a patient is stabilized in treatment.
- ▶ **Benzodiazepine use is a major risk factor for toxicity during induction.** Combined dependence on benzodiazepines and opioids is not rare. Such patients require:
 - ideally, stabilization of benzodiazepine use prior to initiating methadone
 - warnings about risks of benzodiazepine use during the first week of treatment
 - low initial doses of methadone (under 20mg/day)
 - observation for 2-3 hours after the first 3 doses of methadone.In circumstances where this is not possible, benzodiazepine-dependent subjects need to be referred to a specialist service for assessment and initiation of treatment.

A detailed history of drug use in the 3 days prior to interview is the most useful guide to current opioid tolerance, and to the use of other drugs which potentially make induction into methadone treatment more hazardous. The history of recent drug use needs to be supplemented by examination for signs of intoxication or withdrawal. A urine test to confirm recent drug history use may be helpful in some circumstances.

6.1.3 *Informed consent to treatment*

Informed consent requires both a discussion of what is involved, and provision of written materials. The discussion and written information need to cover:

- ▶ an explanation of methadone treatment (aims, rationale)
- ▶ risks, expected benefits and side effects
- ▶ what happens during induction, and the risks during that time
- ▶ the expected duration of treatment
- ▶ program policies and rules (frequency of attendance for dispensing and review; opening hours; urine tests; take-away doses; fees; expectations regarding behaviour)
- ▶ effect of methadone on driving and operating machinery
- ▶ complaints process.
- ▶ ask whether the patient has any questions
- ▶ safety — especially to children.

6.1.4 *Treatment Agreement*

Every person entering the NSW methadone program will be required to sign a Treatment Agreement. This agreement sets out the rules that the patient and service provider must follow. The Treatment Agreement provides information on client rights and responsibilities and sets out sanctions for inappropriate behaviour.

Summary – initial assessment for methadone treatment

- ▶ Establish opioid dependence, supporting the diagnosis with corroborative evidence, (signs of withdrawal, previous treatment history, needle tracks, urine testing, dose assessment, naloxone challenge), or a second opinion from an addiction specialist.
- ▶ Document other drug dependence or abuse, and plan treatment appropriately
- ▶ Obtain informed consent to treatment. Information provided should include written and face-to-face explanation.
- ▶ Seek to establish a therapeutic relationship from the initial interview.
- ▶ Complete Treatment Agreement.

6.1.5 *Contra-indications for methadone treatment*

In certain medical circumstances (such as acute abdomen, head injury, advanced lung disease with compromised ventilation), the administration of any opioid is contraindicated.

The most common contra-indication in practice is decompensated liver disease. Patients with a history or with current evidence of hepatic encephalopathy may have encephalopathy worsened by any CNS depressant drug. **Methadone should not be initiated in the presence of jaundice or ascites.** This can be assessed clinically, and does not require performing liver function tests prior to initiating treatment.

Patients already on methadone who develop decompensated liver disease may require considerable dose reduction.

The manufacturers of methadone list other contraindications to methadone as being acute asthma, acute alcoholism, ulcerative colitis (due to risk of toxic megacolon) biliary and ureteric spasm, and concurrent administration of non-selective MAO inhibitor drugs.

Certain circumstances require special consideration before initiating methadone.

- ▶ Consent from a court is required to treat patients under the age of 16.
- ▶ Patients with psychiatric problems may need to have these problems managed before beginning treatment to ensure that informed consent is possible and treatment progress is not impeded.
- ▶ Allergic or idiosyncratic reactions to methadone are distinctly uncommon. However, a very small number of people will develop an arthropathy associated with receiving methadone, with joint effusions, pain and disability. Such individuals are probably best managed with an alternative treatment.

6.1.6 *Precautions for methadone treatment*

- ▶ Multiple drug use is the major precaution to initiating methadone treatment.
- ▶ Patients who are at risk or suffer from obstructive sleep apnea may have this condition worsened by methadone treatment.

6.2 Urgent initiation of treatment

Patients are most likely to be retained in treatment when there are minimal delays between seeking treatment and induction. Unfortunately, particularly in view of the regulations regarding methadone treatment, delays are sometimes unavoidable. However, some situations have been recognised in which good medical management of a particular patient requires prompt treatment.

6.2.1 *Pregnant women*

During the third trimester of pregnancy, heroin withdrawal is associated with the risk of fetal distress and even intra-uterine death. Therefore, if a woman presents in withdrawal in the third trimester of pregnancy, relief of withdrawal is a matter of urgency, and prompt initiation of methadone treatment is usually the best approach.

Heroin withdrawal during the first trimester of pregnancy may be associated with an increased risk of spontaneous abortion, and again the recommended approach is to initiate methadone treatment.

6.2.2 *Intercurrent acute medical illness*

When a heroin user is admitted to hospital with serious acute illness, management of heroin withdrawal can be a critical component of good care, so long as the underlying diagnosis is not one in which the administration of opioids is contraindicated. For example, consider the hypothetical case of a patient who has been using heroin heavily and then develops bacterial endocarditis. On admission to hospital for prolonged antibiotic treatment, he/she develops moderately severe heroin withdrawal. Treatment with methadone is indicated promptly, to reduce the patient's suffering, and to improve compliance with treatment (by reducing the risk that he/she will inject heroin into their intravenous lines or sign themselves out of hospital.)

The two groups in whom prompt access to methadone may be indicated are:

- ▶ pregnant women
- ▶ those acutely ill with other serious diseases where opiate withdrawal is complicating the clinical picture.

These groups may be appropriate for methadone treatment if they are opioid-tolerant, even though they may have only short histories of drug use and no prior treatment history.

Induction onto methadone in the hospitalized drug user is difficult, as the patient has severe illness, and is often receiving multiple drugs. However, in-patients can be continually observed, and the methadone can be titrated against signs of intoxication and withdrawal. Rather than administering a single daily dose of methadone, small doses should be administered 8th or 12th hourly until the signs of withdrawal are abolished. If signs of intoxication appear, the dose interval needs to be extended and/or the dose reduced. In the acutely ill patient, there is no alternative to close monitoring.

6.3 Induction into methadone treatment

Induction into treatment is a critical time. Patients are at increased risk of death during the first week of methadone treatment. It is also a time of high risk of dropping out of treatment.

The increased risk of death during induction into treatment is due to the individual receiving doses of methadone excessive for his/her current opioid tolerance.

Most of the fatalities during induction into methadone treatment involve the use of alcohol and benzodiazepines in conjunction with methadone. Even in these cases, the level of methadone tolerance is an important factor in the risk of fatal overdose.

This problem has been addressed by the use of starting doses of methadone which have been considered to be safe even in non-tolerant individuals. This has not prevented fatalities during induction. Given that some such fatalities are associated with use of other drugs, which cannot be controlled, it is likely that risks during induction can never be abolished. Nonetheless, steps to increase the safety of induction are essential.

Tolerance testing

Even where there is sufficient corroborating evidence confidently to establish the diagnosis of opioid dependence, **no form of clinical assessment can reliably predict methadone tolerance**. One way to assess the extent of a patient's tolerance to opioids is to administer 20mg of methadone and observe the response.

- ▶ If 2-3 hours after a 20mg dose of methadone, a patient has no signs of intoxication, then he/she almost certainly has a high level of opioid tolerance. Many such patients will require an additional dose of methadone to prevent the development of withdrawal symptoms before their next dose is due.
- ▶ Most opioid-dependent subjects will have mild signs of intoxication — a degree of pupil constriction, but little other evidence of opioid effects 2-3 hours after a 20mg dose of methadone. Such patients are at low risk of toxicity, unless they happen to have abnormal methadone metabolism leading to accumulation during induction.

- ▶ Patients who after a 20mg dose appear moderately intoxicated — slightly drowsy, small or pinpoint pupils, nausea and vomiting — have little or no tolerance, and require at the very least very careful monitoring over the next three days or even reassessment of the appropriateness of methadone treatment.

The assessment of tolerance is complex with a long half-life drug such as methadone. Most deaths during induction occur after two to three days. The key issue is not only whether an individual tolerates a single dose, but also whether the progressive accumulation of methadone can contribute, over several days of daily dosing, to a blood level higher than what the individual can tolerate.

All people entering methadone treatment must be carefully and systematically reviewed prior to their 2nd and 3rd dose of methadone. At these reviews, the practitioner (either doctor or experienced dispensing staff) should:

- ▶ check how patients are feeling
- ▶ assess signs of intoxication and withdrawal
- ▶ ask about other drug use
- ▶ repeat warnings about risks of overdose, particularly with concomitant alcohol and benzodiazepine use.

If patients have any evidence of intoxication prior to when their 2nd or 3rd dose is due, the methadone dose should be withheld.

Suggested Induction Protocol

There has been considerable debate over initiation of methadone treatment, and current guidelines give a variety of approaches to initiation. All readers are referred to National and State guidelines concerning induction into treatment.

Initial dosing with methadone:

- ▶ The initial dose should be based on an estimate of current tolerance, which in turn is based on a documented history of drug use in the 3 days prior to induction.
- ▶ The initial dose should be in the range 20-40mg.
- ▶ Patients should be observed prior to each dose of methadone, and not dosed if they are exhibiting signs of intoxication.
- ▶ Where there is any doubt about tolerance, patients should be observed 2 hours after an initial dose of 20mg (or return to have observations 2 hours post dose). Signs of intoxication (or withdrawal) should be documented using a structured format.
- ▶ Patients exhibiting withdrawal signs two hours after their initial or second dose can have an additional 10mg of methadone administered 2 hours after the initial dose, and their dose for the following day adjusted up by 10mg. (That is, a patient given 20mg, who 2 hours later has dilated pupils and complains of hanging out, could have an additional 10mg on day 1, and on day 2 and receive 30mg).
- ▶ The maximum daily dose in the first week of treatment should be 40mg.

This approach to dosing in the first week enables more rapid dose increments for those who need it, while ensuring that non-tolerant subjects do not receive excessive doses. It places greater demands on those dispensing methadone. This is more appropriate than

approaches which are too casual, with quick assessment and little monitoring, or too restrictive, placing obstacles in the way of patients entering treatment.

Because of the long half-life of methadone, peak serum levels progressively rise during the first week of treatment on a stable dose. There is good reason to be cautious about increasing the dose during the first week, as signs and symptoms of overdose (usually nausea and drowsiness) may first appear on the third or fourth day of treatment.

The great majority of heroin users can have withdrawal symptoms abolished for 24 hours with a dose of 40mg methadone. While higher doses are required in long-term maintenance, it is recommended not to exceed this dose during the first week of treatment. Explanation to the patient, and establishment of a therapeutic relationship, are more important in retaining people in treatment than rapid increases in dose.

6.4 Stabilization on methadone

By the end of the first week of treatment, most patients are generally feeling considerably better, with reasonably stable blood levels of methadone. Many people will have continued to use heroin, at least intermittently, but the effects of heroin will be attenuated by methadone. Symptoms of withdrawal will be markedly diminished. Many subjects will report that the dose of 40mg is not enough, and it is appropriate to commence progressive dose increases.

Despite feeling better, many patients are distinctly ambivalent about being on methadone, and the first month of treatment is a period of relatively high risk of patients dropping out of treatment. It is important to review patients regularly during the first month of treatment.

There are several issues to address:

- ▶ Some patients will be experiencing side effects of methadone — dry mouth, increased sweating, constipation.
- ▶ Even though feeling better, patients should generally have their methadone dose progressively increased to a level which is likely to optimally suppress heroin use. Unless a patient is particularly troubled by side effects, raising the dose progressively to 80mg/day is a sound approach. Rate of increase needs to be slowed to allow people to adapt to increased doses with minimal side effects. **It is preferable to raise doses only at weekly intervals, and by no more than 10 mg increments.**
- ▶ Health and psychiatric screening.
- ▶ Entry to treatment is a major adjustment for people accustomed to the more chaotic and exciting life of the illicit drug scene. This adjustment is not easy, and the establishment of a good therapeutic relationship is an important factor making treatment more acceptable to the patient. If patients have made gains — for example, using heroin only once in a fortnight - it can be a good time to provide them with encouragement and praise.
- ▶ Some patients may have specific issues and referral for counselling — or, if the practitioner feels it is appropriate, provision of counselling — may be indicated.
- ▶ Some patients in unstable circumstances may benefit from welfare assistance — for access to housing, social security, or assistance in dealing with legal issues.

During the initial month of treatment, comprehensive assessment should be completed, the patient brought to a satisfactory maintenance dose, and individual counselling issues identified. It is sometimes helpful in the first month of treatment to invite the patient to bring a family member — usually, a parent or partner — along to an interview, in order to provide the family with information about treatment. There are many misconceptions and prejudices about methadone treatment and it can place patients under considerable stress when their relatives start to ask after three weeks in treatment, Are you still going to that clinic?

6.5 Optimizing the benefits of maintenance on methadone

Once a patient has been stabilized in treatment, the challenge for the practitioner and patient is a long-term one — optimizing the benefits and minimizing the drawbacks of treatment. Research has consistently identified that not all methadone clinics are equally effective; indeed, there appear to be wide variations in treatment effectiveness.

The following factors have been found to be associated with better outcomes for methadone maintenance treatment.

6.5.1 *Methadone dose*

Higher methadone doses (doses of 80mg/day and above) have consistently been found to be associated with lower rates of heroin use and longer retention in treatment. It is particularly important in the first few months of treatment to progressively raise patient s doses to adequate levels. Many patients are ambivalent about being on methadone and have fears about the consequences of higher doses - that they will have more trouble eventually discontinuing methadone, that methadone rots their bones, or that high doses will make them fat. These feelings and fears need to be addressed, and patients gently encouraged to take an adequate dose. Once patients have been stabilized for some time and have discontinued use of heroin or other opioids, many can be maintained on lower doses, but there is no particular advantage in encouraging patients to take lower doses.

One important issue about withdrawal symptoms that has not yet been resolved is how to manage the emergence of withdrawal symptoms, such as the craving for opioids, and persisting heroin use in people being treated with methadone. Up to 1/3 of patients on methadone report symptoms of opioid withdrawal. There are two theories as to how to respond:

- ▶ The traditional assumption has been that to control withdrawal symptoms requires maintaining the blood level of methadone above a threshold value. Once the blood level falls below that (as yet undetermined) threshold, withdrawal symptoms appear. The key to managing withdrawal symptoms is to keep the trough (24 hour) blood level of methadone above the level at which symptoms arise, by administering progressively higher doses until the symptoms resolve.

- ▶ The alternate view is that the determinants of emergence of withdrawal is not the absolute blood level, but the rate at which the level declines. Withdrawal symptoms are therefore most likely in those individuals with rapid methadone clearance. On this view, raising the dose is of no value, as the steepness of the its decay curve is unchanged. Rather, the way to manage withdrawal symptoms is to split dose patients, administering the methadone twice daily to minimize the duration each day during which the blood level is falling rapidly.

There is currently no research evidence to clearly indicate which approach is preferable. Practical considerations make split dosing difficult for most patients. Many pathology laboratories will measure blood methadone levels, but interpretation of the results is not straightforward.

6.5.2 *An orientation to maintenance*

In most areas of medicine, effective treatment is a long-term issue, and the withdrawal of treatment places health at risk. So it is with methadone. Any notion of methadone maintenance as an effective time-limited treatment with the expectation of ‘cure’ is not supported by the research literature. An American study of the results of restricting the duration of treatment to two years illustrated the problems associated with such an approach (Rosenbaum et al, 1988). The authors classified patients into 3 categories.

- ▶ The first group were described as model patients. These were patients doing well in treatment, who on the imposition of a two year time limit were able to leave treatment and maintain their stability, without relapse to heroin use. This group represented 6% of the study sample.
- ▶ The second group were labeled marginal patients. They did poorly in treatment, with persisting poorly controlled drug use, unstable and chaotic interpersonal relationships, and little improvement in social circumstances. This group - 25% of the study sample - did poorly in treatment, and did little worse on leaving treatment after two years.
- ▶ The third group, 69% of subjects, comprised stabilized patients, who did well while in treatment but on leaving treatment after two years relapsed to heroin use.

The message is straightforward. Methadone is a maintenance intervention. Some people can leave treatment without relapse, but for most, leaving treatment is associated with relapse. **Putting pressure on patients to remain in treatment for limited periods makes for less effective programs.** Practitioners and clinics with an orientation to long-term maintenance achieve better retention in treatment, and their patients use less heroin, than practitioners oriented to abstinence.

The pressure to limit treatment comes from many sources. It comes from practitioners own fantasies and hopes about being able to cure people; it comes from patients hopes that by an effort of will they can live drug-free; it comes from families, ashamed of the stigma of methadone treatment; from bureaucrats concerned over the cost implications of long-term treatment; and it comes from politicians anxious to send the right message about drugs. It may not have any scientific basis, but the pressure to leave treatment is powerful.

Most of the valuable interventions in health care relate, not to acute cures of dramatic illness and injury, but assisting people to prevent or adapt to disease, disability and aging. **Health Maintenance** is the greatest contribution to community well being being provided by medical science and technology. Methadone treatment can be an example of effective health maintenance.

Although an orientation to maintenance is a part of effective treatment, practitioners should not stand in the way of patients who request assistance to leave treatment. While it is reasonable to point out the risks involved in doing so, practitioners should make every effort to assist patients who maintain a strong desire to leave treatment.

