Buprenorphine in the management of heroin withdrawal

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Nicholas Lintzeris

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FOREWORD

Statement of original work

For each of the three research trials included in this thesis, I was responsible for:

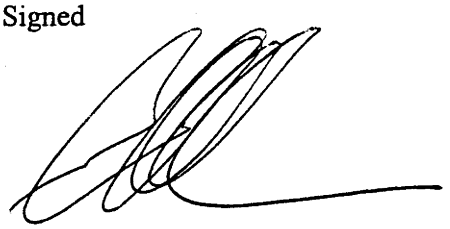
- Development of research questions, study design, methods, treatment and research protocols, applications to Human Research Ethics Committees, training and supervision of research and clinical staff, supervision of data collection, all data entry and analysis, report writing, and presentations of study findings at conferences.

Assistance with the conduct of the research for thesis was obtained in the following areas:

- Whilst the literature reviews were conducted and written by myself, I had access to a reference database (Endnote), which contained many of the references in this thesis. In particular, Dr Nicolas Clarke (Turning Point Alcohol and Drug Centre) had previously entered all references relating buprenorphine into Endnote as part of a systematic literature search regarding buprenorphine maintenance treatment in the management of opioid dependence.
- Research assistants were involved in the collection of data at each site for the three studies, and in the collation and storage of data in research files prior to data entry. In Melbourne (Inpatient Titration Study, Outpatient Titration Study, and Randomised Controlled Trial), the senior research assistant was Louise Rushworth, who conducted the vast majority of research interviews with subjects (it should be noted that I was the senior study medical officer and involved in clinical service delivery, which compromised my capacity to conduct confidential research interviews). In the ACT (Inpatient Titration Study), the research assistant tasks were shared by Nikki Main and Phyll Dance (National Centre for Epidemiology and Population Health); whilst in Sydney, the principal research assistant was Cath Weeks (The Langton Centre).
- Treatment services were provided by clinical teams at each site: - Clinical Services Department of Turning Point Alcohol and Drug Centre, Depaul House of St.Vincent's Hospital in Melbourne, The Canberra Detoxification Unit in the ACT, and The Langton Centre in Sydney. I was the senior medical officer who developed treatment protocols, staff training programs, supervised clinical staff, and was involved in direct service delivery at the Melbourne sites for the vast majority of subjects in the Inpatient Titration Study, Outpatient Titration Study, and Randomised Controlled Trial. Particular recognition should go to Drs Adrian Dunlop and Nadine Ezard, and senior pharmacist Peter Muhleisen from Turning Point Alcohol and Drug Centre, Drs Mazengarb and McQueen in Canberra, and Dr James Bell at The Langton Centre for their significant contributions to the delivery of clinical services as part of this trial.

- Assistance with the health economics components of this research (RCT) was obtained from Elena Godsporevska and Tony Harris from the Centre for Economic Health Evaluation, Monash University. They provided estimates of costs associated with non-trial health services (Appendix 2), and in the computerised analysis of SF-36 data.
- Panacea Research and Evaluation Pty Ltd performed independent monitoring of the Inpatient Titration Study and Randomised Controlled Trial, under the auspices and funding of the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project co-ordinated by the National Drug and Alcohol Research Centre and NCEPH.
- The Clinical Trials Unit of the National Health and Medical Research Centre in Sydney conducted the randomisation of subjects in the Randomised Controlled Trial.
- The research was conducted at the National Centre for Epidemiology and Population Health at ANU and the Research Department of Turning Point Alcohol and Drug Centre. Drs Gabriele Bammer and Alison Ritter (Head of Research at Turning Point) were responsible for co-ordinating research activities at these sites, including matters such as the administration of research funding, staff employment and general staff supervision.
- Dr Alison Ritter was responsible for co-ordinating supplies of the investigational drug buprenorphine (and placebo tablets) through Reckitt and Colman (and later Reckitt Benckiser) of Hull in England.

Signed



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Orientation to thesis

This thesis examines the use of buprenorphine in the management of heroin withdrawal. Chapter 1 begins with an overview of treatment services for heroin withdrawal, including the role and objectives of services, and develops a framework for the evaluation of withdrawal services, prior to considering non-pharmacological approaches in the management of heroin withdrawal. The use of other medications for heroin withdrawal is initially reviewed, including methadone, clonidine and lofexidine, and antagonist-accelerated withdrawal. The rationale and evidence regarding the efficacy of buprenorphine for heroin withdrawal is then systematically reviewed, with identification of the key outstanding clinical research questions regarding buprenorphine in withdrawal.

Three clinical research trials were conducted in order to address some of these outstanding research questions. The Inpatient Dose Titration Study (Chapter 2) and Outpatient Dose Titration Study (Chapter 3) aimed to establish suitable dosing regimes for those settings using sublingual buprenorphine tablets (Subutex®), the preparation becoming commercially available internationally. The largest trial (N=114) was an open label, multisite randomised controlled trial of buprenorphine compared to conventional symptomatic medication (including clonidine and benzodiazepines) for the management of outpatient heroin withdrawal, with a 4-week post withdrawal follow up phase. This study examined a range of outcomes including heroin use during and after withdrawal episode, retention in withdrawal and post withdrawal treatment, psychosocial outcomes, adverse events and cost effectiveness (Chapter 4).

The final chapter (Chapter 5) examines some key issues in the implementation and uptake of buprenorphine in the management of heroin withdrawal, including the application of principles of evidence-based medicine in clinical-decision making for individual patients; and an examination of broader systemic issues likely to impact upon the uptake of this new approach to withdrawal within the drug treatment system in Australia.

Status of buprenorphine during the research period

Buprenorphine has been registered as an analgesic (Temgesic®) in low dose preparations in Australia since the early 1980's, but had not been registered for the management of opioid dependence at the outset of this research. This PhD commenced in August 1997. One multi-centre trial of buprenorphine for maintenance treatment was underway in Australia at that time. Recruitment and service delivery for the trials in this thesis commenced in June 1998, and was completed in February 2000.

Buprenorphine (Subutex®) was registered in Australia for the treatment of opioid dependence in October 2000, although it was not widely available until February 2001. The Australian clinical guidelines and national policy for the use of buprenorphine were published in June 2001, and buprenorphine (Subutex®) has been subsidised by the Commonwealth PBS (Pharmaceutical Benefits Scheme) since August 2001. Cost-effectiveness data from the outpatient withdrawal Randomised Controlled Trial (albeit unpublished data at the time) was the submitted for consideration by the Pharmaceutical Benefits Accreditation Committee in considering the subsidisation of buprenorphine by government Pharmaceutical Benefits Scheme.

Terminology

This thesis uses various terms that warrant clarification:

'Patient' refers to individuals attending treatment services, and can be used interchangeably with the term 'client'.

'Subject' refers to patients enrolled in research trials. The term 'participant' was not used as it may be confused with other individuals involved (or participating) in the research process such as clinicians and researchers.

The term 'withdrawal' is used to describe both a syndrome (e.g. heroin withdrawal), and the process by which individuals undergo this syndrome (also known as 'detoxification').

ABSTRACT

This thesis examines the role of buprenorphine in the management of heroin withdrawal. Prior research suggests that buprenorphine has a number of pharmacological properties well suited to this purpose. A systematic review of randomised controlled trials of buprenorphine for heroin withdrawal indicated that buprenorphine is more effective in reducing withdrawal severity than clonidine. However, research has not adequately addressed buprenorphine's efficacy with regards to other key objectives of withdrawal treatment: retention in withdrawal services, reduction in heroin use during outpatient withdrawal, cost effectiveness, and post-withdrawal outcomes such as retention in treatment and heroin use. There is also uncertainty regarding the optimal dosing regimens for inpatient and outpatient withdrawal, with considerable variation in the range of doses and types of preparations used in earlier research. Three studies were conducted to examine these outstanding issues.

The first study examined dosing regimes of the sublingual tablet preparation, Subutex®, in inpatient settings, using a single-blind dose titration design. 63 dependent injecting heroin users with no significant co-morbidity were recruited, and doses of buprenorphine (2 or 4 mg) or placebo administered 4 times a day over the first 5 days, titrated against withdrawal severity using the Subjective Opiate Withdrawal Scale. 32 subjects completed the withdrawal regime, and generally described mild withdrawal severity. The mean (± SD) daily doses (in mg) were 3.8 ± 2.8 on day 1, 5.8 ± 3.2 on day 2, 4.8 ± 3.3 on day 3, 2.3 ± 2.6 on day 4 and 0.8 ± 1.3 on day 5; with a total mean dose of 17.4 ± 9.7 mg. Multiple regression analysis identified that higher buprenorphine doses were significantly associated with poor baseline psychosocial functioning ($p < 0.01$), female sex ($p < 0.01$), higher frequency of heroin use at baseline ($p < 0.05$) and severity of dependence to heroin at baseline ($p < 0.05$).

The remaining research examined outpatient withdrawal. The first outpatient study aimed to establish a dosing regime suitable for short withdrawal episodes using Subutex®. The open label, single group study recruited 18 dependent injecting heroin users with no significant co-morbidity to an 8-day outpatient withdrawal episode in which buprenorphine was titrated over the first five days. 15 subjects (83%) completed the 5-day dosing regime, and 14 (78%) completed the 8-day withdrawal episode. Withdrawal severity was generally mild, with minimal rebound withdrawal upon the cessation of dosing. The following outpatient dosing regime was recommended: day 1: 6 mg; day 2: 8 to 10 mg; day 3: 8 to 12 mg; day 4: 6 to 10 mg; and 4 mg on day 5.

Finally, the safety and efficacy of buprenorphine in outpatient heroin withdrawal was examined in an open label, randomised controlled trial conducted at sites in Melbourne and Sydney. 114 dependent heroin users with no significant co-morbidity underwent an 8 day withdrawal episode using one of two randomly allocated conditions: the Control group (n=56) using symptomatic

medications, including clonidine and benzodiazepines; and the Experimental group (n=58) using the buprenorphine regime identified in the previous study. At the completion of the withdrawal episode, subjects could self-select a range of post-withdrawal treatment options and were followed up for 4 weeks. Analysis was conducted on an intention-to-treat basis, with 89% of subjects completing the day 8 research interviews, and 80% completing the day 35 interviews.