6.5.3 **Quality of the therapeutic relationship**

In the USA, more effective clinics are characterised by patients having a good relationship with staff (Ball and Ross, 1991). Three distinct issues can be identified as being important:

1. The therapeutic relationship between the individual practitioner and patient.
2. The organisation of treatment - the training, skills and enthusiasm of staff, the policies and procedures followed, and the quality of communication between professionals involved in treatment. These latter issues are of great importance, and will be considered in the section on Quality assurance .
3. Practical issues such as the cost of treatment, accessibility, extended dosing hours, also influence patients' perceptions of treatment and their relationships with service providers.

In considering the therapeutic relationship, remember that counselling is not something different from the way we relate to patients. Counselling skills inform all clinical practice.

Three key factors essential to maintaining a good therapeutic relationship (Carl Rogers):

1. The effective therapist has genuine interest and concern for clients
2. The effective therapist is not possessive of clients. Possessiveness can be a particular problem in relationship to families, as there is a long and unfortunate tradition (in both psychiatric and addiction services) of excluding families from treatment on the grounds that the family has been contributing to the problem (codependency). Possessiveness can also be expressed by failure to refer, to involve other professionals where indicated, or even in failure to acknowledge the patient s autonomy and capacity to manage without our intervention.
3. The effective therapist shows empathy.

Many traditional approaches to counselling take a diagnostic approach, trying to find psychopathology or unresolved psychodynamic issues which are the underlying cause of addiction. This tends to be a distinctly unproductive approach. All too often, practitioners who seek to identify what is wrong with a person create a climate of guilt and blame which is sufficient to dampen anyone s enthusiasm for participating in treatment.

The safest and most useful approach to establishing a therapeutic relationship is to maintain a respectful stance in relationship to patients. Common sense, courtesy, and an appropriate level of neutrality in relating to patients are critical ingredients of treatment. It is easy to present the impression of being excessively distant, remote and authoritarian, in

order to protect oneself from the perceived (or actual) demands and manipulations of the patient. It is also easy to become overly sympathetic to the patient, and for the doctor to become too accepting of the patient's own account of his or her circumstances. Some doctors come to see themselves as supporters of their patients, and can become enmeshed in the patient's issues, blurring the boundaries which define a therapeutic relationship.

6.5.4 *Comprehensive approach to care*

There is mixed evidence regarding the role of comprehensive approaches to care. Some research suggests dramatically better outcomes for patients who receive medical care and access to counselling in conjunction with their methadone treatment. Other studies suggest that access to an adequate daily dose of methadone, provided by caring staff, is the major ingredient of treatment, with counselling, medical and welfare assistance providing little extra benefit. The contradictory research findings are difficult to resolve, as it is not possible to carry out double-blinded comparisons of comprehensive and minimal treatment.

On the available evidence, it seems reasonable to suggest that treatment outcomes are likely to be optimized when patients have access to health advice, referral for welfare, counselling, and management of intercurrent medical problems, if indicated.

Compulsory counselling for all patients is probably not particularly helpful.

6.5.5 *Treatment Plans*

All patients should have a treatment plan developed in collaboration with them. Complete a detailed assessment of the patient during the initial weeks of a methadone program. During this early phase of treatment the therapeutic alliance with the patient should be further defined and consolidated. Assist the patient to achieve pharmacological stability and, if he/she wishes, psychosocial stability.

After the first four weeks of a methadone program, document a treatment plan that has been arrived at in collaboration with the patient.

The treatment plan should include:

- ▶ plans for the patient's methadone dose
(eg, maintenance, reduction, review in one month)
- ▶ strategies to deal with drug use problems (including alcohol)
- ▶ strategies to deal with risk behaviours (eg, needle sharing, overdose)
- ▶ strategies to deal with identified major medical, psychiatric and psychosocial problem areas. Employment, parenting, accommodation, and relationships should all be areas explored and dealt with.

Review the treatment plan at least every three months in collaboration with the case manager, and pharmacist or dispensing staff. Document revisions to treatment plan.

Summary – making methadone treatment more effective.

- ▶ Use adequate doses of methadone.
- ▶ Assume that treatment is long-term, indefinite maintenance.
- ▶ Foster a good individual relationship with patients.
- ▶ Promote patients' access to comprehensive services.

6.6 A framework for quality improvement

Medical practice has undergone a paradigm shift.

Up until relatively recently, medical care continued to be conceptualized primarily in terms of the interaction between the doctor and his/her patient. However, the realities of the complex organisation and delivery of health care have forced abandonment of this individualistic paradigm. While the doctor-patient relationship is still a key ingredient in treatment, it can no longer be conceptualized as occurring in isolation. We work in treatment systems, systems of great and growing complexity. Health care is delivered by teams of people from different professional backgrounds, within a context determined by economics, community values, professional values, and team cohesion (or lack of it).

To adjust to working in systems, a new conception of professional competence has evolved, one no longer based solely on the skill and knowledge of the individual practitioner. Now professional competence embraces *quality improvement* — the approaches to ensuring treatment systems are monitoring and maintaining standards of service delivery.

Generally, medical practitioners have been reluctant to embrace quality improvement (after all, who really wants to become more accountable?). However, quality improvement is an integral part of practice of contemporary medical practice.

Quality treatment depends on clear definition and effective communication of:

- ▶ the Aims
- ▶ the Structure
- ▶ the Objectives

of the treatment program.

Only when these are defined and agreed on can the processes of treatment be evaluated, and outcomes monitored. Such monitoring of process and outcomes is essential to **Quality Improvement**, which is the process of modifying treatment in the light of such evaluation, trying to address shortcomings in process and seeking to improve outcomes.

Quality improvement depends on a thorough understanding of how a treatment program works e.g., regulation, service delivery model, clinical activities and organisational culture. In most health care settings, quality improvement is institutionalised into the process of **accreditation**.

In NSW, a system for accreditation of methadone clinics is being introduced. All practitioners working with methadone clinics should obtain the accreditation standards in order to be aware of expectations based on clinics, and, particularly, on clinic-based practitioners.

However, in addition to participation in formal accreditation programs, several aspects of quality improvement are also fundamental parts of practitioner s competence. The key clinical issues are addressed below, under three headings:

Some examples of key questions which might be asked in assessing the processes of treatment are:

- ▶ How often should patients be seen?
- ▶ How can we involve significant others in treatment, where appropriate?
- ▶ Is there effective communication between professionals involved in treatment delivery?
- ▶ Are we utilizing referral and support services?
- ▶ Are we addressing child protection issues?

These questions all require practitioners to look beyond methadone treatment as simply responding to what the patient brings to periodic review interviews. They mean treatment requires exploration of issues which are unlikely to arise spontaneously.

How often should patients be seen?

There is little benefit in frequent, very brief contacts. Appointments should be long enough to allow a patient to feel he/she is provided with the time and space to be heard.

During induction into treatment, it is desirable that patients are reviewed two to three times (the review may be carried out by an experienced pharmacist or nurse dispensing methadone). Thereafter, patients should probably be seen weekly for the first few weeks. During this time, comprehensive assessment can be completed, problems identified, and a relationship established. Thereafter, it is probably reasonable that patients be seen a minimum of four times annually, and more frequently if indicated.

It is a legal requirement (and also good clinical practice) that on each occasion a prescription for methadone is provided or renewed, the prescriber personally assesses the patient.

Involving significant others

Most of the important things which determine the outcome of a patient's treatment do not happen in the 10—50 minutes per week which the patient spends with his/her doctor.

Patients not only spend more time with their friends and family — what happens with their friends and family is more important in their lives. When we speak of the continuum of care, the most important people to seek to involve is the patient's family.

This is not to suggest that the doctor-patient relationship is not important - it just isn't as important as the big things in people's lives — relationship, job, family. **If we can use our marginal influence constructively, to assist people to have more stable relationships, better relationships with their families, and to find and keep employment — then we are probably contributing to lasting benefits.**

In practical terms, often the most useful approach to involving significant others in the patient's treatment is to offer to provide information about treatment. Given that fear, prejudice and misconceptions are common, working with families to explain treatment can be an important therapeutic intervention.

Involvement of significant others poses difficult issues regarding confidentiality and privacy. It is not appropriate to reveal details of treatment to significant others without the patient's consent. However, it is useful and appropriate to invite the patient to bring significant others to an appointment to discuss treatment.

Working with other professionals

Patients with opioid dependence often have multiple needs in addition to their requirements for medical care, and benefit from access to a range of services. Examples of the types of services include counselling to assist with problem solving, relationship skills training, accommodation and financial management assistance, parenting skills, training, and employment assistance.

The medical practitioner is one clinician within a **team** of service providers involved in the care of people with opioid dependence.

The **pharmacist or nursing staff who dispense/administer methadone** are important clinicians within the treatment team. Assessment and monitoring, support, advice and referral are provided by these professionals. Their roles are to ensure treatment is safe and effective, and that patients receive the additional services they require. Each patient treated with pharmacotherapy can have a **case manager**. The case manager is identified and contacted through Area Health Services. Case managers either provide, or assist patients to access a broad range of health and social services that improve the outcomes of treatment, including the patient's quality of life.

Systematic communication and collaboration amongst those providing care improves the effectiveness of interventions.

Support from Specialist Services

All Area Health Services operate specialist drug and alcohol services that include pharmacotherapy services. Specialist drug and alcohol staff from these services provide support, expert advice, assistance with case management of patients, and training to GPs. There is also usually a designated GP liaison officer within each Area drug and alcohol service, whose role it is to coordinate training, support, and information for GPs in their work with patients who have drug and alcohol problems.

Communication in treatment delivery

Patients spend more time with the professionals who dispense methadone than with their doctors. Dispensing pharmacists or nurses often know much more about patients than doctors are ever likely to find out during consultations.

- ▶ It is highly desirable that all professionals involved in a patient's care act as a team, exchanging relevant information and sharing treatment decisions.
- ▶ Patients should be informed from the outset that such a team approach will be adopted.
- ▶ Where team participants operate in different sites — for example, where a patient is prescribed methadone by a general practitioner, and picks up their methadone at a retail pharmacy, it may assist communication if doctor and pharmacist write brief, formal summaries of treatment every few months (at the time of prescription renewal).

Referral and support services

Once stabilized in treatment, most patients ask for very little. However, in a healthy treatment system, issues will be periodically identified which require referral.

Practitioners should establish a referral network which includes:

- ▶ Welfare services.
- ▶ Counselling services.
- ▶ Drugs in pregnancy service.
- ▶ Specialist addiction treatment services.
- ▶ Psychiatric services.
- ▶ Liver clinic.
- ▶ HIV clinic.

6.7 Safety

Safety is a critical component of quality treatment. It is the primary consideration in all health care interventions. It is of particular importance in effective methadone treatment, as the challenge for service providers is to create a treatment environment in which patients and staff experience safety. In concrete terms, this means that staff and patients should be:

- ▶ Treated with respect and dignity.
- ▶ Treated with care and skill.
- ▶ Free from harassment and intimidation.
- ▶ Free from exploitation.
- ▶ Aware that their privacy and confidentiality are respected.

Maintaining such a therapeutic environment requires program rules and policies which are clear, well-publicized, and thoughtfully enforced by trained and supported staff.

Many patients, particularly early in treatment, are alienated and angry. They often have difficult relationships with authority figures, and act this out in relation to clinic staff or treating doctors. Conflict between staff and patients, and between patients, is not uncommon. All practitioners, and particularly clinics dealing with large numbers of patients, need to develop policies and procedures to deal with conflict. It is important to create an atmosphere to contain patients' acting out and reduce levels of conflict.

Methadone clinics also have a responsibility to the neighbourhood to minimize loitering and uncivil behaviour in the vicinity of the clinic.

Simple and clear clinic rules should be written down and should also be displayed in the clinic. This information should be made available to patients at the time of admission. Patients should be informed in writing of their rights to register a complaint and the procedures for doing so at the time of admission into methadone treatment. Patients who cannot read should be read their rights and obligations at the time they enter the program.

Staff must strictly respect patients' privacy. Staff should not pass on messages, notes, packages or goods of any kind from anyone. Staff should politely decline to answer even simple requests like 'Has X been in yet?' By observing these policies, and explaining them, not only is the patient's privacy protected but the commitment to privacy is demonstrated.

Patients have the right of access to procedures intended to resolve conflicts between themselves and those responsible for their treatment. Where possible, patients should be retained in the current treatment program pending the resolution of the complaint.

6.8 Record Keeping

An essential component of quality treatment is maintenance of comprehensive records which are secure and confidential. Case records should be legible and reveal an assessment, treatment plan, and record of each interaction between doctor and patient. Periodic review of the patient's progress should be documented. Each entry should be dated and signed.

6.9 The logistics of methadone treatment

6.9.1 *Take-away methadone doses*

Methadone treatment in Australia is based on the administration of a supervised daily dose. This highly structured approach is designed to reduce risks of diversion and misuse of prescribed methadone. It is the optimal treatment approach for patients new to treatment, and for those patients for whom the provision of take-home doses of opioids is likely to contribute to instability rather than rehabilitation.

Daily attendance at a clinic or pharmacy is irksome, and for many people is a major deterrent to remaining on methadone. Research suggests that provision of take-home doses improves retention in treatment. There is strong clinical consensus that stable patients should have access to take-home medication. However, indiscriminant provision of take-home medication by methadone clinics in Sydney has contributed to a large black market in methadone and to a culture of methadone injecting.

All practitioners have a responsibility to minimize methadone diversion.

Defining stable is not easy. If a patient is easy to like, it is tempting to think that they are stable. If they are oppositional, manipulative, or have a strong sense of entitlement, it is tempting to conclude that they are not unstable. It is clearly desirable to go beyond impressions, justifying responses in terms of a vague notion of clinical judgment in deciding when take-away doses are appropriate. **Practitioners need to document in the patient's medical record, at the time of each prescription, the basis on which the decision about how many takeaways to prescribe is made.** The discipline of documenting why patients are suitable (or unsuitable) for take-home medication is the best check against inappropriate prescribing practices.

Persistent use of heroin is generally regarded as an indication for insisting on daily pickup of methadone. However, occasional heroin use by people in treatment may not be an indicator of instability. Moreover, if takeaways - which are highly valued by those in treatment - are contingent on not using heroin, people will cease to give accurate accounts of their drug use. It is crucial to avoid the absurd and adversarial situations which arise in some clinics, where patients make strenuous efforts to appear to be not using heroin, and staff go to great lengths to detect heroin use.

In general terms, patients are less appropriate for regular take-home methadone if:

- ▶ they have fresh track marks consistent with continuing regular IV drug use
- ▶ they are dependent on or abusing benzodiazepines, alcohol, or psychostimulants
- ▶ they present intoxicated for dosing
- ▶ they are socially unstable - involved in crime or prostitution.

They are more appropriate if:

- ▶ they have no evidence of continued use of heroin or other drugs
- ▶ they are socially and emotionally stable and functional.

All patients access to take-home methadone should be reviewed regularly.

6.9.2 *Missed doses*

A review of fatalities associated with methadone treatment suggested that patients who miss three or more consecutive doses were at risk of overdose. Presumably, this reflects a degree of reversal of neuroadaptation, and possibly the use of other sedative drugs. Therefore, when a patient misses three or more doses they need to be reviewed by an experienced clinician before resuming treatment. As in all situations, where patients are intoxicated, no methadone should be administered.

Practitioners should consult jurisdictional guidelines concerning responses to missed doses. Where patients are not intoxicated on presentation, one recommended procedure is:

- | | | |
|----------------------------|---|---------------------------------------|
| Missed 1 dose | - | provide usual dose |
| Missed 2 consecutive doses | - | if dose >80mg, administer 1/2 dose |
| | - | if dose 40-80mg, administer 40mg |
| | - | if dose < 40mg, administer usual dose |

Missed 3-5 consecutive doses — review by experienced clinician

- ▶ Investigate why missed doses.
- ▶ History of drug use over preceding three days.
- ▶ Monitor for signs of intoxication and withdrawal.
- ▶ If not intoxicated, administer 1/2 usual dose, or 40mg, whichever is lower.

Missed > 5 doses — treat as re-induction onto treatment.

6.10 **Review of treatment**

Most patients in methadone maintenance adapt to the routine of picking up daily, seldom require anything of staff, and once stabilised on a particular dose ask little of treatment. Other patients can be very demanding and difficult, requiring considerable time from staff and prescribers with complaints about dose, or presenting intoxicated, or with other crises. Invariably, such patients receive considerably more staff attention.

It is important that all patients, including those who appear to be doing well, should have a periodic review — at a minimum, once every three months once they are stabilised. Indeed, it should be a matter of principle in prescribing any psychoactive drug that patients have a

regular medication review. Each review represents a reassessment of treatment, and, if necessary, revision of the treatment plan.

The aims of the review are to monitor treatment, document progress, and provide the patient with feedback.

Each formal review should document:

- ▶ the patient's recent drug use
- ▶ social functioning
- ▶ psychological and physical health
- ▶ address any concerns the patient may have
- ▶ identify the need for a change in treatment (dose, referral for counselling, etc).

6.10.1 *Monitoring continued drug use*

At each review, patients should be asked about their recent use of drugs (including cannabis). It is desirable to supplement self-report with corroborative evidence — urine test results and examination of veins for signs of injecting drug use. In patients thought to be abusing alcohol, drawing blood for LFTs may be useful.