The key findings indicate that the Experimental group had significantly better outcomes than the Control group during the withdrawal episode: higher rates of treatment retention (86% compared to 57%, $p < 0.01$, 95% CI NNT = 3 to 8); used heroin on fewer days during the 8 day withdrawal episode (2.6 ± 2.5 compared to 4.5 ± 2.3, $p< 0.001$, 95% CI = 1 to 2.5 days); had more subjects completing withdrawal with opiate negative urines on days 5 and 8 (21% compared to 4%, $p < 0.01$; 95% CI NNT = 4 to 18); experienced less severe withdrawal symptoms and reported greater improvements in various measures of psychosocial functioning. Examination of incremental cost effectiveness of the two withdrawal regimes demonstrated considerable advantages in favour of the Experimental group. Post-withdrawal outcomes were also significantly enhanced for the Experimental group on most measures, most notably higher treatment retention at day 35 (62% compared to 39%, $p< 0.05$, 95% CI NNT = 3 to 25); and heroin use on fewer days in the 4 week post-withdrawal period (9.0 ± 8.2 compared to 14.6 ± 10, $p < 0.01$, 95% CI = 1.8 to 9.4).

In conclusion, buprenorphine is a significant advance in the pharmacological interventions for heroin withdrawal. This research has established suitable inpatient and outpatient dosing regimes using the commercially available sublingual tablet preparation, and has demonstrated that short buprenorphine dosing regimes have superior outcomes compared to clonidine and other symptomatic medications in outpatient withdrawal settings. Buprenorphine has considerable potential as a 'gateway' medication for heroin users entering treatment, facilitating the transition into a range of post-withdrawal treatment modalities, most notably naltrexone and substitution maintenance treatment. Buprenorphine's safety and efficacy in improving withdrawal outcomes and enhancing the transition to post-withdrawal treatment should considerably enhance the future role of withdrawal services. The thesis concludes with an examination of key issues in the uptake of buprenorphine in treatment systems, including the development of clinical guidelines and training programs for service providers.

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1. Overview of heroin withdrawal services

1.1.1 The heroin withdrawal syndrome

Heroin withdrawal is a specific syndrome following the cessation or reduction in heavy and prolonged heroin use. The syndrome is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning (Diagnostic and Statistical Manual of Mental Disorders 1994). The characteristic features of the heroin withdrawal syndrome are shown in Table 1.1. Physical symptoms generally commence eight to twelve hours after last heroin use, peak in severity at about 36 to 72 hours, and generally subside by day seven, while the psychological features of dysphoria, anxiety, sleep disturbances and increased cravings may be protracted for weeks to months (Himmelsbach 1941; Martin and Jasinski 1969). Heroin withdrawal is rarely (if ever) life threatening on its own, although it can complicate concomitant medical or psychiatric conditions.

Table 1.1 Features of the heroin withdrawal syndrome

increased sweating, lacrimation, rhinorrhoea, urinary frequency
diarrhoea, abdominal cramps, nausea, vomiting
muscle spasm leading to headaches, back aches, leg cramps, arthralgia
piloerection, pupillary dilatation, elevated blood pressure, tachycardia
anxiety, irritability, dysphoria, disturbed sleep
increased cravings for opiates

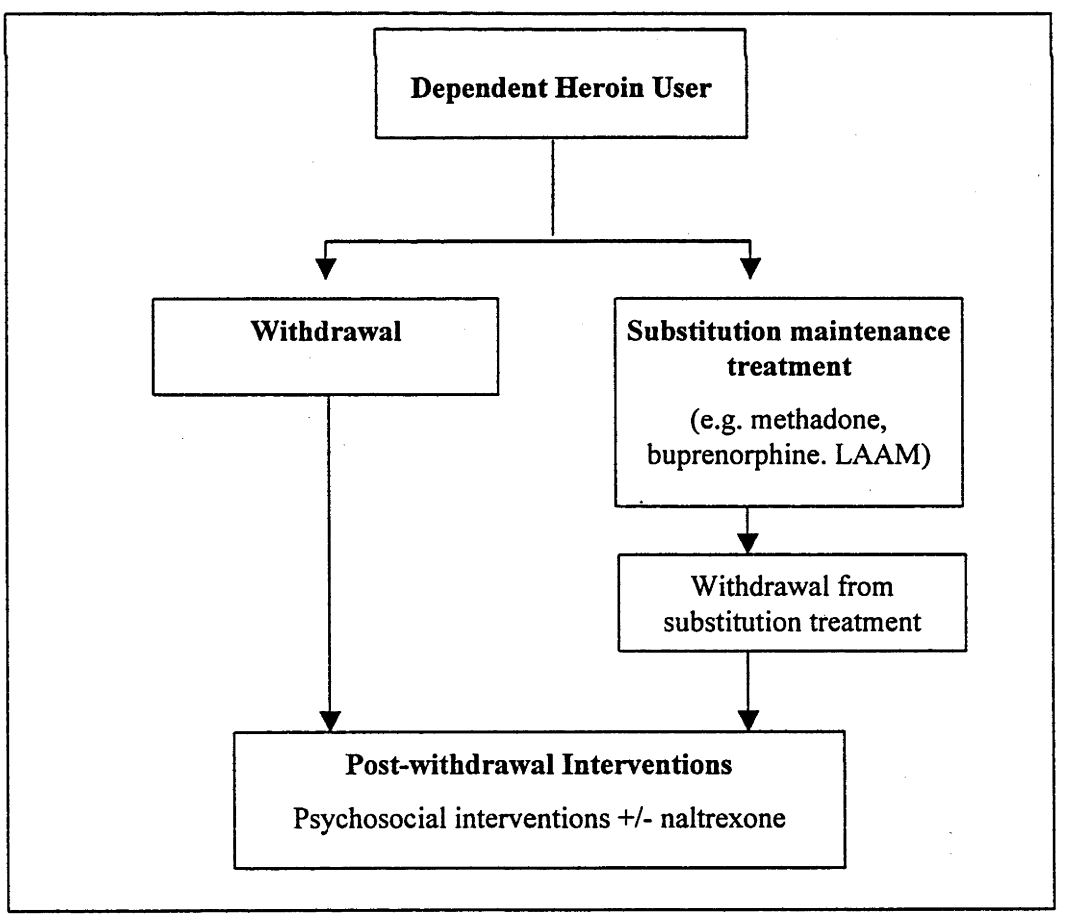
There is debate regarding the phenomenology of protracted withdrawal: symptoms of persistent cravings, sleep and mood disturbances lasting for weeks or months are common following the cessation of various drug classes (alcohol, opiates, stimulants, benzodiazepines) and as such, may not be part of a drug specific withdrawal syndrome, but rather may represent difficulties in adjusting to life without drugs (West and Gossop 1994). This review will focus upon the acute aspects of the heroin withdrawal.

1.1.2 Treatment pathways for dependent heroin users

Many heroin users undergo withdrawal without seeking assistance from structured services (Gossop, Battersby et al. 1991). There is nevertheless, considerable demand among heroin users for elective withdrawal services from specialist alcohol and drug treatment and primary health care providers (such as general practitioners). Withdrawal services are also required to assist individuals undergoing non-elective withdrawal, such as following incarceration or admission to hospital. The place of withdrawal services can be better understood by considering the treatment options available for dependent heroin users in most comprehensive service systems. These can be broadly categorised into two treatment pathways (Figure 1.1).

Substitution maintenance treatment involves the use of (usually) long acting opioid medications (such as methadone, buprenorphine or LAAM), with the rationale that regular administration of prescribed opioids will diminish the need and desire for continued heroin use, resulting in a corresponding reduction in heroin related morbidity and mortality. The basis of substitution treatment is that it is a long-term approach, generally years, thereby providing patients sufficient time and stability to distance themselves from heroin using lifestyles. Withdrawal from long-term maintenance substitution treatment is not the focus of this review.

Figure.1.1: Treatment pathways for dependent heroin users



The other main treatment pathway for dependent heroin users involves a variety of withdrawal and post-withdrawal treatment services. Post-withdrawal services (e.g. counselling, therapeutic communities, 12 step self-help groups) generally emphasise psychosocial aspects of recovery, and in some cases may include pharmacotherapy, such as naltrexone. These treatment services generally require the individual to have previously undergone drug withdrawal, and as such withdrawal services provide an important avenue into subsequent treatment.

1.1.3 Evaluating withdrawal services

The role of withdrawal services

The role and objectives of withdrawal services remains subject to debate, with different understandings within consumer groups, service providers, researchers, and the broader community. These different functions have been recognised by various authors (Mattick and Hall 1996), and neatly summarised in the following excerpt: "although detoxification is often the route into treatment, many who begin detoxification do not complete it, and many completers do not go on to more definitive treatment. Some enter detoxification only to lower their level of dependence and make their habit cheaper; others fully believe that detoxification is all that is necessary and that they will be able to remain drug-free." (Kleber 1997, page 79). It is possible to identify four different, though not necessarily mutually exclusive, common understandings of the role of withdrawal services:

- *Withdrawal as a 'cure' for heroin use.* This model frames withdrawal as a treatment approach that results in long term abstinence, with completion of a withdrawal program being all that is required for individuals to stop their heroin use and return to a drug-free lifestyle. This understanding is (unfortunately) common among many drug users, their families, and workers in the generalist health and welfare sectors, and the broader community, who often identify 'detoxification' or 'withdrawal' as definitive treatment. However, this position is generally not supported by the research literature. Prospective follow up studies of heroin users undergoing withdrawal suggests that only a minority cease their heroin use on a long term basis following single episodes of withdrawal treatment (Valliant 1988; Gossop, Green et al. 1989; Bale, Van Stone et al. 1980). This has led most commentators to accept that long term abstinence is not a common outcome of detoxification itself, and should therefore not be considered a primary aim or objective (Blaine, Ling et al. 1994; Mattick and Hall 1996; Kleber 1997; Johns 1994; O'Brien and McLellan 1996; Frank and Pead 1995).

- *Withdrawal services are the first step in a longer-term process of rehabilitation towards abstinence.* This model recognises the need for longer-term post-withdrawal treatment in order to sustain abstinence from heroin use. A central tenet in this model is that heroin users enter withdrawal with the goal of long-term abstinence, and that withdrawal services are the first of many steps in achieving this goal. However, research suggests that only a minority of heroin users attempting withdrawal will continue in some form of treatment. In a review of the opiate withdrawal studies, Lipton and Maranda (1983) estimated that only approximately 15% continue in structured post-withdrawal treatment. Various authors (Blaine, Ling et al. 1994; Mattick and Hall 1996) have argued against too closely linking withdrawal services with post-withdrawal treatment, emphasising that many heroin users are not interested in ongoing treatment, and that willingness to enter longer-term treatment should not be a prerequisite for entry into withdrawal programs. Nevertheless, most commentators recognise that withdrawal services should aim to have longer term benefits: if detoxification itself is not associated with longer term changes in drug use, then retention in post-withdrawal treatment which can achieve these benefits should be considered an aim for withdrawal services (Kleber 1997; Blaine, Ling et al. 1994; O'Brien 1993).

- *Withdrawal services facilitate a safe and comfortable reversal of neuoradaptation.* The main role of withdrawal services within this framework is the reversal of tolerance to opioids and the alleviation of the acute withdrawal symptoms associated with the cessation of heroin use (or neuroadaptation reversal). The principle endpoint for withdrawal success is a period of abstinence from opiate use and / or a negative response to an antagonist challenge, emphasising short-term biological outcomes. This model has received increased prominence in recent years (Mattick and Hall 1996), in part due to the acknowledgment of the limitations of withdrawal in achieving longer term outcomes; and due to an increasing emphasis upon pharmacological initiatives in withdrawal research and management, such as the use of opioid antagonists which enable an 'objective' end point for conducting research upon the withdrawal syndrome. However, there are also limitations with this approach. The emphasis upon withdrawal completion and neuroadaptation reversal does not recognise potential benefits for individuals who reduce, but do not cease, their heroin use during a withdrawal attempt. Furthermore, this model pays little attention to longer term outcomes such as changes in heroin use, severity of dependence, psychosocial functioning or other parameters of drug related harm; and it is difficult to justify the allocation of treatment resources to services whose primary objective is limited to short term (biological) objectives.

- *Withdrawal services are a means by which heroin users can reduce their level of heroin use and dependence in order to reduce some of the more deleterious effects of dependent drug use.* This model emphasises that the primary function of withdrawal services is to assist heroin users to reduce their level of heroin use, severity of dependence (including tolerance) and related harms. Withdrawal serves a range of functions that do not require a cessation of heroin use or the 'completion' of withdrawal, and to this extent, it differs from the previous model, which emphasises withdrawal 'completion' as the primary objective. The following excerpt from a review of withdrawal services conducted by a drug user group highlights this position:

  > ".... we have received many comments about detoxification services which have as their common theme: "why do I have to lie about wanting to give up heroin (or speed or pills) to get into a detox?" Why must consumers pretend that their goal is eternal abstinence when their real goal may be "to get my heroin use back under control", "to give it a miss for a few days", "to dry out and get my head together", "to save up some money", or a hundred other reasons"? (NSW Users & AIDS Association (1994): page7).

  This model operates within a harm reduction framework and emphasises the potential benefits of withdrawal services to reduce the physical, psychological and social harms associated with dependence. However, it remains uncertain as to whether such broad benefits actually arise from participation in withdrawal services, or the extent to which any changes can be sustained. The capacity for dependent heroin users to sustain a period of controlled heroin use following withdrawal has not been established in the research literature, and remains a highly contentious issue within the treatment sector. Research has not adequately addressed this issue - most withdrawal studies have no (or inadequate) long-term follow up of subjects, and sensitive measures of heroin use, severity of dependence or broader levels of psychosocial functioning are generally not recorded or reported. One study conducted in the United Kingdom in the 1980's (Tennant 1985) suggested that there were indeed benefits in psychosocial functioning for heroin users undergoing multiple withdrawal episodes over a period of time, however further work is required in order to substantiate this premise.

Heroin users present for withdrawal services for a range of reasons and motivations, and each of the above models may be valid for different individuals, or for the same individual at different times. This heterogeneity is to be expected given the variety of heroin users and their circumstances at treatment entry. There are however, considerable differences in the key objectives and corresponding primary outcomes for each of the models discussed, and the

extent to which a withdrawal attempt is considered 'successful' will largely depend upon the model being prioritised. The following 'common' clinical scenarios highlight the difficulties in assessing the 'success' of a particular withdrawal episode.

Case 1. A homeless patient successfully completes an 8-day inpatient withdrawal episode, but fails to keep any subsequent counselling appointments and resumes heavy regular heroin use within days of discharge.

This could be considered as a treatment failure under the first two models, as no long term abstinence or treatment retention were achieved; a treatment success with regards to successful neuroadaptation reversal; and a partial treatment success within the last model, as the patient at least had their short term accommodation needs addressed.

Case 2. A patient attempts outpatient heroin withdrawal using reducing doses of methadone over several weeks. He initially ceases using heroin whilst on methadone doses above 15 mg per day, but resumes heroin use when his methadone dose reduces below this level. Following discussion with his treatment staff, he decides to transfer to a methadone maintenance program. He subsequently ceases all heroin use and remains in long-term methadone maintenance treatment.

This could be considered a treatment failure with regards to long-term abstinence from opiates or neuroadaptation reversal. However, this is a treatment success from the perspective of the patient being retained in post-withdrawal treatment, not using heroin, and achieving long term stability.

Case 3. A patient undergoes a rapid opiate withdrawal under heavy sedation in hospital using naltrexone. She is discharged from hospital after two days, but takes her naltrexone for only a further 4 days prior to discontinuing all treatment. At follow-up several weeks later she admits to having used heroin on three or four occasions, has resumed part-time employment, broken up with her heroin-using boyfriend, and is living at home with her parents.

This could be considered a treatment success with regards to neuroadaptation reversal or getting her habit under control with improved psychosocial functioning; however, she did not fare well with regards to maintaining abstinence, or remaining in post-withdrawal treatment.

Developing a framework for evaluating withdrawal services

The extent to which each of the above scenarios is considered a 'treatment success' depends upon the understanding of the role of withdrawal services. An unfortunate limitation of research examining the efficacy of withdrawal services is that it has often been unclear as to the primary goal of the withdrawal program being examined, or withdrawal studies have often used measures that prioritise particular outcomes and ignore others. For example, many withdrawal studies have examined the severity of withdrawal symptoms or response to an antagonist challenge as their primary outcome measures, but have included no follow-up of post-withdrawal outcomes. In a review of treatment services for opiate dependent users, Wayne Hall and colleagues (National Drug Strategy 1993) identified:

> There is still some debate about the goals of detoxification and therefore what the criteria for success are. Many papers do not indicate whether, for example, the detoxification process is intended as a stand alone treatment that is supposed to produce enduring abstinence; whether it is seen as a precursor of further drug treatment and therefore should result in high rates of entry to other forms of treatment; or whether the goal is simply successful detoxification itself (p.12).

A framework for evaluating clinical withdrawal services is required that encompasses the various roles of withdrawal services. Indeed, this is important given that different treatment approaches may be effective in achieving certain outcomes, but may be less effective in achieving others, as suggested by the previous case examples. Such a framework requires the identification of a set of objectives for withdrawal services, with corresponding outcomes and outcome measures. There have been previous attempts at this task. In a review of methodological issues in conducting drug treatment research, Blaine and colleagues (1993) identified several key outcomes for drug withdrawal research: cessation of drug use, reduction in cravings and severity of withdrawal features, and treatment retention. Mattick and Hall (1996) identified a set of outcomes consistent with their emphasis upon withdrawal services as a means of reversing neuroadaptation: rates of completion of the withdrawal process, the severity of symptoms, and medical complications. They recognised that there are also secondary objectives of opiate withdrawal, such as providing a period of respite from drug use and its consequences; and overcoming the barrier that withdrawal often poses to subsequent treatment and longer-term abstinence.

I propose the following set of objectives as the basis for evaluating withdrawal services. This framework emphasises multiple treatment objectives for withdrawal services, and aims to accommodate the various understandings of the role of withdrawal services previously

discussed. Furthermore, each treatment objective has outcomes and measures that can be practically assessed. This discussion is summarised in Table 1.2.

1. *To prevent the development of severe withdrawal sequelae and complications.* Although heroin withdrawal on its own is rarely (if ever) life threatening, there are three dimensions of safety particularly pertinent to the management of heroin withdrawal. Firstly, withdrawal in the context of concomitant medical or psychiatric conditions can result in severe complications (for example, precipitation of an acute psychotic episode in a patient with schizophrenia in remission; dehydration in an individual with poor baseline nutritional status). Treatment services themselves can have severe adverse events (Kleber and Riordan 1982), (e.g. methadone toxicity, anaesthesia-related complications in ultra-rapid opiate withdrawal). Finally, increased risk of overdose and death has been reported following attempts at heroin withdrawal (Gearing and Schweitzer 1974). A number of factors may contribute to this scenario: the resumption of heroin use following a reduction in opioid tolerance; the combined sedative effects of heroin and medications used for the management of withdrawal (e.g. benzodiazepines, clonidine); and the mood disturbances (dysphoria, anxiety) of opiate withdrawal which may contribute to suicidal behaviour.

   Measures regarding the safety of withdrawal services require careful clinical monitoring and recording of adverse events. A period of monitoring following the completion of the withdrawal episode is necessary in order to detect overdoses.

2. *To alleviate the symptoms and distress of withdrawal.* Palliation of the discomfort of heroin withdrawal is an important reason for patients presenting for treatment and one of the primary aims of any withdrawal service. Reduced withdrawal severity has benefits not only for the patient, but also potentially places fewer demands upon community supports and service providers.

   For the purposes of evaluating withdrawal services, instruments should be used that independently measure subjective (symptoms) and objective ratings (signs) of opiate withdrawal severity. Subjective ratings are more sensitive than objective measures of opiate withdrawal (Turkington and Drummond 1989; Loimer, Linzmayer et al. 1991; Handelsman, Cochrane et al. 1987), and there is evidence to suggest that subjective ratings of withdrawal are ultimately better predictors of treatment outcome (Kosten, Rounsaville et al. 1985).

   There are a number of ways of expressing the severity of withdrawal experienced during a withdrawal episode (Law, Melichar et al. 1998). The total withdrawal discomfort experienced over a period of time can be expressed as an 'Area Under the Curve' with

repeated measures over time. Hence, an individual experiencing mild symptoms over a prolonged period may have greater overall withdrawal discomfort than a different regime associated with severe symptoms for a short period of time. Peak withdrawal severity is also an important clinical parameter, as some individuals may not tolerate severe discomfort. It should be recognised that measures of withdrawal severity may be difficult to interpret in the context of continued heroin use, such as may occur with outpatient withdrawal.

3. *To interrupt a pattern of heavy and regular drug use.* Withdrawal arises from a cessation or reduction in regular heavy drug use (DSM-IV), and this serves as a main objective for all withdrawal services. Complete cessation of heroin use is generally considered the optimal outcome regarding drug use during a withdrawal attempt, and is usually a prerequisite of inpatient admission. However, a large proportion of withdrawal attempts occur in outpatient settings where continued heroin use is possible, and reduction in heroin use may still represent a positive and worthwhile outcome for some patients. Withdrawal efficacy studies should also incorporate a period of follow-up beyond the immediate treatment episode in order to examine the longer-term impact of the intervention upon drug use. (McLellan and Durell 1996) have identified the first two to four weeks after the completion of acute substance abuse treatment episodes as the most relevant period to examine the impact of the intervention - outcomes beyond one month can be difficult to attribute to the initial intervention, and may for example, reflect the impact of ongoing treatment services.