Periodic inspection of veins for evidence of recent injection is useful in assessing the extent of continued injecting drug use. Old track marks usually fade, and are pale in colour. Regular recent self-injection is associated with darker, livid track marks. Patients who inject infrequently may have a recent puncture mark, but do not usually do not have fresh track marks, which only develop as a result of regular injecting. Thus, the presence of recent track marks is a reasonable indication that a patient is not stable in treatment, but is regularly injecting - usually heroin, methadone, or amphetamine. Performed every three or four months, inspection of veins can be a useful adjunct to self-report in assessing the extent of injecting drug use. It is not foolproof, but no system of monitoring illicit drug use is.

6.10.2 *Urine drug testing*

Urine drug testing is one method of monitoring the performance of patients during treatment and detecting extraneous drug use or methadone diversion.

Urine drug testing is something of a ritual in many methadone programs, with great importance being attached to the results. It is important not to use urine tests as an alternative to talking to patients. As long as programs are not punitive, patients are usually quite open about their drug use. Often patients value urine tests so that they can prove that they are not using other drugs. However, such proof has many flaws, and it is not wise to encourage patients to prove their progress in treatment when progress is best assessed by looking at patients and talking with them.

Steps should be taken to ensure that if urine samples are taken, substitution of specimens is minimised. Steps to do this include ensuring that only one person is allowed into the toilet at a time. Freshly voided urine should be at body temperature, and checking the temperature of samples with thermometer strips is a useful way to check that it is a freshly voided sample. Many clinics observe urine specimens being passed, either by direct vision or by the use of video cameras, although this is usually unnecessary and intrusive.

Urine drug testing is most useful when conducted randomly - it is far less useful when patients know when they will be expected to provide a urine sample. Urine drug testing is not only helpful in monitoring the patient's progress, but is a useful way of monitoring the effectiveness of a treatment program.

The decision to use urine testing, and the frequency of collecting specimens, should be part of an overall, coherent treatment approach. No clinic should collect urine specimens simply because that is part of the ritual of methadone maintenance. There is no evidence that collecting urine tests contributes to reducing drug use by patients. Whether urine tests are employed as part of monitoring the effectiveness of the program, as part of a contingency management approach to treatment, or as a way of monitoring the progress of individuals, the reasons for doing the tests need to be understood by staff and patients.

The Health Insurance Commission will rebate a maximum of 21 urine drug tests per annum per patient. Consequently, a suggested schedule for urine tests for all patients is that they be performed weekly (on a day selected at random each week) in the first three months of treatment, and on a monthly basis thereafter if required.

6.11 Responding to continuing drug use

The continued use of heroin, psychostimulants, benzodiazepines and alcohol during methadone treatment is not uncommon. Responses to this clinical situation vary widely. Common sense is called for, along with a measure of patience.

Some inexperienced practitioners become preoccupied with gazing at urine test results, scanning the reports eagerly for clean specimens, grieving over the positive tests, pondering what all the positive tests for benzodiazepines actually mean in practice. This can be quite vexing. Most doctors have had the experience of asking a patient why all their urine tests are positive for benzodiazepines and being told that the patient takes one tablet at night to help them sleep. A common scenario is for the patient to be nodding off in front of you during the interview, difficult to rouse. In this situation, the response to any suggestion that they are under the influence of some drug is likely to be an indignant denial. They assure you that the reason they are nodding off is because they are tired, because they sleep very badly at night. Indeed, this is precisely why they need benzodiazepines. There is, it must be admitted, a certain logic to this.

There is, however, little logic in trying to argue with an intoxicated patient. The question is, how to respond to someone abusing benzodiazepines (or whatever).

Some practitioners, confronted with a patient who is continuing to use drugs, regardless of what drug is being used, raise the methadone dose, convinced that enough methadone will solve everything. There is no convincing evidence that massive doses of methadone will suppress benzodiazepine or alcohol use, although dose increases may sometimes be worth trying on an empirical basis.

Others practitioners, confronted with evidence of continuing drug use, find discretion is the better part of valour. Talking to patients about their drug use can cause much unnecessary grief and conflict, and it is simpler for both doctor and patient to ignore it.

None of these options is satisfactory. If drug use is going to be monitored, there needs to be some principles as to how to respond.

6.11.1 *Responding to high risk intoxication*

Safety concerns are paramount, and there is a very small number of patients in whom episodes of chaotic drug abuse makes remaining in methadone treatment either unsafe or unworkable. **Withholding doses from intoxicated patients is an essential safety step.**

Patients who learn to present straight each morning for their dose, but are then found dangerously intoxicated (for example, through presenting unconscious to Emergency Departments, or being picked up grossly intoxicated by police), need a prompt response.

One useful safety measure is to ask these patients to attend for split dosing, coming twice daily to be observed and receive smaller doses of methadone. Such an approach conveys a strong message to the patient, and reduces risks without removing them from treatment. Under extreme circumstances, discontinuation of methadone treatment may be required.

6.11.2 *Responding to moderate-low risk continued drug use*

- ▶ Bring it to the attention of the patient at regular reviews, and explore whether the patient perceives their drug use to be a problem.
- ▶ Seek more information. Clinic or pharmacy dispensing staff see the patient daily, and their observations on whether the patient attends for dosing regularly, attends intoxicated, appears to relate appropriately, are essential in assessing the seriousness of the situation.
- ▶ Try to persuade the patient to take an adequate dose of methadone, particularly, if the patient is using heroin.
- ▶ Discuss the possibility of selective detoxification (detoxification from a drug while remaining on methadone).
- ▶ Adopt a long view. Threats and exhortations do not appear to be effective.

6.11.3 *Alcohol*

Hazardous alcohol consumption is common among patients on methadone programs. The combination of alcohol abuse and HCV infection can cause fairly rapidly progressive liver disease, and evidence of alcoholic liver disease is the commonest histological finding in cirrhotic injecting drug users.

In general, patterns of alcohol use during methadone treatment are a continuation of alcohol use prior to treatment. However, a significant proportion of individuals overcome heroin dependence only to later experience problems resulting from alcohol. It is therefore prudent to be alert to the serious health risks of alcohol abuse in this population.

Urine toxicology does not routinely test for alcohol. The identification of alcohol problems generally occurs in one of three ways:

- ▶ patient may report on his/her alcohol consumption
- ▶ dispensing staff may note that the patient regularly or occasionally presents drunk
- ▶ screening of liver function tests may reveal a raised GGT; by far the most common cause of this finding is alcohol.

Having identified alcohol abuse, it is essential to respond. The initial response should be either to assess the patient, discussing alcohol use, identifying problems associated with alcohol use, and providing information about safe drinking levels. Dependence should be assessed, and in particular, need for detoxification assessed. Practitioners uncomfortable at dealing with alcohol problems may prefer to refer the patient for specialist assessment at this point.

In some circumstances, particularly where there is established alcoholic liver disease, disulfiram (Antabuse) or Campral (acamprosate) may be helpful. Although unsupervised disulfiram is fairly ineffective in treatment of alcohol dependence, supervised disulfiram appears more effective. The patient attending a methadone clinic daily for supervised methadone can also be administered a supervised daily dose of disulfiram. (This can only be done following detoxification from alcohol, and with information provided to the patient).

Methadone syrup as supplied by Glaxo-Wellcome contains 18.5% alcohol. The quantity in a dose of methadone is so small that it is unlikely to provoke a reaction in the presence of disulfiram. However, an alternative formulation of methadone (Bioglan) is about to be released, and is expected to be alcohol free.

6.11.4 *Benzodiazepines*

Benzodiazepine use is common among patients on methadone. High dose benzodiazepine abuse and dependence is relatively uncommon, but is a major headache, as it is associated with patients doing poorly in treatment. Several treatment approaches have been proposed, but there is clearly no satisfactory approach. Where benzodiazepine dependence is a management problem, specialist referral is suggested.

6.11.5 *Cannabis*

Cannabis use is common among patients on methadone (about 50% of Australian patients report regular cannabis use), but few patients or practitioners identify it as a problem. Many laboratories do not screen urine specimens for cannabis, and when urine testing is performed, the significance of a positive result is unclear — telling little more than that at some time recently, the patient used cannabis. It does not help to identify heavy cannabis users.

There is evidence that cannabis use during methadone treatment can be an obstacle to rehabilitation. Cannabis use is expensive, and there is research evidence that heavy cannabis use during methadone treatment is associated with greater likelihood of involvement in property crime.

Patients who report regular cannabis use should be provided with warnings about the adverse health consequences (respiratory disease) and warned that cannabis use can be a barrier to rehabilitation. Patients who request further assistance can be referred to a specialist program for cannabis users.

6.11.6 *Psychostimulants*

Amphetamine use is common in Australia. Cocaine use remains relatively uncommon. Patients using amphetamine report higher levels of psychiatric symptoms (particularly, depression and psychosis) than other methadone patients, and detecting amphetamine use should alert the practitioner to the possibility of treatable psychiatric illness.

Observational studies suggest that amphetamine use during methadone treatment appears to decline over time.

An approach to amphetamine use is:

- ▶ screen for depression and psychosis
- ▶ clarify with patient whether use is a problem
- ▶ observe.

There is little Australian data on cocaine. American research suggests that the availability of cocaine destabilized many patients in methadone treatment.

6.12 **When a change in treatment is indicated**

There are several points during methadone treatment when a significant change in treatment is indicated. Changes need to be approached with caution, particularly in patients who are doing well, as practitioners often underestimate the impact of change.

6.12.1 *From clinic to pharmacy*

In NSW, most patients commence treatment in a methadone clinic. There are strong arguments for encouraging stable patients to transfer to dosing in retail pharmacies. Pharmacies are less institutionalized, more anonymous, and generally more accessible than clinics. Pharmacies generally have long opening hours, increasing the flexibility of treatment. If entering methadone treatment represents an important transition, from drug user to patient, transfer to a pharmacy signals a further transition, from patient to customer. The increasing autonomy implicit in this transition is usually reflected in pharmacy customers receiving regular take-home doses.

Many patients are reluctant to make changes to treatment. Once they have come to feel safe in attending a clinic, and becoming familiar with the routine and the individuals, they are uneasy about making changes, even if the changes mean greater convenience. Patients should not be compelled to make the transition, but can be encouraged over time. While patients are experiencing significant problems in social functioning they are usually not suitable for dosing in a retail pharmacy.

Some clinics are reluctant to encourage pharmacy dosing, for various reasons. This sometimes represents the possessiveness which is an obstacle to a healthy therapeutic relationship. The overall aim of treatment is restoring patients autonomy and independent functioning, and institutionalizing patients by keeping them attending a clinic may undermine that aim.

6.12.2 *Leaving treatment*

Most people on methadone would like to come off. One of the important tasks for practitioners is addressing patients sense of discomfort at being in treatment, reframing methadone to minimize stigma, shame and guilt.

However, despite information and encouragement, many patients decide they wish to leave treatment, and ask to be withdrawn. It is appropriate to explore reasons for this request, and to provide information about the prognosis after leaving treatment. If the patient remains determined, a withdrawal plan should be developed, and close-spaced, regular reviews of progress should be arranged. As part of the treatment plan, the patient should be reassured that they can re-enter treatment after leaving if they should change their mind. At subsequent follow-up visits, post-withdrawal planning should be included, as well as review of the patient's commitment to ceasing treatment.

The rate of withdrawal should be flexible, at the patient's discretion. However, too rapid a rate of dose reduction is likely to result in distressing withdrawal symptoms.

Individuals whose daily methadone dose is between 40mg and 80mg will generally tolerate a dose reduction of 5mg/week. People on doses greater than 80mg will generally tolerate reductions of 10mg/week down to around 70-80mg. However, individuals vary greatly, and it is best to allow the patient control over how often and by how much his/her dose is reduced during voluntary detoxification. When the dose gets below 40mg, the likelihood of a patient experiencing withdrawal symptoms becomes greater. It is preferable to slow the rate of dose reduction to 2.5mg per week. **Even at this slow rate of reduction, it is common for patients to experience some withdrawal distress.** During this detoxification period, many patients need psychological support. It may be appropriate to maintain a patient at a low dose for a prolonged period until he/she feels ready to reduce further.

Buprenorphine

There is currently a research project under way investigating whether the use of buprenorphine may be a way to assist patients to withdraw from methadone treatment without relapse and without severe withdrawal symptoms. At this stage, there is no evidence that withdrawal using buprenorphine will be easier, or relapse to heroin use will be less in patients withdrawn using buprenorphine.

Rapid detoxification

In recent years, many patients have been encouraged to withdraw from methadone by undergoing rapid detoxification — using naltrexone to accelerate the withdrawal process. Systematic studies of naltrexone-accelerated detoxification from methadone have been conducted in Australia. Published results to date indicate two key findings:

1. Rapid detoxification from methadone is associated with severe withdrawal symptoms, which persist for several weeks. Symptoms occur in 3 phases:

- ▶ The acute phase of withdrawal lasts about 4-6 hours from the administration of a bolus of naltrexone. Most approaches to rapid detoxification involve placing patients under a general anaesthetic or deep sedation for the duration of acute withdrawal.
- ▶ Subacute phase lasts from 12-72 hours in which time subjects report high subjective withdrawal scores and are often unwell, reporting severe fatigue and asthenia. Vomiting is quite common and most people are anorectic. Almost all subjects report severe difficulty sleeping. Many report feeling depressed.
- ▶ Chronic phase. Subjective withdrawal symptoms significantly higher than baseline persist for 3-4 weeks in patients who have been detoxified from methadone.

2. Relapse to heroin use is common

In view of the high rate of relapse and symptomatic distress, it is difficult to recommend rapid detoxification as a way of withdrawing from methadone.

Reflecting on the recent experimentation with buprenorphine and naltrexone, it is hard not to suspect that practitioners and patients alike are being distracted by detail. The important issue is not to focus on techniques for withdrawing from methadone, but to remember that most people who leave methadone treatment will relapse to heroin use. The problem is not how withdrawal is accomplished, the problem is — and has always been — that sustaining abstinence is difficult for people who have been opioid-dependent. No amount of research on methods of withdrawal will address that problem.

6.12.3 Discharge from treatment

When patients behaviour compromises their own safety, the safety and well being of other patients, or the safety of staff, it may be necessary to discharge the patient from treatment. Examples of unacceptable behaviour include carrying weapons, buying or selling drugs within the clinic precinct, intimidating staff or other patients.

Responding to incidents requires thought. Ideally, a patient should be interviewed, and the incident discussed. The following case vignette illustrates how clarification of an incident can be valuable.

Case Study – Discharge from treatment

For those who can remember, December, 1988 was a very hot month. A new methadone prescriber has just been appointed at Clinic X, (which, incidentally, was not air-conditioned). He arrives for his first morning session, moderately nervous, and is greeted by clinic staff who inform him that his first job that day is to interview patient CK, and inform him that he is being discharged from treatment. On the previous day, CK had presented to the clinic late, about 6 minutes after dosing had closed for the day. The clinic door was locked, but staff were all still present. CK knocked on the door, called out. No response. He kicked the door with increasing vigour. The glass cracked. Alarmed, staff came to the foyer, told CK he was too late to be dosed. He swore vigorously, threatened one nurse with unspecified consequences if he was not dosed, then stormed away, leaving the staff shaken and the front door broken. Staff resolved that he should be discharged from treatment, and that it was the doctor's responsibility to break this news to him.

*CK arrived at the clinic quite early — no surprise, he had missed his dose the previous day. He came to the doctor's office, and the new doctor noted glumly that CK was a large man. He introduced himself, and then commented *We have a problem. I don't know what happened yesterday, but the nurses say it was pretty bad. They are upset, and want me to discharge you from treatment. It strikes me that this is a big problem for both of us. Perhaps you could tell me what happened?* CK explained that on the previous afternoon he had been attending a lunch with his parents and (adult) siblings. He had a difficult relationship with his family, from whom he kept secret the fact that he was on methadone. The lunch was tense and stressful. At the end of the lunch, CK discovered to his dismay that in his anxiety before the lunch, he had locked his car keys in his car. He knew he had to get back to the clinic for dosing, but could explain his anxiety to no-one. He waited nearly two hours in the blazing sun before the road service van arrived to open his car. He drove rapidly to the clinic, but did not make it in time — and exploded, releasing all his pent-up frustrations.*

The doctor suggested that CK apologise to the nursing staff for the incident. He did so. Staff were happy for him to continue in treatment, which he did for several years without further incident.

This vignette illustrates the importance of not adopting adversarial approaches to difficulties in treatment. However, not all stories have a happy ending, and occasionally it is essential to take discharge a patient from treatment. In some situations, an alternative to discharging a patient may be to transfer the patient to an alternative dispensing site. Such a transfer is a concrete warning that certain behaviours are unacceptable, but that they are being given the opportunity to continue treatment in another setting.

6.12.4 Transfer to another treatment

There is currently considerable interest in buprenorphine as a maintenance drug. Many patients on methadone are interested in switching to buprenorphine.

Buprenorphine is a satisfactory maintenance drug, possibly marginally less effective than methadone in unselected patients. It is likely that a proportion of patients will prefer the pharmacological effects of buprenorphine, while others will do better on methadone. However, there are currently no grounds for predicting who might benefit from one drug or the other.

There is considerable stigma associated with methadone, whereas buprenorphine does not carry such stigma. Therefore, for reasons which are nothing to do with the different effects of the two drugs, many patients will be keen to make a change.

It is important in discussing a potential change in treatment to explore a patient's expectations and beliefs, and provide accurate information.

Issues relevant to choosing between methadone and buprenorphine are discussed in more detail in section 8.2.

It is possible that in the future a further option in treatment, LAAM may become available in Australia.

6.13 Methadone and pain management

Methadone maintained patients who require analgesia

Methadone-maintained patients who require analgesia following trauma or surgery should be given appropriate analgesia in addition to their regular methadone. Drugs with mixed agonist/antagonist properties, such as pentazocine (Fortral) should not be administered to methadone-maintained patients as this may precipitate an acute abstinence syndrome.

Methadone maintenance patients who are nil-by-mouth, as may occur after abdominal surgery, should be given parenteral narcotic analgesics, preferably by continuous infusion, in doses adequate to give pain relief. When they are able to take medication by mouth, oral methadone should be restarted, and the dose of parenteral narcotic progressively reduced. However, resumption of methadone dosing in this situation can be complex, particularly in acutely ill patients. If it is more than 48 hours since their last oral dose, resumption of oral methadone should involve the administration of small doses (20mg or less), repeating the dose at 8th hourly intervals according to the patient's response.

Patients with pain conditions who become opioid-dependent

Many patients with chronic pain states become dependent on medication. People who have come to regularly abuse prescribed analgesics for chronic pain states often function much better if placed on regular oral methadone. If there is no prior history of illegal drug abuse, and the patient can readily control their use of medication, patients can be treated by prescribing Physeptone tablets, regularly dispensed. However, there are some patients who cannot control their drug use, use in excess of their prescribed amounts, and who are best managed by a daily pick-up of methadone syrup.

6.14 Management of pregnant, opioid-dependent woman

Heroin use is often associated with amenorrhea or oligomenorrhea. One mechanism for this is that opioids, particularly injectable opioids, increase prolactin levels; prolactin suppresses FH and LSH, leading to reduced production of sex hormones. Many women who are successfully stabilized on methadone will experience a normalization of hormone levels and return of regular periods.

Despite diminished fertility, pregnancy is not uncommon in heroin-using or methadone using women.

Heroin use during pregnancy is associated with:

- ▶ an increased likelihood of premature delivery
- ▶ reduced birthweight, even controlling for confounders.

Multiple factors may contribute to these adverse outcomes, but the major issues are:

- ▶ lifestyle (smoking, lack of self-care, inadequate diet)
- ▶ opioid withdrawal can precipitate premature labour
- ▶ lack of ante-natal care (treatment of infections, provision of health advice) may contribute.

There is no evidence that opioids are teratogenic. However, babies born to opioid-dependent women may exhibit a *neonatal abstinence syndrome*. There is also evidence that opioid use during pregnancy increases the subsequent risk of Sudden Infant Death Syndrome.

There is little doubt that the ideal pregnancy involves a woman being drug free throughout, minimizing the risk of problems in the neonatal period. However, there are serious obstacles to achieving this outcome.

Opioid withdrawal is dangerous during pregnancy, particularly during the third trimester, and most particularly during labour. At this time, opioid withdrawal can contribute to foetal distress and foetal death. It has also been suggested that opioid withdrawal during the first trimester of pregnancy may increase the risk of miscarriage. **For these reasons, it is recommended that if opioid withdrawal is to be undertaken during pregnancy, it should be during the second trimester.**

About 50% of appropriately selected women, who have been stabilized on low doses of methadone (20mg), are able to withdraw during the second trimester, and be drug free at the time of delivery. Among unselected patients — including those who are on higher doses of methadone, or who are continuing to use other drugs — it is not realistic to expect many patients to be able to detoxify and remain drug free at delivery.

Pressure on women to do so is likely to be seriously counterproductive. Pregnancy is a time of considerable emotional challenge, and for drug-dependent women who are struggling with guilt and shame, adding to their sense of personal failure by an unsuccessful attempt to detoxify during pregnancy is potentially seriously destabilizing.

- ▶ The treatment of choice for a pregnant, opioid-dependent woman is methadone maintenance.
- ▶ Detoxification during the second trimester may be attempted in selected patients. However, a majority of women should remain on methadone until delivery.

6.14.1 *Methadone maintenance during pregnancy*

Critical issues in methadone treatment during pregnancy:

- ▶ It is better to engage the women in treatment by administering methadone than to insist on complete abstinence.
- ▶ Women engaged in methadone programs do better, irrespective of their continued illicit use

- ▶ Practitioners should make strong efforts to ensure that patients receive ante-natal obstetric care.
- ▶ High-risk pregnancies (psychologically unstable, unstable social circumstances, poor housing, continued illicit heroin use at time of delivery, history of previous child protection problems) require a case-management approach, preferably instituted in anticipation of problems, rather than waiting until they occur.

Specialist Drugs in Pregnancy services may be helpful in addressing these issues. The interaction between mainstream health services and drug users can be an unhappy one. Drug users attract disapproval, and pregnant drug users attract particularly strong disapproval. This deters patients from attending for care. Trained, non-judgmental, staff can contribute to improved compliance with appointments and antenatal care.

- ▶ Drugs in Pregnancy services can provide, where indicated, comprehensive case management that will last through pregnancy and the first months of the baby's life.
- ▶ Information to the women is vital and enables her to make informed decisions about her own drug use

Case management may include:

Prior to delivery

- ▶ Provision of information about what to expect .
- ▶ Assistance in gaining stable housing .
- ▶ Assistance in preparing for the arrival of a baby.
- ▶ Counselling and support.
- ▶ Preparation for parenting.
- ▶ Engaging her partner in treatment (80% chance of him being a drug user).

Post delivery

- ▶ Coordination of care during management of neonatal abstinence (this is particularly valuable in facilitating early discharge from hospital and safe ambulatory management).
- ▶ Case management during the first months of life is critical in identifying child protection issues, and in coordinating agencies which may need to intervene where there are concerns about child abuse and neglect.

Long-term outcomes

Adjusting for lifestyle factors (which disadvantage the children of socially marginalized patients), there is no evidence of adverse effects on children born of mothers who were maintained on methadone throughout pregnancy.

6.14.2 *Methadone dose during pregnancy*

During the third trimester of pregnancy, hormonal changes contribute to accelerated methadone metabolism, and many patients need higher doses or split doses to avoid withdrawal symptoms.

Some practitioners try to minimize the methadone dose during pregnancy in the belief that this will lessen neonatal abstinence syndrome. However, methadone dose at delivery

does not appear to be a strong predictor of the severity of neonatal withdrawal. Factors predicting the severity of the neonatal abstinence syndrome have not been clearly defined. It is likely that concomitant dependence on drugs other than opioids (particularly, nicotine dependence) may contribute to more severe neonatal abstinence.

Because of the risk of exacerbating withdrawal symptoms and precipitating relapse to heroin use, **it is not recommended that the methadone dose be lowered during the third trimester.**

- Q1. A 27 year old heroin user presents requesting methadone maintenance the day after discharging himself from an in-patient detox, where he was treated with clonidine for 5 days. A suitable starting dose for methadone would be:**
1. 10mg
 2. 20mg
 3. 30mg
 4. 40mg
 6. As he has almost completed detoxification, he should be encouraged to hang on for a few more days rather than enter maintenance treatment.
- Q2. During the first week of treatment, the recommended maximal dose of methadone should not exceed:**
1. 30mg
 2. 40mg
 3. 50mg
 4. 60mg
 5. 10mg more than the initial dose.
- Q3. A patient presents to a pharmacy at 8.35pm for his dose of methadone (60mg), but is initially refused a dose by the pharmacist because he is heavily intoxicated. The pharmacy shuts at 9.00pm, and attempts at contacting the doctor are not successful. The patient becomes agitated and abusive of the pharmacist and the sales attendant, demanding his dose. The pharmacist relents and dispenses a 60mg dose. The pharmacist contacts the prescriber the next day regarding the incident. This is the first such incident with the patient. What course of action do you take?**
1. Cessation of methadone treatment.
 2. Rapid withdrawal from methadone treatment.
 3. Reduction of the methadone dose until the patient attends for an appointment to discuss the incident.
 4. Review the patient as soon as possible and reinforce rules and expectations regarding behaviour.
 5. No specific action - wait and see if the problem recurs.
- Q4. A methadone-maintained patient on 70mg/day misses her Wednesday and Thursday doses, and presents on Friday for dosing, complaining of withdrawal, and requesting her regular weekend takeaways. Which of the following would you recommend:**
1. Dose the client with 70 mg methadone but not dispense take-aways.
 2. Prescribe 8 x Panadeine forte tablets and 10 mg diazepam and resume normal dosing regime on Monday.
 3. Dose the client with 40mg methadone and dispense usual takeaways.
 4. Dose the client with 40mg methadone but not dispense take-aways.
 5. Dose the client with 30mg methadone but not dispense take-aways.

See answers page 121

Preparations

Buprenorphine is currently available in Australia as 0.2mg sublingual tablets for the management of moderate to severe pain (Temgesic). A new formulation, Subutex, is now registered in Australia for the treatment of opioid dependence. Subutex come in sublingual tablets containing 0.4mg, 2mg, and 8mg buprenorphine.

Combined buprenorphine/naloxone

A further preparation may become available in the future, but is not currently registered in Australia. **Suboxone** comes in sublingual tablets, containing a combination of buprenorphine and naloxone in the ratio 4:1. It will come in strengths 2mg buprenorphine/0.5mg naloxone, and 8mg buprenorphine/2mg naloxone.

The aim of the combination product is to deter intravenous abuse of the drug and diversion of the drug to the black market. Naloxone has low bioavailability when taken sublingually (about 10%); and naloxone has little action in antagonizing buprenorphine. For these reasons, when a patient is stabilized on buprenorphine, the sublingual administration of naloxone has little, if any, effect. However, if a person dependent on other opioids injects the combination product, the result will be a significant and unpleasant precipitated withdrawal reaction. Given that intravenous naloxone is only moderately effective in antagonising buprenorphine, in a patient maintained on buprenorphine the injection of crushed Suboxone would not be predicted to precipitate a withdrawal reaction. Previous experience with the combination product has confirmed that the abuse liability of buprenorphine is diminished (but not abolished) by the addition of naloxone.

Deterring abuse and minimizing diversion are important public health issues in making any opioid available. However, it will require considerable clinical experience to confirm that Suboxone is as effective as Subutex, and that it significantly reduces diversion.

Initiation of buprenorphine in an opioid-dependent person should always be with Subutex. If Suboxone is used, it should not be introduced until a patient has received at least two doses of Subutex. This is because some (although not all) heroin users will experience a significant precipitated withdrawal reaction if treatment is initiated with Suboxone.

7.1 Pharmacology of buprenorphine

Buprenorphine is described as a partial mu receptor agonist. 1mg subcutaneous (s.c.) buprenorphine produces similar subjective effects as 30mg s.c. morphine, or 30mg s.c. methadone. The duration of subjective effects (euphoria, sedation) of the 3 drugs is similar, but buprenorphine and methadone produce more prolonged pupil constriction than morphine.

The distinctive properties of buprenorphine relate to the fact that it has:

- ▶ high mu opioid receptor affinity
- ▶ low intrinsic mu opioid receptor activity.

This combination produces three distinct properties:

1. There is a ceiling effect with buprenorphine

Like methadone, buprenorphine in a dose-dependent fashion reduces opioid craving and attenuates the effect of injected opioids. However, studies comparing the administration of methadone and buprenorphine in volunteers have demonstrated that, while on every subjective and physiological measure of response to opioids, the higher the dose of methadone, the greater the response, with each measure of buprenorphine activity, however, there was a ceiling dose, above which higher doses did not produce greater effects. Thus, the dose-response curve for buprenorphine becomes fairly flat once a certain minimum dose is reached. The impact of increasing doses of buprenorphine is to prolong, rather than intensify, opioid agonist effects.

The ceiling effect of buprenorphine has two important implications:

- ▶ Like all opioids, buprenorphine produces respiratory depression in non-tolerant subjects; however, the ceiling effect of the drug means that with increasing doses this does not usually produce increasing effects, making buprenorphine safer in overdose than full opioid agonists.
- ▶ With maintenance dosing buprenorphine may be less sedating. For some patients, this is an advantage; for others, who value the slight blunting of dysphoric moods, it probably means that buprenorphine may be less effective than methadone.

2. Buprenorphine is not reversed by naloxone

The high affinity of buprenorphine for the mu opioid receptor means that buprenorphine is not reversed by naloxone. (The fact that laboratory animals maintained on buprenorphine did not exhibit withdrawal when challenged with naloxone led early researchers to conclude that buprenorphine was non-addicting, a claim which is still occasionally made). In fact, when high doses of naloxone or naltrexone are administered to someone maintained on buprenorphine, withdrawal symptoms gradually emerge (after many hours), presumably reflecting the slow dissociation of buprenorphine from opiate receptors.

The important implication in practice is that cases of buprenorphine overdose (which, like most opioid overdoses, usually involve concomitant administration of benzodiazepines and/or alcohol) cannot be satisfactorily treated with naloxone, and assisted ventilation is probably required.

3. Buprenorphine can act as an opioid antagonist

The third distinctive feature of buprenorphine pharmacology is that as a result of the combination of high receptor affinity and low intrinsic activity, buprenorphine can act as an opioid antagonist when administered to someone with established opioid tolerance. Administered to a patient on methadone, or a person who has just used heroin, buprenorphine displaces these drugs from opioid receptors, and a mild-moderate precipitated withdrawal ensues. **The clinical implication is that administration of buprenorphine should be delayed until there is minimal circulating full opioid agonist present.** This means waiting until six hours after the last use of heroin. In

switching a patient from methadone to buprenorphine, it is desirable to reduce the methadone dose to 40mg or less (preferably, 30mg or less), and leave an interval of 24 hours before administering the first dose of buprenorphine. Even then, mild withdrawal may be experienced for the ensuing 12 hours.

7.2 Pharmacokinetics

Buprenorphine undergoes extensive first-pass metabolism, and is unsatisfactory for oral use. It is available for sublingual use. Sublingual tablets take about seven minutes to dissolve. Dissolution of the tablets can be accelerated by crushing the tablets to a coarse powder before placing them under the tongue. The drug is then slowly transferred from the buccal mucosa to the circulation, with peak blood levels being achieved about one hour after administration. Peak subjective and physiological effects of buprenorphine are not seen until about 2-4 hours after administration.

Buprenorphine has a fairly rapid distribution half-life of 3-5 hours and a prolonged terminal half-life (>24 hours), as a result of entero-hepatic recycling. With daily dosing on a stable dose, steady state is achieved after about seven days. The bioavailability of sublingual tablets is about 30% the bioavailability of subcutaneous doses. Buprenorphine is metabolized in the liver by CYP 3A4, and is excreted in faeces (70%) and urine (30%). The dose does not appear to require adjustment in renal impairment. Liver disease is associated with lower clearance of buprenorphine, but the clinical implications of this are uncertain. In fact, there is marked inter-individual variation in buprenorphine pharmacokinetics, with widely differing peak and trough blood levels being observed after the same sublingual dose administered to different individuals. However, in view of the fairly flat dose-response curve of buprenorphine, the implications of such variability may not be great. **As with other opioid drugs, the important aspect of management is to observe each individual's clinical response, and titrate the dose accordingly.**

Because of its long half-life, buprenorphine can be administered thrice weekly in many patients. However, for a proportion — presumably those with more rapid clearance — thrice weekly dosing appears unsatisfactory.

7.3 The effectiveness of buprenorphine maintenance treatment

Being a relatively recent drug, experience with buprenorphine maintenance is considerably more limited than experience with methadone. However, the available evidence is that buprenorphine is an effective maintenance drug. Subjects maintained on buprenorphine exhibit significant and substantial improvements in psychosocial functioning and in their opioid use.

The key issue in relation to the efficacy of buprenorphine is to investigate whether it is as effective as methadone.

<i>Double-blind, double dummy comparisons of methadone and buprenorphine as maintenance treatment</i>					
STUDY	GROUPS	n	WEEKS	RETENTION (%)	% NEG URINES
Johnson, 1992	B 8mg (sol)	53	17	41	*48
	M 20mg	55		20 (p<0.05)	*31
	M 60mg	54		31	*42 NS
Kosten 1993	B 2mg (sol)	28	26	50	27
	B 6mg (sol)	28		39	24
	M 35mg	34		68	52
	M 65mg	35		60 (p<.0005)	51 (p<0.0003)
Ling 1996	B 8mg (sol)	75	52	20	**41.9
	M 30mg	75		20	**49.8
	M 80mg	75		31	**64.9
Schottenfeld 1997 (heroin and Cocaine users)	B 4mg (sol)	29	24	34.5	23
	B 12mg (sol)	29		55.2	42
	M 20mg	30		46.7	28
	M 65mg	28		64.3 NS	55
Strain 1994a	B 8mg+(sol)	84	16	56	45
	M 50mg +	80		56	53
Strain 1994b	B 8mg+(sol)	24	16	53	45
	M 50mg +	27		53	40

What this table illustrates is that in most of these double-blind trials, retention was similar for both buprenorphine and methadone, and drug use was similar. There appears to be a suggestion of better retention on methadone than on buprenorphine, and slightly less heroin use in the high dose methadone groups. However, these outcomes were not observed in all trials. On current evidence, it appears that buprenorphine is a satisfactory maintenance drug, comparable in efficacy to methadone.

The data also suggests that there is a dose-response for both methadone and buprenorphine, with higher doses associated with less drug use and better retention in most studies. While experience with buprenorphine is limited, it is likely that doses of 12mg sublingually may be needed for optimal outcomes.