   Measures of drug use are required that are sufficiently sensitive to identify the extent of heroin use during a (outpatient) withdrawal episode, and in the post withdrawal period. For example, most commentators would recognise that a withdrawal episode in which a patient used heroin on two occasions over a ten-day outpatient episode is a 'better' outcome than an episode in which the same patient used on 10 occasions over the same period. The most sensitive measures of drug use are often based upon self-report, allowing for even small changes in the quantity and frequency of drug use to be estimated; however, there are limitations in relying exclusively upon self-report data, and objective measures of drug use (such as urine drug screens) should also be incorporated (Del Boca and Noll 2000; Darke 1998; Finch and Strang 1998). An antagonist challenge is a useful investigation for those patients considering ongoing naltrexone treatment, however it should not otherwise be conducted for routine clinical purposes, given the potential for adverse events.

4. *To provide linkages to appropriate post-withdrawal services that address the individual's drug use, physical, psychological and social needs.* Heroin dependence is generally a chronic relapsing condition, and long-term participation in treatment is required in order to

achieve long-term outcomes. An important role therefore of withdrawal services is to facilitate linkages with post-withdrawal services. This includes drug treatment services that aim to maintain abstinence or reduce heroin use and related harms, such as: 'drug free' counselling (e.g. relapse prevention); naltrexone treatment; residential therapeutic communities; self help programs; and substitution maintenance programs (e.g. methadone or buprenorphine). Some individuals may be unwilling or unable to continue in ongoing drug treatment programs, but may nevertheless benefit from linkages to welfare services (e.g. accommodation); general support and case management services (e.g. outreach workers); or primary or specialist health services.

Measures of participation in post-withdrawal services require a description of the treatment modality and duration of treatment. Outcome measures of psychosocial functioning are also required in order to assess the broader impact of the withdrawal service upon the individual's quality of life.

Neuroadaptation reversal has been omitted from this framework as an objective for withdrawal services. A key problem with the construct of neuroadaptation reversal as an objective within a framework for evaluating withdrawal services is that it is difficult to operationalise, particularly in routine clinical practice. Neuroadaptation reversal is 'best' assessed using a challenge with an opioid antagonist, such as naloxone. However, the use of naloxone challenge tests is inappropriate during routine clinical practice unless the patient is considering ongoing naltrexone treatment, a treatment choice traditionally made by only a minority of heroin users entering withdrawal services. (Furthermore, routine naloxone challenge tests cannot be easily interpreted in the context of recent buprenorphine treatment (see Section 4.4 in this Chapter for discussion), complicating the assessment of neuroadaptation reversal in such patients). Thus, whilst neuroadaptation reversal can be easily assessed in studies incorporating naloxone or naltrexone treatment, the practical difficulties in establishing neuroadaptation reversal usually results in clinicians using 'proxy' measures – such as a patient going several days (often 5 to 7 days) without any heroin or other opiate use and with the resolution of acute withdrawal symptoms and signs. The patient who has accomplished this is assumed to have 'completed' neuroadaptation reversal. Hence, the assessment of neuroadaptation reversal usually involves the use of measures of drug use and withdrawal severity. These two outcome measures have already been accommodated in the proposed framework.

Recent trends in health care evaluation (Sederer and Dickey 1996; Miles and Lugon 1996) emphasise that a comprehensive evaluation of health services should include measures that go beyond the assessment of a particular clinical condition (such as the syndrome of drug withdrawal), and should include measures of the impact of intervention upon the general health

status and quality of life of the individual patient. This requires a broader assessment of the patient's physical, psychological and social status, and the impact of the intervention in leading to improvements in these areas. Within the proposed framework for evaluating withdrawal services, the first two objectives (preventing complications and alleviating symptom severity) are particularly oriented towards the management of the primary clinical condition (opiate withdrawal); whereas the third and fourth objectives accommodate a broader base for withdrawal service evaluation, incorporating measures that reflect changes in drug use, psychosocial functioning and treatment participation over time.

Table 1.2. Objectives and outcome measures for evaluating withdrawal services

Objective	Outcome measures
To prevent the development of severe complications	Assessed by the monitoring of adverse events, medical and psychiatric conditions. Overdoses should be recorded during and in the period immediately after the withdrawal episode.
To alleviate the severity of withdrawal discomfort	Frequent and regular measures of withdrawal symptoms (subjective) and signs (objective). Measures should continue until withdrawal features have returned to baseline following the cessation of any opioid medications.
To interrupt a pattern of regular and heavy drug use	Measures of levels of heroin use over time. Objective (e.g. urine drug screens) and self-report measures during and after the withdrawal episode. Measures should have sensitivity to record abstinence, and to be able to describe amount of heroin use (quantity, frequency) for those continuing heroin use (e.g. outpatient withdrawal, post-withdrawal follow-up). For inpatient withdrawal, treatment retention is often a de-facto measure of abstinence from heroin use. In addition to measures of levels of heroin use, measures of severity of dependence can assist to describe an intervention's impact in interrupting a pattern of regular and heavy drug use
To provide linkages to post withdrawal services that address the individual's drug use, physical, psychological and social needs.	Participation in ongoing alcohol and drug treatment and other health and welfare services, including description of the treatment modality and duration of treatment. Secondary outcome measures of psychosocial functioning are also required in order to assess the broader impact of the withdrawal service upon the individual's quality of life.

In addition to a framework of outcome measures, there are important process measures fundamental in health service evaluation that also need to be considered in evaluating withdrawal services. These include:

1. *Retention in withdrawal treatment.* Retention in withdrawal treatment can be expressed as the proportion of patients who complete a predetermined protocol or end point, or in terms of time retained in treatment (particularly for longer term withdrawal regimes such as gradual methadone reductions).

2. *Utilisation and cost of services.* The cost of health services is increasingly becoming important in decisions regarding the relative allocation of resources, particularly when considering alternative withdrawal regimes and settings. For example, although inpatient withdrawal services are generally more expensive to provide than outpatient services, they may be justified given the higher rate of withdrawal completion (Gossop and Strang 2000). The large variation in costs associated with the different methods of providing services for heroin withdrawal (see next section) emphasises the need for cost effectiveness studies in order to inform decisions regarding resource allocation.

3. *General measures of patient satisfaction.* Measures of patient satisfaction are becoming increasingly important in health service evaluation (Sederer, Dickey et al. 1996). They provide an opportunity for patients to broadly comment upon the services provided, identify areas for further improvement, and can provide insights into the interpretation of other treatment outcomes.

These outcome and process measures together form a more comprehensive framework for evaluating clinical withdrawal services. The incorporation of a multiple treatment objectives and outcome measures allows for the possibility that some withdrawal programs may have advantages in achieving certain treatment objectives, but be less successful in meeting others. Identification of the strengths and weaknesses of different withdrawal approaches should also assist the process of patient-treatment matching.

The scope of any evaluation, and the emphasis placed upon different outcomes will relate to the context in which withdrawal services are provided. For example, issues regarding safety and prevention of complications are paramount when evaluating non-elective withdrawal services provided to heroin users undergoing intensive medical or surgical inpatient hospital procedures. Alternatively, elective withdrawal services provided at the commencement of a long-term rehabilitation program (e.g. a therapeutic community, naltrexone treatment) should focus upon post-withdrawal treatment induction as its primary outcome.

1.2. Non-pharmacological interventions for heroin withdrawal

There are several components to the delivery of heroin withdrawal services, including assessment and planning, treatment settings, supportive care, pharmacotherapy, and facilitating post withdrawal linkages. Non-pharmacological interventions will be briefly described prior to examining pharmacotherapies for heroin withdrawal in detail. This section aims to provide an overview of contemporary practice (emphasising the Australian treatment context), rather than a systematic review of the efficacy of such services.

1.2.1 Assessment

The two main objectives of assessment are: (a) to ascertain valid information in order to identify the most suitable treatment plan for the patient, and (b) to engage the patient in the treatment process - including the establishment of rapport with the patient and facilitating treatment plans. Key dimensions of assessment for withdrawal include: recent and past drug use, prior withdrawal and other treatment history, concomitant medical and psychiatric conditions, and assessment of psychosocial factors, including reasons for presentation, expectations regarding withdrawal, and current social circumstances with an emphasis upon barriers and supports for withdrawal (Frank and Pead 1995; NSW Health Department 1999; Senay 1997). The process of assessment and patient selection for withdrawal programs (and research studies) can have a considerable impact upon outcomes (Blaine et al 1993). For example, prolonged assessment periods and waiting times may discourage less motivated heroin users, such that only more motivated and organised patients are prone to complete the assessment process. Alternatively, outpatient programs that require their patients to have considerable home supports (e.g. drug free environment and support people), may select patients with better prognoses and result in more favourable outcomes than other programs without such stringent criteria.

1.2.2 Settings for withdrawal

Withdrawal services for heroin users can be located in intensive inpatient units (such as hospital wards, specialist alcohol and drug detoxification units), in community residential units (providing supported accommodation with limited medical staffing or monitoring), or in ambulatory settings (including outpatient and home-based services). Non-elective withdrawal also occurs in a range of settings, such as prisons or police cells.

The clinical indications for heroin withdrawal to be conducted in an intensive inpatient setting are generally limited to the presence of concomitant medical or psychiatric conditions, or

concurrent withdrawal from heavy alcohol or benzodiazepine use (Frank and Pead 1995; NSW Health Department 1999; Chang and Kosten 1997; American Society of Addiction Medicine 1991). Community residential units are suited to those individuals with inadequate social supports and for those with repeated failure at outpatient withdrawal attempts.

There are potential advantages and disadvantages to different treatment settings. Inpatient withdrawal settings have been shown to have higher rates of retention and completion than outpatient settings (Gossop, Johns et al. 1986), although improved longer-term outcomes have not been clearly demonstrated (Wilson, Elms et al. 1975). However, intensive inpatient services are usually expensive to operate, and are generally less accessible for heroin users than outpatient services. Outpatient withdrawal can also be associated with a more seamless transition between withdrawal and post-withdrawal services, with the same treatment providers involved in service delivery. For example, in the study by Gossop and colleagues (Gossop, Johns et al. 1986), the inpatient setting had a higher rate of withdrawal completion than the outpatient program (81% versus 17%), however, a significantly higher proportion of outpatients engaged in ongoing counselling after the withdrawal episode (55% versus 29%).

1.2.3 Supportive care

Supportive care refers to the provision of psychosocial support during the withdrawal episode and is an important component of withdrawal services, particularly as psychological factors appear to have a considerable impact upon withdrawal severity and outcomes (Phillips, Gossop et al. 1986). Supportive care usually involves regular monitoring, counselling, provision of information, and modification of the patient's environment (e.g. a quiet environment away from other drug users) (Frank and Pead 1995; NSW Health Department 1999).