7.4 Side effects of buprenorphine

The following profile of side effects lists the percentage of patients who reported any side-effect during a major trial of buprenorphine maintenance. It should be noted that in such situations, everything reported by patients is recorded. Most of the side-effects were minor, and very few necessitated a change in treatment.

Asthenia	19%	Flu syndrome	12.5%
Headache	35.5%	Infection	29.6%
Pain	31.6%	Abdominal pain	14.0%
Back pain	18.2%	Withdrawal syndrome	30.5%
Constipation	12.6%	Nausea	14.4%
Anxiety	17.2%	Depression	16.0%
Insomnia	31.5%	Rhinitis	16.5%
Sweating	17.3%		

This list of side effects includes two distinct clusters of symptoms:

- ▶ symptoms of opioid withdrawal (asthenia, flu, pain, abdominal pain, back pain, withdrawal syndrome, rhinitis)
- ▶ symptoms of opioid toxicity (or side effects) (constipation, nausea, sweating).

In addition, headache is commonly reported. It is sometimes suggested that this may be a symptom of withdrawal.

7.5 Safety of buprenorphine

There is considerable experience with buprenorphine from France, where more than 50,000 people have been treated with the drug for opioid dependence. Post-marketing surveillance has indicated that the rate of serious adverse events is quite low. In particular, the overall incidence of opioid overdose appears to have dropped dramatically since the widespread introduction of buprenorphine treatment.

There have been a small number of fatal overdoses associated with buprenorphine, almost all of which have involved concomitant administration of benzodiazepines.

There have been a small number of reports of an acute hepatitis, with jaundice and raised transaminases, in patients treated with buprenorphine. In all cases, the problem appears to have resolved completely, usually after ceasing the drug. Although it is not clearly established that this represents an idiosyncratic reaction to buprenorphine, it is prudent to assume that if patients become jaundiced during buprenorphine treatment, the drug should be discontinued.

Chapter 7 – Self-assessment questions

Q1. Which of the following statements is/are true?

1. Buprenorphine can act as both an agonist and antagonist at the mu opioid receptor.
2. Buprenorphine has a higher affinity at the mu opioid receptor than naloxone.
3. Buprenorphine has a lower intrinsic activity than naloxone at the mu opioid receptor.
4. Buprenorphine has a higher affinity at the mu opioid receptor than methadone.
5. Increasing the dose of buprenorphine increases the duration of action.

Q2. Which of the following statements regarding the pharmacokinetics of buprenorphine is/are correct?

1. Steady state equilibrium is generally achieved within 4 to 6 days of daily dosing.
2. Buprenorphine has a high oral bioavailability.
3. Buprenorphine is principally metabolised by the liver.
4. There is wide inter-individual variation in pharmacokinetics of buprenorphine.
5. The dose of buprenorphine does not need to be adjusted in renal impairment.

See answers page 121

8.1 Buprenorphine Maintenance

There is limited experience with buprenorphine treatment. All that has been said about assessment and factors influencing methadone maintenance treatment is presumed to apply to buprenorphine. Issues about review of treatment and the importance of the therapeutic relationship, are all assumed to pertain to buprenorphine as they do to methadone treatment, and will not be repeated here. This chapter only addresses the pharmacological factors which differentiate buprenorphine from methadone treatment.

8.1.1 *Choosing between methadone and buprenorphine*

As with treatment of any condition, the choice of drug is largely determined by individual patient factors in terms of effects and side effects. However, in the case of maintenance treatments, issues of cost, availability, and regulatory requirements also influence the choice of drug.

Factors to consider in choice of maintenance drug:

1. Efficacy
2. Side effects
3. Concomitant medical conditions
4. Patient preferences
5. Logistics of treatment
6. Setting for treatment

Efficacy

Initiating and continuing treatment with any drug is contingent on the drug achieving or contributing to the objectives of treatment. On current evidence, both buprenorphine and methadone are effective maintenance drugs, with more research support for the efficacy of methadone. What is most likely is that some individuals (possibly due to differences in drug metabolism and response) will do markedly better on one or the other drug. It is critical that at regular formal review of treatment, the question of whether treatment outcomes could be improved by changing treatment be considered. If a patient is continuing to use heroin heavily despite adequate doses of buprenorphine, it is appropriate to propose a switch to methadone. Patients who experience withdrawal symptoms on methadone, and who are found to be rapid metabolizers of methadone, may be more readily stabilized on buprenorphine.

Side effects

There has been a wide range of side effects reported by patients on both buprenorphine and methadone. As in the treatment of many conditions, the choice of drug probably comes down to individual experience of side effects. This is difficult to predict in advance. Patients who experience nausea and often vomit after taking methadone may feel better on buprenorphine. Some patients prefer the lighter effect of buprenorphine, while others prefer the sedating effect of methadone.

Concomitant medical conditions

Patients who require enzyme-inducing medication in management of medical conditions may be unsuitable for methadone treatment. Reports suggest that patients with chronic pain conditions may be better managed on methadone than buprenorphine.

Patient preferences

Preferences are a key factor in treatment of heroin addiction, and are likely to be the major determinant of choice of treatment. Such preferences, if based on experience of efficacy and side effects, are totally valid, and should be accommodated if the logistics of treatment permit. However, practitioners should be aware that the new drug brings with it unrealistic expectations, and the hope — which is unlikely to be sustained — that buprenorphine will never be stigmatised in the way methadone is. Where preferences are based on unrealistic expectations, the practitioner has a duty to gently point this out.

Logistics of treatment

Availability, cost and ease of travel all modify choice of treatment. Dosing with buprenorphine is considerably slower (it takes around seven minutes to dissolve a sublingual dose of buprenorphine), and this may make clinics and retail pharmacies reluctant to take on large numbers of patients. On the other hand, the appeal of thrice weekly dosing will be a major source of enthusiasm for buprenorphine. The major logistic issue, cost, will be determined by regulatory decisions as to whether buprenorphine will be subsidized through the Pharmaceutical Benefits Scheme.

Setting for treatment

At this time, it seems likely that at least in some specialist clinics, buprenorphine will be employed as the introduction to treatment for heroin users, providing the flexibility to either detoxify or choose maintenance. Used in this way, patients will probably commence on buprenorphine, and transfer to methadone if treatment is not proving effective, or side effects are troubling.

What is clear is that the advent of buprenorphine (and, for that matter, naltrexone) as medications for treatment of heroin addiction has made treatment more diversified, and considerably more challenging for practitioners.

8.1.2 Induction onto buprenorphine maintenance

Induction onto buprenorphine may involve a patient:

1. Commencing maintenance from heroin use.
2. Transferring from methadone.
3. Undergoing buprenorphine detoxification from heroin.

► *Commencing maintenance from heroin use*

As with induction into methadone treatment, precautions must be taken concerning multiple drug use during induction into buprenorphine treatment.

The initial dose of buprenorphine should be in the range 2-8mg.

Where patients are not currently opioid-tolerant, the initial dose should be 2-4mg; higher doses may produce unpleasant side effects of intoxication. When there is uncertainty about the level of tolerance, 4mg should be the initial dose. In tolerant individuals (for example, those manifesting symptoms of withdrawal) the initial dose should be in the range 6-8mg. The initial dose should be administered at least 4-6 hours after the last dose of heroin, as precipitated withdrawal may otherwise make induction uncomfortable.

For patients with symptoms of withdrawal on the next day, the dose of buprenorphine can be increased 2mg. For patients who do not appear in withdrawal, the dose should be raised slowly if at all in the first week, to avoid the risk of accumulation and symptoms of intoxication. For patients who appear intoxicated, the dose should be reduced.

Careful attention to these issues should minimize the risk that a patient will drop out of treatment during induction onto buprenorphine. It is important that patients are reviewed during the first week of treatment. The following minimal schedule of reviews by the treating doctor is recommended:

- ▶ The day after their first dose of buprenorphine. This enables the prescriber to identify the onset of any precipitated withdrawal and the general adequacy of the first dose.
- ▶ Every two to four days until stabilisation.
- ▶ Every week during the following four to six weeks.
- ▶ Every two weeks during the following six to eight weeks.
- ▶ Monthly reviews are recommended thereafter, although the prescriber may wish to extend reviews to up to three months for very stable clients.

Individuals with continuing high risk patterns of drug use or concomitant medical, psychiatric or social problems may require more frequent review.

Transferring from methadone to buprenorphine

As noted in the chapter on opioid pharmacology, buprenorphine can act as an antagonist when administered to patients who are tolerant to full agonist drugs. When a patient on methadone takes his or her first dose of buprenorphine, a mild precipitated abstinence syndrome ensues.

Patients on low doses of methadone (e.g., less than 30mg) generally tolerate this transition with minimal discomfort. However, patients on higher doses of methadone may find the replacement of methadone with buprenorphine causes quite unpleasant withdrawal reaction for the first 12 —24 hours. This is only a problem after the initial dose.

Recommendations for transfer from methadone to buprenorphine:

- ▶ Progressively reduce methadone dose to 30mg/day or less.
- ▶ Initiate treatment with low doses of buprenorphine — 4mg initial dose, or 2mg initial dose if the patient is on 10mg/day or less of methadone.
The second dose of buprenorphine can safely be increased.

Undergoing buprenorphine detoxification from heroin

Heroin users who commence a withdrawal regime on buprenorphine may elect to remain on the drug longer term. In general, withdrawal regimes are based on the assumption that patients are neuroadapted (hence the need for detoxification) and usually begin with 6-8mg of buprenorphine (see below).

8.1.3 Stabilization on buprenorphine

At low doses, small increments have a greater impact in dose response, whereas at higher buprenorphine doses, larger changes are required to substantially alter the effect. The following increments are proposed:

- ▶ Below 16mg buprenorphine: dose changes of 2 - 4mg.
- ▶ Above 16mg buprenorphine: dose changes of 4 - 8mg.

As a long half-life drug, it is sensible to increase doses at intervals of 4-5 days, not more rapidly. If there are symptoms of intoxication, prompt reduction in the dose is required. As with methadone treatment, it is important to review patients regularly during induction, reviewing the patient and completing comprehensive assessment.

At each review, the buprenorphine dose should be titrated in the light of:

- ▶ signs and symptoms of intoxication, or reports of significant side effects indicate a need to reduce the dose
- ▶ adverse events (such as intoxicated presentations, overdoses) may be an indication to reduce the dose
- ▶ cravings for heroin use, use of heroin and other drugs, reported withdrawal symptoms, are reasons for increasing the daily dose.

8.1.4 Maintenance dosing

Buprenorphine doses should be individually titrated according to the patient's response to treatment. Effective maintenance doses that result in reduced heroin use and improved treatment retention, are achieved with high buprenorphine doses in the range of 12 to 24mg buprenorphine per day.

If patients are doing well, and feeling comfortable on doses of 8mg or more, their dose probably does not need adjusting. Patients on lower doses should have their doses raised (so long as this is tolerated).

There is little evidence to suggest that daily doses higher than 24mg will result in improved outcomes or effects. Little is known regarding the nature of adverse events at maintenance daily doses greater than 32mg, therefore, ***the maximum daily dose of buprenorphine routinely recommended is 32mg.***

Patients who continue regular heroin use despite being on buprenorphine doses of 24mg or more may well benefit from being transferred to methadone treatment. Such limited data as is available suggests that high dose methadone is more effective in suppressing heroin use than is high dose buprenorphine.

8.1.5 *Frequency of dosing*

Daily dosing with buprenorphine is required during induction and stabilization.

Many patients stabilised on buprenorphine can be maintained on alternate day dosing, and in some cases even three times a week dosing, without compromising treatment effectiveness. For most patients, thrice weekly dosing requires multiples of their stable daily dose. Thus, for example, a patient on 8mg daily could switch to 16mg on Mondays and Wednesdays, and 24mg on Fridays, without experiencing intoxication post-dosing or withdrawal symptoms between doses.

The convenience of reduced frequency of dosing appeals to patients and staff. **However, a minority of stabilized patients (estimates suggest up to 15%) will experience craving, withdrawal symptoms, and return to heroin use if transferred to thrice weekly dosing.**

A patient is suitable for a trial of alternate day or three times a week buprenorphine dosing on the following conditions:

- ▶ On a stable dose of buprenorphine for at least two weeks.
- ▶ No high risk drug use (high risk drug use refers to frequent abuse of other sedatives including alcohol, benzodiazepines, heroin or other opiates, intoxicated presentations to the pharmacy or medical practitioner, or recent history of overdose).
- ▶ The patient must be informed that the move to less than daily dosing will need to be reviewed, and may need to be reversed if the change leads to increased withdrawal symptoms, craving, or heroin use.

Some practitioners suggest that the patient initially switch to alternate day dosing regime of buprenorphine for two weeks. If this is successful, the patient can then be trialed on a three times a week regime.

An absolute limit of 32mg in any one dose is recommended for buprenorphine, as there is little experience with higher doses. In switching to alternate daily dosing, doses up to 16mg are doubled; above 16mg, daily doses are increased to 32mg. In switching to thrice weekly dosing, a patient who had been stabilized on 12mg/day would receive 24mg Monday, 24mg Wednesday, and 32mg Friday; a patient stabilized on 16mg/day would receive 32mg on each of the three dosing days; as would any patient stabilized on a daily dose above 16mg.

If a patient cannot be stabilised on such dosing regimes due to the onset of withdrawal, cravings, side effects or features of intoxication, then they should be returned to a more frequent dosing regime.

8.1.6 *Missed doses*

If a patient on daily doses of buprenorphine misses one or two doses, the usual dose should be administered the next day, so long as the patient is not intoxicated when presenting for dosing. If a patient misses three consecutive doses, they should be reviewed by the prescriber, and if not intoxicated recommenced according to the table below.

Usual 24 hour buprenorphine dose	Recommencement dose
> 8mg	8mg 4mg if > 7 days with no dose
6 - 8mg	4mg
2 - 4mg	2 - 4mg

Having recommenced, dose can be increased by increments of 4mg every 4 days to the maintenance dose.

If a patient on an alternate day regime or a three times a week regime dose not attend on a dosing day, but rather attends on the following (non dosing) day, then a lower dose of buprenorphine should be dispensed. The pharmacist should contact the medical officer. The dose prescribed should be sufficient to last until next scheduled dose (if 24 hours until next scheduled dose, prescribe a 24 hour dose; if 48 hours then give a 48 hr dose).

8.2 When a change of treatment is indicated

8.2.1 *Withdrawal from buprenorphine*

As with withdrawal from methadone, in considering how to withdraw from buprenorphine it is very tempting to distract oneself with techniques for withdrawal — slow or fast, linear or geometric, with or without counselling — the range of choices is dazzling, but largely irrelevant. The problem with withdrawal from maintenance treatment is that it is followed by abstinence, and abstinence is all-too-often associated with relapse to heroin use. While optimists hope that the different pharmacology of buprenorphine will mean that eventual withdrawal from buprenorphine maintenance is easier than withdrawal from methadone, there is no reason to believe that abstinence following buprenorphine differs greatly from abstinence following methadone. Such research evidence as is available confirms that both severity of withdrawal, and relapse post-detoxification, appear similar for methadone and buprenorphine.

Nonetheless, patients will request to withdraw from buprenorphine, and as practitioners we need to support their aspiration. Withdrawal from buprenorphine should only be conducted with the consent of the patient. Graduated reduction over weeks results in better outcomes (less relapse to heroin use) than rapid reductions. The following rates of dose reduction are recommended:

Dose of buprenorphine	Reduction rate
Above 16mg	4mg per week or fortnight
8 - 16mg	2 to 4mg per week or fortnight
Below 8mg	2mg per week or fortnight

Source: Dr Nick Lintzeris

8.2.2 *Transferring from buprenorphine to methadone*

Consideration should be given to transferring a client from buprenorphine to methadone under the following circumstances:

- ▶ Patient experiencing intolerable side effects to buprenorphine.
- ▶ Inadequate response with buprenorphine treatment. Treatment with buprenorphine should be considered unsuccessful if it has not resulted in marked improvements in the patient's drug use, injecting risk practices or other outcomes identified by the patient and practitioner as treatment goals.
- ▶ Transferring to location where buprenorphine is not available. As buprenorphine is a relatively new drug, it may not be available in certain jurisdictions, overseas, during periods of incarceration, nor in some hospitals. Patients should be transferred to methadone in such circumstances. To facilitate the subsequent return to buprenorphine treatment (if planned), the lowest effective methadone dose should be used.
- ▶ Patients who are suspected of diversion, and cannot satisfactorily be observed during dosing — for example, as may occur in a retail pharmacy, where the prolonged dissolution time may mean patients are not fully supervised — may need to be transferred back to methadone syrup, which can more effectively be observed.

Transferring from buprenorphine to methadone treatment is less complicated than methadone to buprenorphine transfers.

- ▶ Patients should be stabilised on daily doses of buprenorphine
- ▶ The buprenorphine dose should be reduced to 16mg or less for several days prior to transfer.
- ▶ Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of 30mg.
- ▶ Patients transferring from low doses of buprenorphine (eg 4mg or less) should be commenced on lower doses of methadone.

Subsequent methadone doses can be titrated according to patient's response, but as in all situations, the dose of methadone should not be rapidly increased, as buprenorphine can diminish the effects of methadone for several days (blockade effect). There should be adequate time to allow wash out of buprenorphine prior to prescribing methadone doses greater than 40mg.