Monitoring includes frequent review of the patient to identify their general progress and motivation, severity of withdrawal symptoms (which can be facilitated by the use of withdrawal scales - see discussion below), drug use (particularly in an outpatient context), response to the medication(s) and complications. This is important for the individualisation of treatment (such as the titration of medication doses or tailoring of ancillary services) and for ongoing treatment planning. Evidence from other medical disciplines suggests that encouraging patients to self-monitor their progress during treatment (such as symptom severity, side effects) improves treatment adherence (Fishman, Wilsey et al. 2000; Waeber, Burnier et al. 2000; Denolle, Waeber et al. 2000).

Although there have been numerous opiate withdrawal scales developed, few of them are suited to routine use in clinical settings. In order for withdrawal scales to be clinically relevant for

monitoring withdrawal severity, the instruments should be quick and easy to administer - clinicians are busy and patients in withdrawal can often have poor attention or concentration. The scales must have robust psychometric properties, particularly inter-tester reliability to accommodate different staff administering the instrument at different times during the withdrawal episode; sensitivity to detect changes in withdrawal severity over time; and specificity to ensure that the instrument is measuring opiate withdrawal and not some other condition. The instrument should also incorporate (and ideally differentiate) subjective and objective measures of withdrawal. Subjective measures can be self-completed by patients over the course of withdrawal, and as previously identified, tend to be more sensitive and are better correlated to treatment outcome. Kosten, Rounsaville et al. (1985) demonstrated that subjective features are better correlated to withdrawal completion than objective withdrawal ratings, and the authors recommended that subjective ratings be used to guide withdrawal treatment practices. In contrast, clinician-completed scales (usually assessing objective signs) require trained staff, and are less applicable for regular monitoring in outpatient withdrawal programs where contact with clinicians may be limited to once a day or less. There are several published opiate withdrawal scales that meet these requirements for use in clinical withdrawal settings, including the Short Opiate Withdrawal Scale (Gossop 1990) and the Subjective and Objective Opiate Withdrawal Scales developed by Handelsman and colleagues (Handelsman, Cochrane et al. 1987).

The provision of information regarding the nature and duration of withdrawal, treatment procedures and coping strategies can reduce the severity of opiate withdrawal symptoms (Green and Gossop 1988). Patients often have limited concentration during withdrawal, and information generally has to be repeated. To this end, specific withdrawal literature designed for patients has been developed (e.g. Lintzeris, Dunlop et al. 1996; Law and Dean 1998) and may be of benefit, although they have not been extensively evaluated.

Counselling during the withdrawal episode is generally aimed at supporting the patient through the withdrawal period and facilitating post withdrawal linkages. Contemporary approaches to withdrawal counselling generally recommend strategies that aim to allay the mood disturbances of withdrawal (anxiety, dysphoria), cravings, sleep disturbance and to maintain motivation (see for example Frank and Pead 1995; National Health and Medical Research Council 1991; NSW Health Department 1999). Although many patients may wish to address a range of long standing personal, emotional or relationship problems during withdrawal, such attempts can have the adverse consequence of increasing agitation and cravings, thereby jeopardising the withdrawal episode. It is usually recommended that these

issues are deferred until after the withdrawal episode, and this can serve to motivate patients into considering post-withdrawal treatment options.

There is limited research examining the impact of counselling during heroin withdrawal. Rawson and colleagues (Rawson, Mann et al. 1983) examined the impact of mandatory counselling with a therapist during a 21-day outpatient withdrawal compared to subjects receiving no counselling in a randomised trial of 50 subjects. There was no difference noted in numbers heroin use or completion rates, however those receiving counselling had higher rates of participation in post-withdrawal treatment. These findings suggest that the provision of structured counselling sessions during withdrawal that specifically address ongoing participation in treatment may increase post-withdrawal treatment retention. Several studies indicate that behavioural interventions employing contingency management strategies can enhance completion rates in outpatient withdrawal programs (Bickel, Amass et al. 1994; McCaul, Stitzer et al. 1984). Bickel and colleagues examined 39 heroin users undergoing a gradual buprenorphine reduction (over 6 months). Patients were randomised to receive either 'standard' counselling, or contingency management and community reinforcement approaches. The group receiving behavioural interventions had higher rates of retention and less heroin use during the withdrawal episode. McCaul and colleagues likewise demonstrated enhanced retention and reduced drug use for subjects randomised to contingency management interventions compared to those receiving standard approaches, although there were no differences in post-withdrawal outcomes for the two groups. Unfortunately, the capacity for routine withdrawal services to incorporate intensive behavioural interventions of contingency management is often limited.

1.3. Pharmacotherapies for heroin withdrawal

In a review of historical methods for the management of opiate withdrawal, Kleber & Riordan (1982) identified that numerous pharmacological approaches have been used to manage opiate withdrawal during the past century. The authors reflected how these had often been introduced with considerable initial enthusiasm, only for most approaches to be abandoned as concerns regarding their effectiveness or safety emerged, or newer approaches were developed. The changes in 'conventional' clinical practice and 'wisdom' over time emphasises the need for thorough evaluation of pharmacotherapies and an evidence-based approach to clinical practice.

Medication regimes for heroin withdrawal in the contemporary research literature can be broadly classified into four approaches (Gowing, Ali et al. 2000):

1. reducing doses of an *opioid agonist*, usually *methadone*;

2. *symptomatic medications*, most notably the *α_2 adrenergic agonists, clonidine* and *lofexidine*, which aim to reduce the severity of withdrawal symptoms, without fundamentally changing the course of the withdrawal syndrome;

3. *opioid antagonists*, predominantly naloxone or naltrexone;

4. *partial opioid agonists*, predominantly *buprenorphine.*

The literature regarding each of these approaches will be reviewed in the remainder of this chapter. Each of these approaches has been the subject of recent systematic literature reviews (Gowing, Ali et al. 2000); including recent Cochrane reviews of buprenorphine for opiate withdrawal (Gowing, Ali et al. 2000) and antagonist-assisted withdrawal (Gowing, Ali et al. 2000). Recent systematic reviews have also been published regarding the 'newer' approaches with lofexidine (Strang, Bearn et al. 1999), and antagonist-assisted withdrawal (O'Connor and Kosten 1998). Thus, a systematic review of the research literature regarding the use of methadone, adrenergic agonists and opioid antagonists in heroin withdrawal has not been repeated as part of this thesis. Rather, key issues regarding the use of these medications, and relevant comparative randomised controlled trials regarding efficacy will be examined. The use of a number of other symptomatic medications (such as benzodiazepines) will also be briefly described, as they are frequently used in clinical practice (Frank and Pead 1995; NSW Health Department 1999; Fishbain, Rosomoff et al. 1993), although they have not been comprehensively evaluated. The role of buprenorphine in heroin withdrawal will be examined in detail in the Section 4 of this chapter.

1.3.1 Methadone and other opioid agonists

Methadone is an agonist at μ opiate receptors and can fully substitute for heroin in dependent individuals, thereby preventing heroin withdrawal. Although there is considerable variation in the manner in which methadone has been used in the treatment of heroin withdrawal, the general clinical principles involve:

1. Initial titration of the methadone dose to prevent features of heroin withdrawal (usually in the range of 20 to 40 mg daily).

2. Reduction in the methadone dose over a period of time. 10 to 21 days of methadone tapering is frequently described in the research literature, extending to longer programs in some cases (e.g. 6 week reduction regimes). There have been descriptions of longer reduction programs (extending up to 6 months), although these are often in the context of patients having limited access to methadone maintenance programs (often because of regulatory restrictions thereby these programs serve as 'de-facto' maintenance programs), or in the

context of withdrawal from methadone maintenance treatment (rather than methadone-assisted heroin withdrawal regimes).

3. Adjuvant psychosocial interventions and symptomatic medication are often employed towards the end of the methadone reduction regime, corresponding to the period when withdrawal severity is greatest.

The use of methadone delays the emergence of peak withdrawal symptoms and prolongs the duration of withdrawal symptoms (Gossop, Griffiths et al. 1989). Methadone generally prevents significant withdrawal symptoms until the dose reduces to low levels, at which point opiate withdrawal symptoms emerge. Several studies have demonstrated that withdrawal symptoms peak at about the time of the last methadone dose or in the first few days after the cessation of methadone, with withdrawal discomfort persisting for approximately 10 to 14 days following a 10 to 21 day methadone reduction regime (Gossop, Griffiths et al. 1989; Strang and Gossop 1990; Bearn, Gossop et al. 1996; Kasvikis, Bradley et al. 1990). The emergence of withdrawal features after the cessation of the therapeutic agent (in this case methadone) is referred to as *rebound withdrawal.* The prolongation of withdrawal discomfort and severity of this rebound withdrawal are among the main limitations of using methadone for heroin withdrawal, particularly in inpatient withdrawal programs of short duration (see discussion below).

It can be postulated that very short courses of low methadone doses (for example, 3 to 5 days of up to 30 mg per day) may result in minimal rebound withdrawal upon the cessation of methadone, but still provide relief of symptoms during the period traditionally associated with peak heroin withdrawal. Unfortunately, this has not been systematically investigated in the published literature. There have been several accounts of short methadone withdrawal regimes (e.g. Jonas, O'Dwyer et al. (1972) used a 5 day regime; Silsby and Tennant (1974) and Stern et al. (1974) used 7 day regimes), however these studies did not monitor withdrawal symptoms following the cessation of methadone dosing to examine for rebound withdrawal.

A consistent finding in the studies of methadone assisted heroin withdrawal is the high rate of relapse to heroin use following cessation of methadone doses. Most studies of methadone assisted heroin withdrawal do not report on outcomes in the post-withdrawal period, however studies that have reported post-withdrawal outcomes suggest very high rates of relapse to heroin use (for example, Wilson, Elms et al. 1974) reported that all 30 heroin users relapsed to heroin use within one month of ending a methadone reduction withdrawal regime; whilst in a later study (Wilson, Elms et al. 1975), only 5% (2 / 40) were opiate-free three months after the end of a methadone reduction regime). In a review of outpatient methadone assisted heroin

withdrawal studies (n=20) conducted in the USA in the 1970's, (Maddux, Desmond et al. 1980) reported that between none to 38% of subjects in these studies were abstinent at follow-up, and concluded that outpatient withdrawal did not lead to prolonged abstinence in most heroin users. Patient and treatment factors impacting upon outcomes associated with methadone-assisted heroin withdrawal are considered below.

From the perspective of safety, methadone is generally well tolerated by heroin dependent individuals, although there are concerns regarding methadone toxicity and diversion. Methadone doses which are generally considered to be in the therapeutic range (for example, as low as 20 to 30 mg) may be fatal in individuals with low levels of tolerance to opiates (Drummer 2000; Zador, Sunjic et al. 1997), particularly in the context of repeated dosing, inadequate clinical monitoring and concurrent use of other sedative medications. Diversion of methadone, with the concomitant risks of toxicity in non-treatment populations and methadone injecting are also a concern, particularly in treatment systems where take-away doses of methadone are widely available (Darke, Ross et al. 1996; Lintzeris, Lenne et al. 1999; Waldvogel and Uehlinger 1999).

The use of methadone to assist heroin withdrawal is well suited to facilitating continued methadone treatment as a maintenance program, particularly for those patients who do not cease their heroin use during the withdrawal episode, or relapse to heroin use on discontinuing methadone treatment. However, the prolonged withdrawal following the cessation of methadone can often be a barrier to entry into abstinence-oriented post withdrawal treatment modalities. For example, the commencement of naltrexone is generally recommended 10 days after the last methadone dose (Bell, Kimber et al. 1999); while many residential rehabilitation programs will not accept patients until several days after the cessation of methadone treatment.

Treatment factors impacting upon outcomes

The manner in which methadone-assisted withdrawal regimes are delivered may impact upon outcomes. There has however, been considerable variation between reported studies with regards to these treatment variables, thereby limiting the capacity to identify an 'optimal' approach for the use of methadone in heroin withdrawal. Treatment variables that appear to be important include:

- *The treatment setting.* Historically, long term inpatient withdrawal programs involving gradual methadone reductions over weeks were not uncommon. Studies examining such programs indicated that inpatient withdrawal programs using methadone generally resulted in a greater rate of program 'completion' than outpatient based programs. Two randomised trials have examined the impact of setting upon heroin withdrawal completion rates using

methadone. Gossop, Johns et al. (1986) compared outcomes for subjects allocated to a 21-day inpatient reduction or to an 8-week outpatient reduction regime. The inpatient group had a significantly higher completion rate (81% compared to 17%). However, the study also reported that the outpatient group had a significantly higher rate of post-withdrawal treatment retention than the inpatient group; suggesting that inpatient services may result in better short term outcomes, however post-withdrawal treatment retention may be better achieved with outpatient services. Wilson, Elms et al. (1975) compared outcomes for 40 heroin users randomly assigned to either an inpatient or outpatient 10-day methadone reduction regime. The authors reported that few subjects completed either regime, and 98% of subjects had relapsed to heroin use within 2 months of treatment. Given the poor completion rates for both groups, the authors concluded that outpatient services were a more cost-effective treatment approach. A recent systematic review of methadone withdrawal literature reported 78% of opiate dependent subjects attempting inpatient methadone withdrawal completed the regime (referring to the proportion of subjects reaching 0 mg of methadone), compared to 31% of outpatient attempts ($p< 0.001$) (Gowing, Ali et al. 2000). It should be noted that these proportions are for studies of heroin and/or methadone dependent subjects, and completion rates for stable methadone dependent subjects may be greater than for heroin dependent subjects (Gowing, Ali et al. 2000). Rates of successful completion of outpatient methadone reduction regimes (without any heroin use) vary considerably, with most reviewers commenting that successful rates of completion are low - in the range of 10 to 20% (Johns 1994; Kleber 1997; Mattick and Hall 1996).

The trend in recent years has been towards shorter inpatient withdrawal programs, often no longer than 7 to 10 days. This has restricted the utility of methadone as an inpatient withdrawal medication, given that opiate withdrawal symptoms persist for several days beyond the last methadone dose. Despite anecdotal reports of programs using brief inpatient methadone regimes (3 to 5 days), there were no published evaluations of such short methadone regimes identified (Gowing, Ali et al. 2000; Gowing, Ali et al. 2000).

- *The initial stabilisation period on methadone prior to dose reduction.* Initial stabilisation on methadone can disrupt a pattern of heavy daily heroin use, enhance the patient's sense of self-efficacy, and improve their capacity to cope with subsequent withdrawal symptoms (Reilly, Sees et al. 1995). Although not systematically examined in the research literature, the extent of continued heroin use during the period of initial stabilisation on methadone may impact upon subsequent withdrawal outcomes. In a study examining a 90-day outpatient methadone reduction regime for heroin users, subjects who continued to use heroin during the initial two week stabilisation period had worse outcomes than those

subjects who had ceased heroin use during stabilisation (Stitzer, McCaul et al. 1983). There may be advantages in enabling sufficient time (and methadone doses) during the initial stabilisation period to ensure cessation of heroin use prior to dose reduction, although further research on this issue is required.

- *The rate and frequency of dose reduction.* There are both advantages and limitations with methadone withdrawal programs of different duration. Shorter reduction regimes appear to be associated with greater peak withdrawal discomfort, shorter duration of withdrawal symptoms (Gossop, Griffiths et al. 1989) and greater 'completion' rates (subjects reaching zero mg of methadone according to protocol) (Gowing, Ali et al. 2000). However, the higher completion rates for shorter regimes may merely reflect that longer programs have more time in which subjects can relapse to heroin use and / or drop out of treatment. Some authors have argued against rapid reduction regimes (e.g. 10 to 21 days), stating that many individuals are prematurely withdrawn and consequently resume heroin use (Maddux, Desmond et al. 1980). Unfortunately, most studies of outpatient reduction regimes have reported very low rates of abstinence from heroin following the cessation of methadone, regardless of the duration of the reduction regime. A longer program may be associated with benefits whilst treatment is being continued due to the stability afforded by (adequate doses of) methadone. Little is known regarding the extent to which the duration of the methadone reduction program impacts upon other post-withdrawal outcomes.

- *The degree of flexibility in dosing regimes.* The literature examining the impact of flexibility (or patient involvement) in dosing reduction regimes is equivocal. Two studies have reported higher 'completion' rates (subjects reaching zero mg of methadone) for fixed dosing regimes, although the findings regarding other outcomes, such as rates of heroin use, are mixed (Raynes and Patch 1973; Dawe, Griffiths et al. 1991). A larger study of 108 heroin dependent adults using a 22-week methadone reduction regime (Senay, Dorus et al. 1984) showed no difference between subjects randomly assigned to physician or patient-regulated dose reduction on any outcome measure.

- *The level of psychosocial and supportive care.* The research literature regarding the role of psychosocial interventions in methadone-assisted heroin withdrawal is limited. The structured provision of information to patients undergoing an inpatient 21-day methadone taper resulted in enhanced treatment retention and less severe withdrawal severity than subjects receiving information on request (Green and Gossop 1988). Another randomised trial examined the impact of structured counselling regarding post withdrawal treatment options in the context of an outpatient methadone-assisted withdrawal for heroin users (Rawson, Mann et al. 1983). The structured counselling group had a significantly greater

uptake of alternative treatment options (48%) compared to the Control group receiving information on request (12%). A randomised trial of the use of contingency management in an outpatient methadone assisted heroin withdrawal resulted in improved short term outcomes (such as less severe withdrawal symptoms, heroin use and treatment retention), however did not demonstrate any longer term benefit, with all subjects relapsing to heroin use after methadone was discontinued (McCaul, Stitzer et al. 1984).

- *The use of adjuvant symptomatic medications.* Systematic evaluation of adjuvant medications in addition to methadone reductions has been limited. The use of a high-dose clonidine regime throughout a 10-day inpatient methadone reduction resulted in higher drop out rates than the placebo and methadone group, due to hypotensive side effects of clonidine (Ghodse, Myles et al. 1994). Little systematic research has examined the use of benzodiazepines in this context. Diazepam was found to enhance treatment retention and reduce heroin use during an outpatient methadone regime compared to the tricyclic antidepressant doxepin (McCaul, Stitzer et al. 1984). Srisurapanont and Jarusuraisin (1998) found amytriptilline and lorazepam to be equally effective in managing sleep disturbances during withdrawal from methadone maintenance treatment.

- *The availability of transfer to maintenance substitution treatment* (and the extent to which this is encouraged by treatment staff). Many patients undergoing methadone-assisted heroin withdrawal will take up the option of transferring to methadone maintenance treatment if it is available (Rawson, Mann et al. 1983), and the enhanced long term outcomes associated with methadone maintenance treatment warrants its promotion to all patients undergoing heroin withdrawal, particularly in circumstances where other effective treatment modalities are not being considered. However, the decision for a patient to discontinue a withdrawal regime and transfer to methadone maintenance complicates the interpretation of withdrawal outcomes, and withdrawal research studies have not usually included (or reported) such options in their protocols.

Patient factors impacting upon outcomes

The importance of patient characteristics upon withdrawal outcomes is even less clear. Whereas anecdotal reports and conventional 'wisdom' (Kleber 1981) suggests that withdrawal severity is related to duration and levels of heroin use, findings from research directly examining this issue are equivocal. Significant associations between withdrawal severity and quantity of opiate use have been reported (Andrews and Himmelsbach 1944; Smolka and Schmidt 1999); however most researchers have found no significant association between baseline heroin consumption and subsequent withdrawal severity (Phillips, Gossop et al. 1986;

Gossop, Bradley et al. 1987; Gossop and Strang 1991). Smolka and Schmidt (1999) also identified a relationship between route of administration and withdrawal severity, with greater withdrawal reported by those injecting, rather than smoking, equivalent amounts of heroin.

Psychological factors have been shown to impact considerably upon withdrawal severity and treatment retention. Phillips, Gossop et al. (1986) examined a range of patient and treatment factors in heroin and methadone users undergoing a 21-day methadone assisted withdrawal. Methadone dose at the commencement of the withdrawal and duration of opioid use were not predictive of withdrawal severity, whereas level of neuroticism and expectancy regarding withdrawal severity were significantly associated with withdrawal severity. Similar findings have been reported for individuals undergoing withdrawal from methadone maintenance treatment. Kosten, Rounsaville et al. (1984) found higher scores for depression at baseline (as measured by the Beck Depression Inventory) to be a significant predictor of failure at attempts to withdraw from methadone maintenance treatment. Kanof, Aronson et al. (1993) reported that subjects with increasing levels of dysphoria during the withdrawal episode (but not necessarily high scores at baseline) complained of greater withdrawal discomfort and had less success in completing withdrawal; however directions of causality cannot be determined from such findings (increased dysphoria may have been a consequence of greater withdrawal discomfort).

Perhaps one of the most important factors impacting upon withdrawal outcomes is the extent to which patients presenting for treatment are committed to long-term abstinence and have the (psychological and social) resources available to achieve abstinence. These are difficult parameters to measure in both clinical and research settings, and as such, their importance may be underestimated in the research literature.

Other opioid agonists in the management of heroin withdrawal

A range of opioid agonists has been used historically in the management of withdrawal from other opiates. Injectable morphine was used in the nineteenth century to treat withdrawal from opium until concerns were raised regarding the difficulties of withdrawal from morphine. By the turn of the century, heroin was being advocated as a treatment for morphine addiction (Kleber & Riordan 1982). As heroin became an ever-increasing drug of abuse, opiates such as morphine and codeine were used to assist in the management of heroin withdrawal. The 1960's saw the introduction of methadone for treating heroin dependence, and since the 1970's it has become the primary substitution withdrawal medication. A number of other opioid agonists have also been used and evaluated for heroin withdrawal, most notably propoxyphene, codeine, and LAAM.