8.3 Buprenorphine in heroin withdrawal

Buprenorphine has some distinct advantages in the treatment of heroin withdrawal.

- ▶ As an opioid agonist, buprenorphine provides better symptomatic relief of withdrawal symptoms than does clonidine, or other non-opioid agents used to ameliorate withdrawal. Patients are symptomatically quite well, and after day 2 of detoxification, patients can engage meaningfully in counselling and treatment planning.
- ▶ It can be administered as a single daily sublingual dose, making it simple to use in ambulatory detoxification, without the need to dispense carry medication which may not be used as directed.
- ▶ In people withdrawing from heroin, after short courses of buprenorphine (3-8 days), there is only a mild rebound withdrawal syndrome on discontinuing the drug.
- ▶ Buprenorphine allows options:
 - in patients who experience the benefits of stabilization on buprenorphine, they can remain on the drug as a maintenance treatment
 - patients who want to remain drug free after a short course of buprenorphine experience only mild rebound withdrawal
 - patients wishing to take naltrexone for relapse prevention can introduce naltrexone early in the course of detoxification. In contrast, use of full agonists such as methadone for detoxification do not allow introduction of naltrexone until considerably later.

The advantages of buprenorphine in detoxification relate to the flexibility of the drug, and the chance it provides to initiate a comprehensive treatment plan. Buprenorphine has less value if it is simply prescribed in the assumption that it can alleviate withdrawal; rather, to use the drug optimally it should be employed in the context of assessment, monitoring and reassessment, with a view to engaging the patient in ongoing treatment. For these reasons, a structured approach to withdrawal, incorporating daily monitoring and review is recommended.

8.3.1 *Limitations of buprenorphine in withdrawal*

- ▶ The first dose, if administered within six hours of last use of heroin, may precipitate a mild withdrawal reaction, which deters patients from persisting with detoxification.
- ▶ Buprenorphine has a range of side-effects, some of which appear to be symptoms of intoxication — particularly, dizziness, nausea, constipation, and itch — and some appear to be symptoms of withdrawal — headache, pain, and asthenia. When these side effects occur, dose adjustment may be required.
- ▶ Buprenorphine should not be employed in pregnant women or in nursing mothers. Care should be exercised in the use of buprenorphine in the medically ill, and in patients dependent on multiple drugs. Referral to specialist services is indicated in these situations.

8.3.2 *Withdrawal regimes*

If buprenorphine is used in detoxification with the option of continuing in maintenance treatment, practitioners should ensure that subjects are suitable for maintenance treatment before commencing the buprenorphine withdrawal regime.

There are many ways to manage withdrawal, and there probably is no single optimal approach. However, for a variety of reasons, it is desirable to adhere to a protocol which sets out the approach to treatment and doses of medication to be employed. The following schema sets out an approach to ambulatory (or residential) heroin detoxification using buprenorphine.

Day 0: **Assessment**

Presenting problem

Drug use history

Rate intoxication and withdrawal

Medical and psychiatric history

Social circumstances

⇒ Establish opioid dependence

⇒ Identify treatment goals

Explain treatment options

⇒ treatment plan

⇒ informed consent

MEDICATION MAY BE INITIATED ON DAY 0 OR DAY 1, DEPENDING ON CIRCUMSTANCES. DAY 1 IS THE FIRST DAY OF MEDICATION

A suggested approach to ambulatory buprenorphine detoxification

- Day 1: **Induction** (First day of medication)
Check drug use in preceding 24 hours
Re-explain treatment
⇒ **Administer buprenorphine 6mg**
⇒ **Observe 1 hour**
- Day 2: **Review 1** (plus discussion of health issues)
Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss appropriate dose
⇒ **Administer buprenorphine 10mg (+2mg)**
Counselling and screening (if appropriate) for blood borne viruses
Other health issues
- Day 3: **Review 2** (plus discussion of post-withdrawal treatment)
Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss appropriate dose
⇒ **Administer buprenorphine 10mg(+2mg)**
Discuss post-withdrawal treatment options
Referral for counselling assessment may be indicated
- Day 4: **Review 3** (plus screening for psychiatric symptoms)
Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss appropriate dose
⇒ **Administer buprenorphine 8mg(+2mg)**
Interview patient re psychiatric symptoms (depression, anxiety, psychosis)
- Day 5: **Review 4** (plus post-withdrawal treatment plan)
Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss appropriate dose
⇒ **Administer buprenorphine 4mg(+2mg)**
Discuss post-withdrawal treatment options
Review treatment experience (and test results, if any)
Arrange follow-up visit
- Days 6-7:(optional) patient may request symptomatic medication
- Day 8: **Follow-up 1**
Discuss drug use over 72 hours
Review treatment experience (and test results, if any)
Revise or follow treatment plan

8.3.3 *Post-withdrawal treatment*

On day 8, options include induction onto naltrexone, induction onto methadone, continuation on buprenorphine maintenance, or drug-free treatment. The essential benefit of buprenorphine treatment as outlined above is that it allows a progressive assessment over time, with development of a treatment plan based not only on the patient's preferences, but on their experience of buprenorphine treatment. If patients are to be offered the alternative of maintenance treatment, it is essential to check prior to initiating detoxification that they are suitable, from both a regulatory and clinical perspective. This means that they have corroborating evidence of opioid dependence, a 12 month history of opioid dependence, and patients are able to give informed consent. While it may be appropriate to use buprenorphine to detoxify patients not suitable for maintenance treatment, it is essential to clarify this before starting treatment, otherwise misconceptions about the goals of treatment may hold sway.

8.3.4 *Transfer to naltrexone*

Patients who have completed a buprenorphine-assisted detoxification and have abstained from heroin and all other full opioid agonists during the detoxification can be commenced on naltrexone. The longer the delay between the last dose of buprenorphine and the first dose of naltrexone, the less severe will be the precipitated withdrawal. It is recommended that after a 5-day buprenorphine detoxification, patients commence naltrexone on the morning of day 8.

- ▶ Although milder than the precipitated withdrawal which would follow if naltrexone were administered to someone dependent on heroin, the administration of naltrexone to someone who has completed heroin withdrawal using buprenorphine can be moderately severe.
- ▶ It cannot be predicted by performing a naloxone challenge test (as naloxone does not reverse buprenorphine).
- ▶ In subjects who have undergone buprenorphine-assisted detoxification from heroin, any precipitated withdrawal after induction onto naltrexone tends to be delayed several hours — often, after the patient has gone home, apparently well.

Some patients have a reasonably uneventful induction onto naltrexone, others experience considerable distress. It is best to warn prospective patients to expect symptoms. Patients will tolerate induction onto naltrexone better if they have been clearly warned what to expect. They will not mind being pleasantly surprised. It is probably desirable to prescribe two to three clonidine tablets to take in the 24 hours after induction, in the event of symptoms of precipitated withdrawal.

If patients have used heroin between days 3-8 of detoxification, induction onto naltrexone may be more severely symptomatic. Patients must be warned of this, but practitioners should be aware that for obscure reasons, some patients who have used heroin but are eager to commence naltrexone will deny heroin use in order to proceed with induction.

Under circumstances where there is any doubt, a naloxone test before the first dose of naltrexone may be useful. It will not predict some degree of precipitated withdrawal due to residual buprenorphine being gradually displaced by naltrexone, but will identify patients who have other opioids present.

The first dose of naltrexone should be 12.5mg, administered on the morning of day 8. Patients should be kept three hours, warned of possible delayed withdrawal, and an appointment made to see them next day. For the next two days they should receive 25mg/day naltrexone, and thereafter 50mg per day as tolerated.

Chapter 8 – Self-assessment questions

Q1. The first dose of buprenorphine should be administered to a heroin user

1. At least 2 hours after last use of heroin.
2. At least 4 to 6 hours after last use of heroin.
3. Prior to the commencement of any opiate withdrawal symptoms in order to prevent ongoing heroin use.
4. At least 24 hours after last use of heroin.
5. As soon as the features of heroin intoxication (myosis, sedation) have subsided.

Q2. The recommended first dose of buprenorphine for a patient transferring from 30 mg methadone is:

1. 4mg
2. 8mg
3. 12mg
4. 20mg
5. 32mg

Q3. A client has stabilised on a daily buprenorphine dose of 20 mg, and now requests transfer to alternate-day dosing. What dose do you prescribe for a 48 hour interval?

1. 20mg
2. 24mg
3. 32mg
4. 40mg
5. 48mg

See answers on page 121

9.1 Naltrexone pharmacology

Naltrexone hydrochloride is available in Australia as REVIA , and is presented as a scored pale yellow coated capsule shaped tablet. REVIA is available as 50mg tablets in bottles of 30 tablets.

9.1.1 Actions

Naltrexone is a highly specific opioid antagonist which has a high affinity for opiate receptor sites. It competitively displaces opioid agonists if they are present, such as methadone, heroin, and LAAM and to a lesser extent buprenorphine. Naltrexone then blocks the effects of subsequent opioid administration, for periods up to 48 hours in a dose-dependent fashion.

Clinical studies indicate that 50mg of naltrexone can block the effects of 25mg of intravenously administered heroin for up to 24 hours. 100mg and 150mg can lengthen the blockade for approximately 48 and 72 hours respectively.

Naltrexone has few intrinsic actions besides its opioid-blocking properties. It does produce some pupillary constriction by an unknown mechanism. Naltrexone does not cause any physiological tolerance or dependence. Naltrexone does not block the physiological or psychological effects of any other class of drugs.

9.1.2 Absorption, Distribution, Metabolism, Excretion

Naltrexone is rapidly absorbed after oral administration, with peak plasma concentrations within one hour. Approximately 20% is bound to plasma protein, and it is distributed widely, with relatively high amounts of the active metabolite in the brain, fat, spleen, heart, testes, kidney and urine. 6-b-naltrexol and naltrexone undergo enterohepatic recycling and are excreted primarily by the kidney. Less than 1% of an oral dose of naltrexone is excreted unchanged.

9.1.3 Side-effects of naltrexone**Side effects reported by more than 10% of patients include:**

difficulty in sleeping	loss of energy
anxiety	abdominal pain
nausea & vomiting	joint and muscle pain
headache	

Other side effects reported by less than 10% of patients include:

dysphoria	constipation
diarrhea	reduction in appetite
increased thirst	dizziness
skin rashes	difficulty ejaculating
decreased potency	chills
increased energy	irritability

9.2 Naltrexone treatment for relapse prevention

There have been several studies of naltrexone in relapse prevention. In general, the outcome of these studies has been high attrition from treatment. Even before commencing naltrexone, a significant proportion of people are unable to complete detoxification and commence on naltrexone. Among those who do commence, drop-out rates in the first two weeks are very high — averaging 39% drop-out in published studies (Tucker, 1998). Thereafter, attrition continues to be a problem, with the average retention in treatment ranging from one to eight months. Retention in most forms of drug abuse treatment (other than methadone maintenance) is generally poor, as motivation for treatment is generally transient (Ling, 1978). However, studies on patients with better social supports have found considerably better retention (Washton, 1984). Most importantly, there is evidence that naltrexone in combination with a psychosocial intervention is significantly more effective than either naltrexone alone or psychosocial treatment alone (Rawson, 1979).

The only moderately long-term, published follow-up study of patients treated with naltrexone (Rawson, 1984) reported that more than 90% of subjects became re-addicted to heroin at some time over the following five years. Patients in that study reported that they had found naltrexone helpful, as it had helped them to remain heroin-free for periods of time. This study concluded that naltrexone is not a cure for heroin addiction, but was a useful medication in protecting patients from re-addiction for periods of time.

The experience with naltrexone indicates that it is not a toxic drug, with few serious adverse events. Although some years ago it was noted that high doses of naltrexone administered to morbidly obese subjects resulted in transaminase elevations, subsequent experience with use of naltrexone in alcohol dependence has not found hepatotoxicity to be a problem.

9.2.1 *Risk of overdose*

However, while naltrexone may be looked on as a valuable addition to treatment options, and one that appeals to patients (and their families) as being preferable to maintenance on an opioid drug, there is one serious problem with naltrexone. There appears to be an increased risk of death after treatment with naltrexone (Miotto, 1997). This is probably primarily due to loss of tolerance to opioids. An increase in the risk of death by overdose occurs in any recently detoxified group of former heroin addicts, including people within 12 months of leaving methadone treatment (Zanis, 1999). After discontinuing naltrexone, a dose of heroin which the user had been accustomed to injecting during their last period of addiction, may now prove fatal. Another factor contributing to the risk of death is that some people become depressed after discontinuing heroin, and may deliberately suicide.

These are serious considerations limiting the use of naltrexone, since there have now been several reports that subjects treated with naltrexone are at increased risk of death compared to subjects treated with other pharmacotherapies.

9.3 Naltrexone and rapid detoxification

Although first used in the 1970s, the disappointing results of trials of naltrexone led to it being largely abandoned in the treatment of opioid dependence for many years. During the 1990s, there has been a resurgence of interest in naltrexone, for three reasons:

- ▶ Consistent evidence from randomized trials has indicated that naltrexone is effective in the treatment of alcohol dependence.
- ▶ Addiction treatment has become more professionalized, recognizing the need for an array of treatment options.
- ▶ There has been vigorous commercial promotion of rapid detoxification — the process of accelerating acute opioid withdrawal by the administration of an antagonist.

In the last three years, several studies of rapid detoxification have begun appearing. It is important that all practitioners involved in treatment of heroin users are familiar with this research, and are able to provide patients with accurate information.

In general, the quality of the research is low, and the results not definitive. Three serious limitations of the studies are:

- ▶ Most studies do not differentiate between patients withdrawing from methadone and patients withdrawing from heroin. Both clinically and pharmacologically, these groups are quite distinct.
- ▶ The methods by which relapse, compliance and any other treatment outcomes have been measured are fairly unreliable (telephone interviews, self-report, sometimes urine toxicology) — this may tend to overestimate the number of patients doing well.
- ▶ End-points are difficult to define. For some studies, stopping naltrexone is defined as treatment failure, for others a single episode of relapse is still consistent with a successful outcome. All these are valid ways to define outcomes, but the problem in reviewing the literature is that consistent definitions of outcome have not been used.

Despite the limitations of the studies, there are some consistent trends emerging, as illustrated in the following table.

Long term outcomes following rapid detoxification				
STUDY	N	WEEKS	METHOD	RELAPSE RATE (Intermittent use excluded)
Cucchia et al (1998)	20	26	Not specified	80% (60%)
Rabinowitz et al (1998)	83/120	52 (variable)	Telephone IV	60% (43%)
Bell et al (1999)	30	13	IV (variable)	77% (63%)
Gold et al (1999)	18/20	Variable Up to 78	Telephone IV	85% (65%)
London et al (1999)	13/20	13	IV (variable) & random urinalysis	75% (70%)
Albanese et al (2000)	111/120	26	Patient self report	45%
Hensel & Kox (2000)	66/72	52	Telephone IV & random urinalysis	26%

As the table illustrates, rapid detoxification seldom proves to be the beginning of a cure for heroin addiction. Relapse rates vary from 26-85%, with the great majority of studies reporting relapse to heroin addiction in more than 2/3 of subjects within six months.

Over the next 12 months, the results of several Australian trials of naltrexone treatment will become available, and should provide practitioners, patients and families with better quality data about the risks and benefits of naltrexone treatment (including rapid detoxification).

10.1 Patient selection for naltrexone

Naltrexone has a limited but potentially valuable role in the treatment of opioid dependence. In unselected heroin addicts, treatment with naltrexone is marked by high rates of attrition from treatment and relapse to heroin use.

However, naltrexone treatment may be beneficial for heroin users:

- ▶ strongly committed to abstinence
- ▶ with reasonable prospect of maintaining abstinence — good psychological and social functioning.

Contraindications to initiating naltrexone treatment:

- ▶ pregnant or breast feeding
- ▶ concurrently dependent on multiple drugs (requires specialist assessment)
- ▶ using opioids for chronic pain states (requires specialist assessment)
- ▶ acute hepatitis or liver failure
- ▶ known adverse reactions/sensitivity to naltrexone.

In addition, caution is advised in prescribing naltrexone to:

- ▶ patients who have impaired renal function, as naltrexone and its active metabolite are excreted in urine
- ▶ patients suffering marked depressive symptoms, or who are at risk of suicide, as a heightened suicide risk and mortality rate have been associated with naltrexone treatment [Miotto, 1997]
- ▶ patients with a history of psychosis (require psychiatric assessment and monitoring)
- ▶ children and adolescents, as the effects of naltrexone in the treatment of opioid dependence in these populations is also unknown - referral to specialist services is recommended.

Patients should only commence on naltrexone:

- ▶ after comprehensive assessment
- ▶ explanation of the risks and benefits of naltrexone treatment
- ▶ obtaining informed consent to treatment.

The treatment plan should include:

- ▶ schedule of regular reviews
- ▶ psychosocial support
- ▶ consideration of involvement of family members or significant others
- ▶ access to counselling services.

In patients seeking to transfer from methadone to naltrexone, it is both courteous and necessary for safety to discuss the patient's planned treatment with their methadone doctor or clinic. **There have been incidents when failure to do this had a fatal outcome.**

10.2 Induction onto naltrexone

In people tolerant to opioids, the administration of naltrexone will precipitate a withdrawal reaction. Because precipitated withdrawal involves a much more rapid process of physiological adjustment than spontaneous withdrawal, it is much more symptomatically severe.