Propoxyphene has been described in a number of trials of heroin withdrawal (Inaba, Gay et al. 1974; Tennant, Russell et al. 1977; Tennant, Russell et al. 1975). Propoxyphene and methadone were directly compared in an outpatient randomised controlled trial of 72 heroin users using 21-day reduction regimes (Tennant, Russell et al. 1975). Subjects randomised to methadone reported significantly less severe withdrawal features and had higher treatment retention rates, although similar rates of heroin use were reported during the withdrawal episode. The initial enthusiasm shown with propoxyphene has been tempered with more recent reports of adverse events and abuse of the medication (Dore 1996; Matusiewicz, Wallace et al. 1999; Jonasson, Jonasson et al. 1998).

LAAM, a long acting synthetic opioid, was compared to methadone for heroin withdrawal in a randomised controlled trial of 61 male heroin users using a 9 week outpatient treatment protocol (Sorensen, Hargreaves et al. 1982). Reported outcomes (withdrawal symptoms, retention rates and heroin use) were similar for the two groups. Despite the generally favourable outcomes of LAAM for managing heroin withdrawal, it has not been widely used in clinical practice for this purpose.

Codeine is another opiate medication used in Australia (and elsewhere) for assisting heroin withdrawal. In Australia this occurs in the context that codeine in combination with paracetamol or aspirin is registered as a 'Schedule 4' medication, and can be prescribed by doctors without the regulatory controls (such as individual permits from jurisdictional health authorities) associated with most other opioids, which are generally 'Schedule 8' medications. No randomised trials of codeine for managing heroin withdrawal were identified in the systematic literature search conducted by Gowing and colleagues (Gowing, Ali et al. 2000).

1.3.2 Alpha adrenergic agonists

A number of α_2 adrenergic agonists have been investigated for the management of heroin withdrawal, including clonidine, lofexidine, guanfacine and guanabenz acetate; although only two, clonidine and lofexidine, are widely used clinically, and the discussion will be limited to these medications.

The main mechanism of action postulated for the alpha adrenergic agonists is that they reduce the noradrenergic hyperactivity in the locus ceruleus seen during opiate withdrawal (Maldonado 1997), although other neurotransmitter systems may be implicated, including serotonergic and cholinergic systems (Greenstein, Fudala et al. 1997). Clonidine appears to be most effective in reducing certain withdrawal features, such as restlessness and the 'autonomic' features of withdrawal (diarrhoea, nausea, abdominal cramps, sweating, rhinorrhoea,

lacrimation); however appears less beneficial in alleviating sleep disturbances, body and muscle aches or cravings (Jasinski, Johnson et al. 1985; Gossop 1988).

The time frame of withdrawal symptoms when using alpha-adrenergic agonists is comparable to unmedicated heroin withdrawal, peaking in severity within the first 2 to 4 days of heroin cessation. Most objective features resolve within 5 to 7 days, although subjective symptoms generally persist for longer. Unlike opioid agonists, clonidine has the advantage of not significantly prolonging the duration of opiate withdrawal. This facilitates shorter treatment programs and enhances the capacity for induction onto naltrexone as a post-withdrawal treatment option.

Clonidine dosing regimes generally involve titration of the dose according to the patient's experience of withdrawal symptoms and adverse events. The main adverse events reported are features of hypotension (experienced as dizziness, fainting, light headedness), fatigue or lethargy, and dry mouth. It is the former cluster of side effects that frequently restricts upper dosing levels, and indeed has often limited the use of clonidine in outpatient settings where patients can be less readily monitored. Whilst most authors suggest doses of clonidine should be individually titrated, maximum dosing levels of 1 to 1.2 mg (or 15 μg / kg / day) orally per day (in three or four divided doses) have been frequently used in research studies (Washton and Resnick 1981; Kleber, Riordan et al. 1985) and recommended in clinical guidelines (Fishbain, Rosomoff et al. 1993; Greenstein, Fudala et al. 1997; Frank and Pead 1995).

Lofexidine is another adrenergic agonist that has the advantage of producing less hypotensive side effects than clonidine, thereby improving its safety and applicability in the outpatient context. Three randomised controlled trials comparing lofexidine to clonidine in inpatient settings have shown similar efficacy regarding withdrawal severity and completion rates (Lin, Strang et al. 1997; Kahn, Muford et al. 1997; Carnwath and Hardman 1998). Unfortunately, lofexidine is not registered in many countries outside of Europe, and is unavailable in Australia at the time of writing. Another (considerable) drawback is its expense, costing in excess of $(AUS) 200 for a typical one week withdrawal regime (compared to less than $10 for a similar duration of clonidine treatment).

There is considerable variation in the reported outcomes for adrenergic agonist-assisted heroin withdrawal. Some studies have reported very high proportions of subjects successfully completing withdrawal - for example, Benos (1985) reported 88% of subjects completed inpatient withdrawal, while Lerner and colleagues (Lerner, Gelkopf et al. 1995) reported 96% completed a home based withdrawal regime using clonidine. In contrast, others have reported very low rates of successful withdrawal completion. For example, Spencer and Gregory (1989)

reported that 5% of heroin addicts completed an outpatient clonidine withdrawal regime, and stated that this outcome was consistent with conventional experience at their clinic. Tennant and Rawson (1984) reported that only 11% of subjects remained opiate-free for at least several days in an outpatient program. There are a number of reasons for the marked difference in reported outcomes between studies: (a) the use of different outcome measures or endpoints between studies; (b) enrolment of patient populations with different characteristics; and (c) differences in the delivery of treatment services. The marked variations between studies emphasises the necessity of considering findings from randomised controlled trials in order to compare the efficacy of different treatment regimes.

Efficacy of alpha adrenergic agonists

The research evidence from randomised controlled trials comparing the efficacy of clonidine or lofexidine and methadone in managing heroin withdrawal is limited (comparisons between clonidine and antagonist-accelerated withdrawal regimes, and with buprenorphine, are considered in detail later in this chapter). In their systematic review of opiate withdrawal, Gowing and colleagues (Gowing, Ali et al. 2000) identified five randomised controlled trials comparing clonidine and methadone in managing heroin withdrawal (Cami, De Torress et al. 1985; Vilalta, Treserra et al. 1987; San, Cami et al. 1990; Jiang 1993; Dawe and Gray 1995), and one randomised trial comparing lofexidine and methadone (Bearn, Gossop et al. 1996). Several other randomised trials (for example, Washton and Resnick 1981; Washton and Resnick 1980; Strang et al 1997) examined subjects withdrawing from either heroin or methadone maintenance programs, without differentiating the findings according to the primary drug of dependence; consequently, these studies are difficult to interpret in considering the management of heroin withdrawal, and will not be considered in detail in this report.

The first published randomised trial comparing clonidine with methadone for the management of heroin withdrawal was by Cami and colleagues (Cami, De Torress et al. 1985) with 30 heroin users enrolled in a 12-day inpatient program. The study demonstrated comparable completion rates between clonidine and an 8 to 10 reduction regime of methadone. The clonidine group experienced greater peak symptoms early in the withdrawal regime, with resolution of withdrawal symptoms by discharge. In contrast, the methadone subjects reported less peak withdrawal severity, but were still complaining of withdrawal symptoms on discharge.

Similar findings have been reported in most other randomised trials comparing methadone and adrenergic agonist medications. No significant differences were reported regarding completion rates in two trials with small subject numbers (n = 22, Vilalta, Treserra et al. 1987; and n = 16,

Dawe and Gray 1995); nor in a larger randomised trial of 200 subjects (Jiang 1993), albeit a proportion of these subjects were undergoing treatment involuntarily and therefore completion rates are difficult to interpret. All these studies consistently demonstrated that methadone subjects reported delayed peak withdrawal severity compared to the subjects randomised to clonidine. The one randomised trial which examined 10-day inpatient regimes of lofexidine versus methadone reductions (Bearn, Gossop et al. 1996) similarly demonstrated comparable completion rates for the two groups (69% for the lofexidine group, 77% for the methadone group).

San, Cami et al. (1990) is the only randomised trial to report a difference in retention rates between the two medication approaches. The 12-day inpatient trial compared 3 groups: methadone, clonidine, and guanfacine (another adrenergic agonist), and continued to recruit subjects until 30 successful withdrawals had occurred for each condition. Methadone had the highest completion rate: 75% of subjects commencing methadone successfully completed the regime, compared to 48% of subjects commencing guanfacine and 44% of subjects commencing clonidine. Again, the methadone group complained of less severe withdrawal early in the withdrawal (days 2 to 5), however, had more symptoms towards the end of the admission.

Unfortunately, there have been no randomised trials comparing methadone reductions to adrenergic agonists for the management of heroin withdrawal in outpatient settings. Studies examining outpatient withdrawal from methadone maintenance treatment suggest that completion rates with clonidine may be comparable (Kleber, Riordan et al. 1985; Rounsaville, Kosten et al. 1985); or inferior (Washton and Resnick 1980) to methadone reductions.

Clonidine has been shown to result in better outcomes than placebo for the management of inpatient heroin withdrawal (Benos 1985; Gerra, Marcato et al. 1995); and less withdrawal severity than tranquillisers (chlordiazepoxide and chlorpromazine) (Gupta and Jha 1988).

Patient and treatment factors impacting upon outcomes

Many similarities can be identified with the methadone-assisted heroin withdrawal literature regarding the impact of patient and treatment factors:

- As for methadone withdrawal, withdrawal services in *inpatient settings* generally report better outcomes (such as completion rates) than withdrawal undertaken in outpatient settings (Gowing, Ali et al. 2000).

- The provision of *psychosocial interventions* would be expected to impact upon withdrawal outcomes, although there has been little research systematically examining psychosocial interventions in clonidine-assisted withdrawal.

- The *availability of post-withdrawal treatment* influences withdrawal retention rates. The option of enrolling in post-withdrawal treatment was shown to enhance withdrawal completion in a study conducted by Rawson, Washton et al. (1984). Subjects who had access to naltrexone at the end of the withdrawal regime had higher rates of completion for clonidine-assisted outpatient heroin withdrawal than subjects without access to naltrexone. Perhaps of even greater importance in interpreting and comparing findings between studies is the extent to which the withdrawal component of a study is the beginning of a long-term treatment program, such as ongoing naltrexone treatment. This may significantly impact upon withdrawal outcomes by recruiting highly motivated patients interested in long-term abstinence oriented treatment. For example, in the study reported by Gerra, Marcato et al. (1995), subjects were enrolling into a 6 month naltrexone study. The initial week of treatment involved a withdrawal episode, however the outcomes for subjects in this group were remarkably positive for an outpatient population (96% 'completion' rates for clonidine group, 74% for placebo). It may be difficult to generalise findings from such studies to conventional withdrawal programs recruiting a population of heroin users with diverse different treatment goals.