Untreated, the acute phase of precipitated withdrawal involves two major clusters of symptoms:

- ▶ gastrointestinal symptoms, comprising unremitting vomiting and diarrhoea, often with cramping abdominal pain, lasting many hours.
- ▶ psychological disturbances, with agitation, dysphoria, and delirium. Delirium can last for up to 12 hours.

In addition, the following problems have been identified:

- ▶ There have been reports of psychotic episodes during precipitated withdrawal.
- ▶ Precipitated withdrawal is associated with significant physiological disturbances, including a marked increase in circulating catecholamines.
- ▶ Without supportive treatment, patients may become dehydrated and develop electrolyte disturbances as a result of severe vomiting.

To avoid precipitated withdrawal, it is desirable to wait until neuroadaptation is reversed and there are negligible quantities of circulating opioids. This means an opioid-free interval; seven days since last heroin use, and 14 days since last use of methadone, are recommended before introducing naltrexone.

Because many patients are unable to remain abstinent for the required opioid-free period, but may not be fully candid about their opioid use, a naloxone challenge is recommended. Naloxone is both rapid and short-acting. Administered to someone with residual tolerance will promptly precipitate a withdrawal reaction, which is, however, of much shorter duration and milder severity than the reaction precipitated by a dose of naltrexone. The use of a naloxone challenge can therefore prevent the development of a prolonged and distressing reaction to naltrexone, and is an important step in improving the safety of induction onto naltrexone.

Induction onto naltrexone

- ▶ Patients should have an opioid-free interval before commencing on naltrexone (seven days without heroin or other short-acting opioid, 14 days without methadone).
- ▶ To avoid inadvertently precipitating a withdrawal reaction, perform a naloxone challenge test prior to the first dose of naltrexone.

10.2.1 *Naloxone (Narcan) challenge*

Procedure

- ▶ Explain the test and the reason for performing it
- ▶ Intramuscular: 0.4mg, repeat another 0.4mg in 10 minutes if no reaction
- ▶ Intravenous: give 0.2mg; if no reaction after 60 seconds, give further 0.6mg and observe for 5 minutes.

Withdrawal signs should peak within 10 minutes:

- a) piloerection (palpable and lasting more than 30 seconds)
- b) rhinorrhoea, lacrimation, yawning (more than 3 times)
- c) sweating (wet rather than moist)
- d) vomiting.

Piloerection is the most decisive withdrawal sign. Restlessness is also a feature of a positive naloxone reaction.

Interpretation:

The naloxone challenge may be interpreted as positive (i.e. the patient is still physically dependent on opioids) if there is:

- ▶ a marked reaction to any one of (a), (b), (c) or (d)
- ▶ a milder reaction to any two of (a), (b), (c), or (d).

An alternative approach to interpreting the response to a naloxone challenge is to administer the Subjective and Objective Opiate Withdrawal Scales prior to naloxone, then repeat the scales at 10 and 20 minutes post naloxone.

A mild reaction - an increase of 2 points or less on the objective scale, or
- an increase of less than 5 points on the subjective scale.

Positive reaction - an increase >2 on objective or 5 or more on subjective scale.

Response:

- ▶ If there is a positive response delay induction and plan to re-challenge after at least 24 hours. Reassure patient that discomfort will pass in 20 minutes. If there is a severe response, administer symptomatic medication and advise detoxification.
- ▶ If there is a mild response to naloxone, ask the patient — can you tolerate this for 24 hours? If the patient feels able to do so, they may take 12.5mg (1/4 tablet) naltrexone and be reviewed later that day.
- ▶ If there is a negative response, naltrexone 25mg may be administered. If there are no signs of withdrawal after two hours, the patient can go home, with instructions to take 25mg naltrexone the next day, and 50mg (one tablet) daily thereafter.
- ▶ Patients should be reviewed at least once during the first week of treatment.
- ▶ If patients complain of significant withdrawal or side effects hold the patient on 25mg until symptoms settle.

10.2.2 *Symptomatic medication*

The following medications may be useful in treating withdrawal symptoms arising during induction onto naltrexone.

Clonidine: a centrally acting alpha-2 agonist, reduces sympathetic overactivity, agitation, and withdrawal distress. The primary side effects are hypotension and bradycardia, which limit the dose which can be used. The usual dose is 150ug (1 tablet) every 4-6 hours, but doses as low as 75ug 6th hourly can be helpful in controlling symptoms of withdrawal.

Octreotide: a synthetic somatostatin analog, is the most effective agent for controlling severe gastrointestinal symptoms associated with precipitated withdrawal. In that

situation, a single dose of 100ug (1 ampoule) may be administered subcutaneously.

Metoclopramide: (Maxolon) 10mg orally q8h is valuable for milder gastrointestinal symptoms of nausea and vomiting.

Buscopan: useful for abdominal cramps (20mg q6h orally).

Quinine sulphate: for leg cramps (300mg q12h).

10.2.3 Re-induction onto naltrexone

Many patients who have discontinued naltrexone for a period, with or without relapsing to heroin use, wish to resume naltrexone treatment. However, patients need to be cautioned that there is rapid reinstatement of dependence (within days of regular heroin use). Somewhat unpredictably, resuming naltrexone can precipitate withdrawal.

- ▶ If it is more than five days since last dose of naltrexone, and the patient has used heroin each day since then, start as though a new patient requiring detoxification prior to reinduction.
- ▶ If within five days of last naltrexone dose, or if the patient has not used heroin within the 48 hours prior to re-induction, it is probably safe to restart naltrexone.
- ▶ If within five days of last naltrexone dose, and there is any uncertainty about recent heroin use, it is judicious to perform a naloxone challenge test prior to re-induction.
- ▶ Restart naltrexone in the morning, at least 24 hours after last use of heroin.
- ▶ Commence with 1/4 tablet (12.5mg).
- ▶ Patients may need symptomatic medication.

Clinical experience to date has been that patients who relapse and return to naltrexone tend to remain in treatment a relatively short time. After multiple relapses, medical practitioners should seriously consider whether the risks of intermittent relapse outweigh the benefits of attempting to continue with naltrexone. It is preferable to actively manage cessation of treatment than for people to drop out and be receiving no treatment. Alternative approaches such as residential treatment or methadone maintenance treatment should be discussed.

10.3 Maintenance on naltrexone

Methadone and buprenorphine exert considerable pharmacological effects in stabilizing mood, reducing craving and suppressing heroin use; the medications are the primary agents in treatment. In the case of naltrexone treatment, there is no drug effect to help people adjust to being drug free, and psychosocial interventions are correspondingly more important.

10.3.1 The role of supervised dosing

Supervised dosing with methadone and buprenorphine is designed to minimize the risk of diversion of opioids to the black market. Supervised dosing with naltrexone aims to ensure the patient actually takes the medication.

Such an approach is not unique to treatment of addiction; supervised dosing has been demonstrated to be effective in treatment of conditions as diverse as tuberculosis and schizophrenia. However, most professionals involved in treating addiction have concluded that the treatment of drug dependence is based on volition and choice, rather than aiming to

control patients' behaviour. This is an empirical conclusion, not an absolute principle; it is based on the lack of demonstrated efficacy of treatment which seeks to control patients. However, should studies establish, for example, that supervised dosing with naltrexone achieves clearly superior long-term outcomes, then - in keeping with evidence-based medicine - it would become standard practice. Such evidence is not, however, currently available.

Some practitioners believe that the outcomes of naltrexone treatment can be improved by involvement of a family member or carer to supervise the patient's daily dose of naltrexone. Such an arrangement should preferably be discussed with patient and carer, and agreed to in advance of commencing naltrexone.

The system of supervised dosing is not foolproof. Some patients spit out the tablet when no one is watching. This has led to suggestions that naltrexone should be administered crushed and dissolved in orange juice to prevent it being spat out. Clearly, there is a slight sense of unease about how far practitioners and family members should go towards enforcing compliance with treatment. One of the risks of the carer system is that it sets up the potential for redefining family relationships into issues of supervision and control — a redefinition many families would find unacceptable except for very short-term periods.

10.3.2 *Naltrexone implants*

One alternative to supervised dosing which has been adopted by some practitioners in Australia is the use of naltrexone implants, which are designed to release therapeutic levels of naltrexone over a period of months. Such an approach potentially resolves issues of compliance, without involving families in supervision. Implants and depot drug preparations have been used in many areas of health care. It is likely that if satisfactory implants are ever developed, they will be suitable for some patients, although it is very difficult to say for what proportion of heroin users.

No naltrexone implant devices are currently registered for use in Australia. Any implants available for use, at the time of writing this manual, are not registered. Any use of such naltrexone implants at this time is investigational; it should be in the context of properly evaluated clinical trials, approved by a duly constituted ethics committee and registered with the Therapeutic Goods Administration.

10.3.3 *Monitoring and review*

Prior to initiation of naltrexone treatment, the patient and practitioner should agree on a schedule of follow-up appointments for the first weeks and months of treatment. Generally, it is helpful to see patients three times during the first week of naltrexone treatment, then weekly for four weeks, with appointments less frequent (but at least monthly) thereafter. In many situations continued weekly contact may be valuable.

10.3.4 *Managing side-effects of naltrexone*

In the first week of treatment, side-effects are common and troubling. Most patients report difficulty sleeping, feeling depressed, gastrointestinal discomfort with frequent bowel motions, and anorexia. Headache and withdrawal-type symptoms are also common.

Most of these symptoms resolve without treatment. When symptoms are severe, or when they persist beyond the first week of treatment, they may be made more tolerable by reducing the naltrexone dose to 25mg/day (half tablet).

Some practitioners treat side effects aggressively, introducing anti-depressants and benzodiazepines early in treatment in the hope of controlling symptoms and enhancing retention in treatment. The limited research available to date does not support the routine use of antidepressants or benzodiazepines, and there are serious concerns about the potential for benzodiazepine abuse and dependence. While the occasional use of benzodiazepines to assist patients to sleep early in treatment may be helpful, regular and routine use is not recommended. Antidepressants are probably best reserved for patients who have persisting or worsening depressive symptoms beyond the first few weeks of treatment.

10.4 Responding to continuing heroin use

Most patients early in naltrexone treatment test the blockade by having a shot of heroin. This should be expected and is not a source of concern.

Some patients continue to use heroin while taking a daily dose of naltrexone (which is both unexpected and a little baffling, as the heroin has no effect). More commonly, patients omit doses and use heroin intermittently, then resume naltrexone again. **Just because a patient continues (mostly) to take naltrexone does not mean that he/she is abstinent from heroin.**

This pattern of occasional heroin use is problematic because patients on naltrexone lose tolerance to opioids, but cannot judge this because naltrexone blocks the effect of any heroin which is used. For 48 hours after their last dose of naltrexone, patients will experience no effect, or only a very mild effect, from a dose of heroin. There then follows a brief window period when the remaining naltrexone is cleared from their bodies, leaving them totally non-tolerant to opioids — as though they were opioid-naïve. A dose of heroin which they were previously tolerant to can be lethal.

The significance of continued heroin use during naltrexone treatment is the risk of fatal heroin overdose due to the patient misjudging their level of tolerance.

Patients on naltrexone should be given repeated warnings about the risk of fatal overdose after discontinuing naltrexone.

Practitioners treating patients who regularly omit a few doses of naltrexone in order to experience a dose of heroin, then resume naltrexone use, have a difficult problem — should they cease naltrexone, or press on despite some concerns about safety? This question probably needs to be considered in each individual case, as circumstances vary. If, on balance, patients appear to be benefiting from naltrexone, making social and psychological changes, then it seems reasonable to continue treatment, albeit with warnings. If the patient appears to be making no progress, remains ambivalent about abstinence, then the risks of continuing naltrexone may not be justified by the benefits.

Practitioners need to remember that ultimately, the major risk factor for heroin overdose is abstinence. No one would argue that abstinence from opioids is not a valid treatment objective, yet it brings with it an increased risk of overdose in the event of relapse.

10.5 Other drug use

An uncertain proportion of former heroin users who enter naltrexone treatment dramatically increase their use of other drugs — in particular, psychostimulants, benzodiazepines, and/or cannabis. While some practitioners may see such a change in drug of choice as an improvement over being dependent on heroin, this is not necessarily so. Each patient's progress must be judged according to multiple objectives — drug use, psychological state, and social functioning.

10.5.1 Urine testing

Doctors, like everyone else, need affirmation that we are doing a good job. Heroin users, being kindly folk, try to take care to provide us with support and reassurance. (This is one of the more interesting, but seldom discussed, aspects of the therapeutic relationship.) They like to protect us from unpleasantness, and it is understandable that they do not always reveal the extent of their drug use and their limited compliance with treatment. This is particularly the case in the context of an abstinence—oriented treatment program, where practitioners are more likely to be distressed by news of heroin use.

For this reason, there are limitations on the value of self-report.

Urine tests are the traditional approach to monitoring drug use in methadone programs. Random urine testing, as employed in methadone programs, where patients attend every day and can be called on to submit specimens at random, is potentially useful (although the way it is usually employed it is not very informative). In naltrexone treatment, where patients have one scheduled appointment each week, it is not too difficult for most patients to work out which day he /she is likely to be asked to submit a urine specimen. In this context, urine testing is likely to seriously underestimate drug use. Unless this difficulty can be overcome, there seems little point in performing urine tests, except perhaps to gain some potentially false reassurance.

10.6 Depression and suicidal ideation

At reviews of treatment, practitioners should be alert to the emergence of symptoms of depression. Limited data to date suggests that there is an increased risk of suicide in people treated with naltrexone. There are many factors potentially contributing to this. The important clinical issue is to question patients specifically about depressive symptoms, including suicidal ideation. If depressive symptoms persist beyond the first few weeks of treatment, practitioners should respond either by referral for psychiatric assessment, or if the diagnosis seems clear cut, initiation of antidepressant therapy.

One issue which may contribute to suicide risk is the difficulty in adjusting to a drug-free life. A supportive doctor-patient relationship, in which this issue can be explored, may be of value. Alternatively, referral for counselling should be considered. Such steps may make adjustment easier, improve outcomes of treatment, and reduce the risk of suicide.

10.7 Duration of treatment

There is no evidence as to the optimal duration of naltrexone treatment. Among detoxified opioid users, the risk of relapse remains high for at least 12 months, and probably for up to three years. This does not imply naltrexone treatment needs to be continued for such a period. In patients who have made significant changes, and appear to have achieved a degree of stable abstinence, it may be reasonable to discontinue naltrexone after 6-12 months.

10.8 Issues for patients on naltrexone

Elective surgery

Naltrexone should be discontinued at least 48 hours before elective surgery (including dental surgery) which is anticipated to require opioid analgesia. The patient should then have an opioid-free interval before resuming naltrexone. The interval depends on the half-life of the opioid used for analgesia, and the duration of use — generally, after a few days of short-acting opioid such as morphine or codeine, naltrexone can be restarted after a break of three days. A cautious approach is to perform a naloxone challenge test prior to naltrexone re-induction, or to wait a full seven days.

Emergency pain relief

It is unwise to attempt to use opioid analgesics in patients on naltrexone. In an emergency, pain management may consist of regional analgesia, conscious sedation with a benzodiazapine, use of non-opioid analgesics (e.g., a NSAID without opioid activity such as ketorolac) or general anaesthesia.

In a situation where patients on naltrexone receive opioid analgesia, their lack of response may lead to very large doses being administered, and the deep and prolonged respiratory depression may result. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalised erythema or bronchoconstriction) and is most likely due to histamine release. Patients should be monitored closely in a setting staffed and equipped for cardiopulmonary resuscitation.

Mild pain

For mild pain relief paracetamol or aspirin should be used. Patients taking naltrexone will not benefit from opioid containing medicines such as cough, cold, and anti-diarrheal preparations.

Naltrexone precipitated opioid withdrawal

Patients should be advised that upon returning to heroin use they can rapidly reinstate their previous level of tolerance. If they recommence naltrexone without an adequate opioid-free interval it will precipitate severe opioid withdrawal. Patients should be cautioned about sharing their naltrexone with opioid dependent friends or engaging in home detoxification .

Patient bearer/medical alert/safety card

Patients should be advised to carry a card or medical alert bracelet which states they will not respond to opioid analgesia. The patient should also let other relevant clinicians (e.g., pharmacist, dentist, other medical officers) know that they are taking naltrexone so that appropriate pain management can be provided.

Pregnancy

Patients should be advised that they may experience an increased sex drive and fertility compared to when they were taking opioids and to use a reliable contraceptive to avoid pregnancy. The safety of naltrexone in pregnancy and while breastfeeding has not been established. The decision to continue naltrexone treatment in pregnancy involves careful assessment of the relative risks to the foetus and the likelihood of relapse to heroin use.

Chapter 10 – self-assessment questions

Q1. Concerning naltrexone, which of the following statements is/are true?

1. Treatment effectiveness is limited by low levels of compliance.
2. Heroin users entering naltrexone treatment are at increased risk of overdose in the ensuing 12 months.
3. Naloxone challenge should be performed before initiating naltrexone treatment for opioid dependence.
4. 50mg of naltrexone blocks the effects of administered opioids for 4-5 days.
5. 25mg/day naltrexone does not produce sufficient blockade to be therapeutically effective.

Q 2 A methadone-maintained patient (dose 80mg/day) presents with severe vomiting, diarrhoea and delirium. His accompanying friend says that he took a 50mg naltrexone tablet in an attempt to detoxify from methadone, as he was sick of attending daily. Which of the following would be appropriate?

1. Administer enough methadone to overcome the naltrexone blockade, then observe the patient.
2. Administer octreotide 100ug subcutaneously.
3. Administer diazepam 20mg hourly until delirium resolves.
4. Advise his friend that within 4-6 hours he will be feeling fine.
5. Recommend observation in a hospital emergency department.

See answers on page 121

Answers to self-assessment questions for section 2

Chapter 4	Q1. 1, 2, & 3
Chapter 5	Q1. 2, 4, & 5 Q2. 1, 2, & 3
Chapter 6.	Q1. 2 Q2. 2 Q3. 4 Q4. 4
Chapter 7	Q1. 1, 2, 4, & 5 Q2. 1, 3, 4, & 5
Chapter 8.	Q1 2 Q2. 1 Q3. 3
Chapter 10	Q1. 1, 2, & 3 Q2. 2 & 5

REFERENCES AND APPENDICES

REFERENCES

- Albanese, A., Gevirtz, C., Oppenheim, B., Field, J., Abels, I., & Eustace, J. (2000). Outcome and six-month follow up of patients after ultra rapid opiate detoxification. *Journal of Addictive Diseases, 19*, 11-28.
- American Psychiatric Association 1994) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (4th edition) Washington: American Psychiatric Association.
- Ball, JC & Ross, A (1991) The effectiveness of methadone maintenance treatment: Patients, programs, services and outcomes. New York; Springer Verlag.
- Bell, J. Australian trends in opioid prescribing for chronic, non-cancer pain, 1986-1996. *Medical Journal of Australia 167*; 26-29, 1997.
- Bell, J., Young, M., Masterman, S., Morris, A., Mattick, R. P., & Bammer, G. (1999). A pilot study of naltrexone-accelerated detoxification in opioid dependence. *Medical Journal of Australia, 171*, 26-30.
- Conrad, P & Schneider, J.W. (1992) Deviance and Medicalization. Temple University Press, Philadelphia.
- Cucchia, A., Monnat, M., Spagnoli, J., Ferrero, F., & Bertschy, G. (1998). Ultra-rapid opiate detoxification using deep sedation with oral midazolam: short and long-term results. *Drug and Alcohol Dependence, 52*, 253-250.
- Dole VP, Robinson JW, Orraca, J et al (1969) Methadone treatment of randomly selected criminal addicts. *New England Journal of Medicine 280*; 1372-75.
- Gold, C., Cullen, D., Gonzales, S., Houtmeyers, D., & Dwyer, M. (1999). Rapid opioid detoxification during general anesthesia. *Anesthesiology, 91*, 1639-1647.
- Gunne, LM & Grondbladh, L. (1981) The Swedish methadone maintenance program: A controlled study. *Drug and Alcohol Dependence 7*; 249-256.
- Hensel, M., & Kox, W. (2000). Safety, efficacy, and long -term results of a modified version of rapid opiate detoxification under general anaesthesia: A prospective study in methadone, heroin, codeine, and morphine addicts. *Acta Anaesthesiologica Scandinavica, 44*, 326-333.
- Hubbard, RL, Marsden, ME, Rachel, JV, et al (1989) Drug Abuse Treatment: A National Study of Effectiveness Chapel Hill, NC: University of North Carolina Press.
- Johnson, RE, Jaffe, JH, Fudala, PJ (1992) A controlled trial of buprenorphine treatment for opiate dependence. *JAMA, 267*; 2750-2755.

Kosten, TR, Schottenfeld, R, Ziedonis, D, and Falcioni, J (1993) Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disease*, 181; 358-364.

Kreek, M.J. (1991) Medical safety and side-effects of methadone in tolerant individuals. *Journal of Psychoactive Drugs* 23; 232-238.

Ling, W, Wesson, DR, Charuvastra, C, and Klett, J (1996) A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives of General Psychiatry*, 5; 401-407.

Ling, W. (1978) Naltrexone: The clinical investigator's dilemma. *International challenge of drug abuse*, 26, 308-314.

London, M., Paul, E., & Gkolia, I. (2000). Ultra-rapid opiate detoxification in hospital. *Psychiatric Bulletin*, 23, 544-546.

Lynskey, M & Hall, W. (1998) Jurisdictional trends in opioid overdose. National Drug and Alcohol Research Centre Technical Report No 54. Sydney, National Drug and Alcohol Research Centre.

McGlothlin, W.H., & Anglin, M.D. (1981) Long-term follow-up of clients of high- and low-dose methadone programs. *Archives of General Psychiatry* 38; 1055-1063.

McKetin, R, Darke, S., Hayes, A., & Rumbold, G. (1999) Drug Trends 1998. NDARC Monograph No 41, National Drug and Alcohol Research Centre, Sydney.

Maddux J F, Desmond D P. (1992) Ten-Year Follow-up after Admission to Methadone Maintenance. *American Journal of Drug Alcohol Abuse*, 18 (3),289-303.

Maddux, J.F., & Desmond, D.P. (1992) Methadone maintenance and recovery from opioid dependence. *American Journal of Drug and Alcohol Abuse* 18(1); 63-74.

Miotto K, McCann M.J, Rawson RA, Frosch D, Ling W (1997) Overdose, Suicide Attempts and Death Among a Cohort of Naltrexone-Treated Opioid Addicts. *Drug and Alcohol Dependence*, 45: 131-134.

Newman RG, & Whitehill, WB (1979) Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet*, Sept 8, 485-488.

NSW Child Death Review Team 1998-1999 Report

Rabinowitz, J., Cohen, H., & Kotler, M. (1998). Outcomes of Ultra-rapid opiate detoxification combined with naltrexone maintenance and counselling. *Psychiatric Services*, 49, 831-833.

Robinson, GM, Dukes, PD, Robinson, BJ, Cooke, RR, and Mahoney, GN (1993) The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug and Alcohol Dependence*, 33; 81-86.

Rosenbaum, M, Irwin, J, & Murphy, S (1988) De facto stabilization as policy: The impact of short-term methadone maintenance. *Contemporary Drug Problems*, 15; 491-517.

Strain, E.C., Stitzer, M.L., Liebson, I.A., & Bigelow, G. (1996) Buprenorphine versus methadone in the treatment of opioid dependence: Self-report, urinalysis, and addiction severity index. *Journal of Psychopharmacology* 16: 1; 58-67.

Strain, EC, Stitzer, ML, Liebson, IA, and Bigelow, GE (1994a) Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American journal of Psychiatry*, 151; 1025-1030.

Strain, EC, Stitzer, ML, Liebson, IA, and Bigelow, GE (1994b) Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. *Psychopharmacology* 116; 401-406.

Schottenfeld, RS, Pakes, JR, Oliveto, A, Ziedonis, D, and Kosten, TR (1997) Buprenorphine versus methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry* 54; 713-720.

Tucker T & Ritter A (1997). Naltrexone: a literature review. In A Ritter, J Kutin, N Lintzeris & G Bammer (Eds.) *Expanding Treatment Options for heroin dependence in Victoria - New Pharmacotherapies Project*. Turning Point Centre, Melbourne.

Washton, A. M., Pottash, A. C., & Gold, M. S. (1984). Naltrexone in addicted business executives and physicians. *Journal of Clinical Psychiatry*, 45, 39-41.

Yancovitz, S.R., Des Jarlais, D.C., Peyser, N.P., Drew, E., Friedman, P., Trigg, H.L., & Robinson, J.W. (1991) A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health*, 81; 1185-1191.

Zanis, D. A. Woody, G. E. (1998). One-year mortality rates following methadone treatment discharge. *Drug & Alcohol Dependence*. Vol 52(3) (pp 257-260).

Pharmaceutical Services Section

Under the Drug Misuse and Trafficking Act 1985, it is an offence to be in possession of or supply a prohibited drug (including methadone) unless the person possessing or supplying the drug is licensed or authorised to do so under the Poisons Act 1966 or is otherwise authorised by the Director-General of Health. PSS has the responsibility of ensuring that the provisions of the Poisons Act and the regulations under that Act are adhered to.

Under Section 28 of the Poisons Act it is an offence for a medical practitioner to prescribe or supply a drug of addiction to a person who, in the opinion of the medical practitioner is an addict (except where the person is being treated in a public hospital, in which case an authority is not required for the first 14 days), or to a person for continuous therapeutic use for more than two months unless the medical practitioner has a written authority to do so by the Department of Health.

Authorisation to prescribe methadone

Section 28A of the Poisons Act provides for a medical practitioner to be approved to prescribe methadone to opioid-dependent persons on the recommendation of the Pharmacotherapy Credentialling Committee. Approval to be a methadone prescriber is subject to conditions which include a limitation on the number of patients that a prescriber may manage, in some instances the sector and place for which the approval holds, and that the prescriber comply with the Department's NSW Methadone Maintenance Treatment Clinical Practice Guidelines. Approvals become ineffective unless these conditions are complied with. All approvals are subject to review.

Where a prescriber is approved to prescribe methadone to opioid-dependent persons, the prescriber must obtain authority from PSS for each person he/she wishes to commence on methadone. The prescriber must complete and submit to PSS an *Authority Application Form* for each patient and can only commence the patient on methadone after authorisation has been received from PSS. Upon receipt of the application, for reasons of safety, PSS check that the prescriber is approved, that the prescriber is inside his/her current patient numbers, and a current authority does not already exist for the proposed patient.

Each patient authorised for receipt of methadone maintenance treatment is issued with a unique identifying number. At the time of authorisation a maximum dose is specified by PSS and that dose should not be exceeded except by further application and authority from PSS.

The authorisation for each patient is valid for up to six months.

While the application for authority to prescribe may be sent by facsimile to PSS, it is stressed that they are dealt with in order of receipt and are not given any priority over mailed applications. The originals of all faxed applications must be forwarded to the Section.

Where it is determined that the prescriber will no longer prescribe methadone for a particular patient, either because the patient has completed treatment, has been transferred to another prescriber, or has been involuntarily discharged from the prescriber's program, the prescriber must complete and forward to PSS a *Termination of Methadone Maintenance Form* within five days of the termination of the patient's treatment.

Requirements for the issue of prescriptions

Before a patient can commence on methadone maintenance treatment a valid prescription, with a current photograph attached, must be forwarded to the clinic or pharmacy where the patient is to be dosed. This is not to be sent with the patient. Where the patient is not to commence methadone immediately, the starting date for treatment should be clearly indicated on the prescription.

The prescription must show the patient's name and address, the daily dose of methadone (this should be recorded in figures and words), and the period of time for which the dose is to be administered. The dosage must be clear, increase dose by x mg/day or maintain present dose are not acceptable notations as the prescriber and clinic/pharmacist may have a different understanding of the current dose. Where a patient is to receive takeaway methadone doses these must also be authorised in writing by the prescriber, either on the prescription or on a separate form attached to it.

Prescriptions are only valid in NSW for six months.

Dosing methadone patients

For the first three months of treatment patients should generally be dosed at public or private clinics and should not have access to takeaway methadone doses. This can be a stabilising period for the patient and allows the doctor to establish a relationship with the patient which will allow him/her to make appropriate decisions later about the most suitable means by which to deliver treatment.

Where there are subsequent changes in administration points, be it from clinic to clinic, or clinic to pharmacy, on either a temporary or permanent basis, these must be arranged through PSS.

Dispensing methadone

No person other than a pharmacist, or an assistant under the direct personal supervision of a pharmacist, can dispense a prescription for a restricted substance. The Pharmacy Act however, does make provision for a medical practitioner to dispense medicine in the ordinary course of medical practice, which includes methadone prescribers dispensing methadone.

Therefore while nurses are able to administer methadone, only a doctor or pharmacist, or nurse under the supervision of a pharmacist may dispense a takeaway methadone dose, or a dose for home or cell dosing. When a methadone dose is dispensed there are specific requirements outlined in the Poisons Regulations and the State policy document that must be met (see Appendix 4).

Optimal care and the safety of the patient should invariably be the objective of all prescribers. It is critical that PSS and others involved in the management of a patient - pharmacists, clinics and hospitals - are fully informed of changes in dose, administration point, or any other significant matter. Unfamiliarity with, or the careless application of the contents of the Department's Procedures and Policy Manual can lead to mismanagement of the patient and jeopardise their safety.

PSS are located within the grounds of Gladesville Hospital

The postal address is:

PO Box 103,

GLADESVILLE, 1675

All Australian states have strict controls over the availability of drugs of addiction, including methadone. In drug substitution therapy the use of methadone is restricted to those who are opioid-dependent. Admission into methadone treatment should only occur after an individual has been assessed by an approved methadone prescriber, determined appropriate for treatment and the patient's identity has been verified.

Authorisation

- ▶ A prescriber must obtain authority for each methadone patient. An Authority Application Form (yellow) should be completed and forward it to Pharmaceutical Services Section (PSS) of the Health Department.
- ▶ A patient must not be commenced on methadone until authority has been granted by PSS.
- ▶ An authority is valid up to a maximum of six months.
- ▶ An exit form (pink) must be completed and forwarded to PSS for each patient discharged from a program or transferred from the prescriber's care.

Prescriptions

- ▶ A current photo and valid prescription must be forwarded to the clinic or pharmacy before the patient can commence on methadone at that clinic or pharmacy. (It is not to be sent with the patient).
- ▶ The prescription must show the patient's name, address, daily dose of methadone in figures and words, and the period of time for which the dose is to be administered. The prescription must be signed.
- ▶ A patient's treatment card must show the dose of methadone in figures and words and the period of time for which the dose is to be administered.

Dispensing

- ▶ Generally, patients must attend an accredited public or private clinic for the first three months of treatment, not a pharmacy.
- ▶ The placement of patients at community pharmacies must be arranged through Pharmaceutical Services Section.
- ▶ Transfers of patients from clinic to clinic or clinic to pharmacy on either a temporary or permanent basis must be arranged through Pharmaceutical Services Section.
- ▶ Patients generally should not be given takeaway doses during the first three months of treatment.
- ▶ All takeaway doses must be prescribed in writing by the prescriber, whether on the same form as the prescription (regular takeaways) or a separate form (special takeaways). Takeaway doses should be prescribed in accordance with the NSW takeaway dose policy.
- ▶ Takeaway doses are to be given at the discretion of the accredited prescriber except for overseas takeaway doses (refer to the NSW Methadone Maintenance Treatment Clinical Practice Guidelines).
- ▶ Takeaway doses must be prepared either by a medical practitioner or a pharmacist or under the direct personal supervision of a pharmacist.
- ▶ Takeaway doses must be packed in containers fitted with child resistant closures and labelled in accordance with provisions of Poisons Regulations.

For further information consult NSW Methadone Maintenance Treatment Clinical Practice Guidelines, or telephone Pharmaceutical Services Section on (02) 98795214.

INSTRUCTIONS: Please score each of the 15 items below according to how you feel **NOW**. Place a tick (✓) in the appropriate column. Only one tick per question. Use the scoring values as provided. Obtain the total score by adding the score given for each item. Please answer all items.

Patients name _____

A. TIME OF FORM COMPLETION |__| |__| : |__| |__| AM / PM

B. FORM NUMBER: 1 2 3 (circle)

SUBJECTIVE OPIATE WITHDRAWAL SCALE					
ITEM	0 Not at all	1 A Little	2 Moderate	3 Quite a Bit	4 Extreme
I feel anxious					
I feel like yawning					
I am perspiring					
My eyes are teary					
My nose is running					
I have goosebumps					
I am shaking					
I have hot flushes					
I have cold flushes					
My bones & muscles ache					
I feel restless					
I feel nauseous					
I feel like vomiting					
My muscles twitch					
I have stomach cramps					
I feel like using now					
Column Scores					
Total Score					

Patients name _____

INSTRUCTIONS: This form is to be completed by a member of clinical staff. Give a score for each of the observations (No.s 1 - 13) according to the scoring values for each given observation and how the client appears within a 5-10 MINUTE OBSERVATION PERIOD. Add up the total score for all of the observations to get the overall withdrawal score for each administration of naloxone.

OBJECTIVE OPIOID WITHDRAWAL SCALE				
Observations	Scoring	Score 1	Score 2	Score 3
1. Yawning	0 = no yawns 1 = > 1 yawn			
2. Excessive nasal discharge	0 = < 3 sniffs 1 = > 3 sniffs			
3. Goose flesh (observe arm)	0 = absent 1 = present			
4. Perspiration	0 = absent 1 = present			
5. Watery eyes	0 = absent 1 = present			
6. Tremor	0 = absent 1 = present			
7. Pupil dilation	0 = absent 1 = > 3mm			
8. Hot and Cold Flushes	0 = absent 1 = shivering/huddling for warmth			
9. Restlessness	0 = absent 1 = frequent shifts of position			
10. Vomiting	0 = absent 1 = present			
11. Muscle twitches	0 = absent 1 = present			
12. Abdominal cramps	0 = absent 1 = Holding stomach			
13. Anxiety	0 = absent 1 = mild - severe			
TOTAL SCORE				

ACKNOWLEDGMENTS

The NSW Health Department would like to acknowledge the major contribution of Dr James Bell, FRACP, Director, The Langton Centre, in the development of this training program which was approved by the NSW Pharmacotherapy Credentialling Subcommittee.

The NSW Health Department would also like to acknowledge the contribution of the following people:

Dr Claire Gerada

Dr Nick Lintzeris

Dr Deborah Zador

Assoc/Prof Steve Allsop

NSW Health Drug Programs Bureau.

NOTES

NOTES