- *Opioid use prior to withdrawal.* A common practice in many studies using clonidine is to stabilise patients on methadone for a number of days prior to commencing clonidine treatment (for example, Cuthill, Beroniade et al. 1990; Washton and Resnick 1981). This practice may result in beneficial withdrawal outcomes, which are attributed to clonidine treatment without adequate recognition of the role of a (temporary) period of stabilisation on methadone. A number of studies with clonidine have demonstrated worse outcomes for subjects actively using heroin at the time of enrolment compared to those stabilised on methadone (McCann, Miotto et al. 1997; Brown and Fleming 1998), and the initial period of stabilisation on methadone may confer benefits that are not associated with clonidine-only regimes.

- *Patient characteristics* may play an important role in determining treatment outcomes. Factors such as the severity of dependence, the extent to which patients are motivated to achieve abstinence, recruitment processes and program selection criteria may impact considerably upon outcomes (Blaine, Ling et al. 1994), although these have not been systematically examined in heroin withdrawal.

Summary of alpha adrenergic agonists in heroin withdrawal

Despite the methodological problems of comparing outcomes between studies, there is sufficient evidence to suggest that clonidine and lofexidine are effective pharmacotherapies for heroin withdrawal. Although not successful in reducing all the features of heroin withdrawal, such as cravings, adrenergic agonists nevertheless have an advantage over methadone in not prolonging the duration of the withdrawal syndrome, which favours their use in short term inpatient withdrawal admissions. The use of clonidine outside of inpatient settings is somewhat restricted by its side effect profile, particularly by inexperienced service providers. Whilst side effects are less of a concern with lofexidine, it is considerably more expensive and has limited availability outside of Europe.

1.3.3 Accelerated withdrawal using opioid antagonists

The opioid antagonists naloxone and naltrexone have been used to accelerate the onset and reduce the duration of acute heroin withdrawal. It is postulated that shortening the withdrawal process reduces the risk (or opportunity) of relapse to heroin use, and enables earlier initiation onto post withdrawal treatment involving naltrexone for relapse prevention.

The compression of acute withdrawal symptoms is associated with a considerable increase in the severity of withdrawal, such that other medications are required to make the process tolerable for patients. Whilst the techniques used have varied considerably (see (O'Connor and Kosten 1998) and (Gowing, Ali et al. 2000) for systematic reviews), two broad approaches have been described:

- *Rapid detoxification* procedures in which the patient is only mildly sedated - antagonists are combined with symptomatic medications such as clonidine, benzodiazepines and anti-emetics. Rapid detoxification programs have been provided in a variety of treatment settings, ranging from intensive hospital settings to (supervised) outpatient day programs
- *Ultra-rapid detoxification* procedures in which the patient is inducted onto antagonists whilst under general anaesthesia or heavy sedation in highly supervised (hospital) setting.

Following the acute withdrawal process, a comprehensive post-withdrawal program involving continuation in naltrexone treatment and structured counselling for several months is generally recommended by service providers.

These treatment approaches have received considerable attention in recent years, and have been the subject of much clinical and media debate. Antagonist accelerated withdrawal programs are available in most Australian cities in the private sector (usually at considerable cost to the

patient), although the research evidence regarding the role of these services is neither comprehensive nor conclusive. Three reviews of the available research literature have recently been published (O'Connor and Kosten 1998; Gowing, Ali et al. 2000; Tucker and Ritter 2000).

Rapid detoxification

Two randomised controlled trials have been published comparing rapid detoxification to conventional approaches for heroin withdrawal. Gerra, Marcato et al. (1995) compared four randomly assigned outpatient treatment groups in 152 heroin users: (1) clonidine only, (2) naltrexone plus clonidine; (3) naloxone plus clonidine; and (4) placebo. Outcomes reported included withdrawal severity; proportion of subjects taking naltrexone on day 8 (withdrawal completion rates); and post-withdrawal outcomes at 6 months follow up. The study reported very high levels of retention in withdrawal treatment for all groups (74% for placebo; and over 90% for the other three groups). Unfortunately the study report had a number of methodological flaws, including lack of clarity regarding: the method of randomisation, the proportion of subjects reporting continued heroin use (the proportions of all urine samples testing positive were reported), and the handling of missing data (e.g. treatment drop outs). The mean proportions (± standard deviations) of morphine positive urine results during the first 5 days were 30 ± 21% for the clonidine group; 5 ± 6 % for the naltrexone - clonidine group, 11 ± 7% for the naloxone - clonidine group, and 48 ± 8% for the placebo group. At six months follow up, the mean proportion of positive morphine urine results was 60 ± 7% in the clonidine group, 74 ± 12% of the placebo group, 20 ± 5 % for the naloxone - clonidine group and 18 ± 4% for the naltrexone - clonidine group.

Despite problems in the way this study was reported, the findings suggest that there are no immediate benefits in using antagonists during withdrawal compared to using clonidine on its own, given the very similar proportions of individuals in the clonidine and antagonist - clonidine groups who were inducted onto naltrexone by the end of the first week. The study findings did indicate a significant difference with regard to post-withdrawal outcomes, suggesting that the early use of antagonists during withdrawal may enhance retention in longer-term naltrexone treatment. However, the study reported remarkably high rates of withdrawal completion and post-withdrawal abstinence rates for all groups - including 74% completion rates for outpatient heroin withdrawal using placebo! As identified earlier, the findings of this study may be difficult to generalise to broader populations of heroin users undergoing withdrawal treatment - subjects in this study were concurrently recruited into a six month naltrexone study, suggesting that they were highly motivated to achieve and maintain abstinence, with good psychosocial supports during and after the withdrawal episode.

The other randomised trial of rapid detoxification was conducted in an outpatient primary care setting in the USA (O'Connor, Carroll et al. 1997). This study examined short term withdrawal outcomes in 162 heroin dependent users randomly allocated to three groups: (1) clonidine only during the first 7 days, receiving naltrexone on day 8; (2) naltrexone commencing on day 2 at 12.5 mg, increasing to 50 mg daily by day 3, together with clonidine; and (3) buprenorphine from days 1 to 3 with clonidine and naltrexone commenced on day 4 at 25 mg increasing to 50 mg by day 5. Findings regarding the use of buprenorphine are considered later in this chapter; however, the data regarding clonidine compared to clonidine - naltrexone indicated that the two regimes were comparable with regards to rates of induction onto naltrexone (both in terms of proportion taking a full 50 mg dose and the proportion in treatment at day 8); and had similar severity of reported heroin withdrawal. Unfortunately, the report did not indicate: (a) the proportions of subjects using heroin during the withdrawal episode; (b) the need for 'rescue' medications during withdrawal; (c) the incidence of adverse events; nor (d) the proportion of subjects in the clonidine group who remained in naltrexone treatment beyond one dose. Nevertheless, the study demonstrated that antagonist-assisted withdrawal is possible in an outpatient setting, with comparable short-term outcomes to a conventional clonidine regime.

There has been considerable variation in the reported outcomes of cohort studies employing rapid detoxification. "Successful" withdrawal outcomes have usually been defined as the proportion of subjects receiving a full dose of naltrexone (e.g. 50 mg) after several days (usually day 3 to day 8). Completion rates have been reported as high as 100% to as low as 7% remaining in inpatient treatment at 2 weeks (Azatian, Papiasvilli et al. 1994), with a mean completion rate of 83% (Gowing, Ali et al. 2000).

Unfortunately, few studies have included any significant follow-up information. The findings of the study by Gerra, Marcato et al. (1995) were previously discussed. Seoane, Carrasco et al. (1997) reported that 93% of 300 heroin users self-reported to be opiate-free and provided an opiate-negative urine test one month after a rapid withdrawal procedure. Bell, Young et al. (1999) conducted rapid detoxification in an inpatient setting on 15 heroin dependent users and 15 methadone patients, with outcomes reported at day 7 and at three months. The methadone group performed better at three months than the heroin group, a finding consistent with previous research with clonidine and methadone-assisted withdrawal programs. 13 (87%) of the heroin users were taking naltrexone at day 7, and 10 (67%) were taking naltrexone after four weeks. At three months follow up, 4 (27%) were taking naltrexone (of whom one was not using heroin), 5 (37%) were in methadone treatment, 4 (27%) had relapsed into dependent heroin use, one person was abstinent but not in treatment, and one person was dead.

The pattern of withdrawal symptoms using rapid detoxification is related to the procedure utilised. The typical profile reported is that of severe withdrawal following the initial dose of antagonist medication, with symptoms abating thereafter, although many studies have described continued (subjective) withdrawal symptoms persisting for several days after the first antagonist dose (Kleber, Topazian et al. 1987; Loimer, Schmid et al. 1990). To this extent, the claims that rapid detoxification procedures markedly reduce the duration of withdrawal symptoms may be exaggerated. Rather, antagonist-assisted withdrawal regimes appear to be a useful means of inducting heroin users into antagonist treatment early in the treatment process, thereby reducing drop out rates and diminishing the capacity for continued heroin use, in those patients for whom long term treatment with naltrexone is indicated.

Ultra-rapid detoxification

This procedure entails the introduction of opioid anatagonists under heavy sedation and / or general anaesthesia. Several case series have been reported in the literature, however there have been no control groups, and different studies have reported markedly different long-term outcomes, thereby limiting the capacity to draw conclusions regarding the efficacy of this approach (O'Connor and Kosten 1998; Gowing, Ali et al. 2000). Some studies have reported longer term outcomes consistent with the naltrexone relapse prevention literature - for example, Cuccia, Bertschy et al. (1996) reported 40% retention on naltrexone at one month, and 20% retention at 6 months; whereas other studies have reported very high abstinence rates that are not routinely seen in naltrexone programs for heroin addicts - Brewer, Gooberman et al. (1997) reported 76% of 510 successfully withdrawn subjects were abstinent at 4 months, while Rabinowitz, Cohen et al. (1997) reported that 57% of subjects followed-up (follow up rate of approximately 70%) self-reported no routine opiate use 12 months after the procedure. Legarda and Gossop (1994) reported that all 11 subjects were still taking naltrexone 30 days after ultra-rapid detoxification.

These widely divergent outcomes raise questions regarding the similarity (or lack thereof) in the treatment populations and post-withdrawal treatment schedules across studies. Properly controlled and carefully monitored research trials are required in order to establish the role of ultra-rapid detoxification procedures (Kleber 1998; O'Connor and Kosten 1998; Tucker and Ritter 2000). There have also been a number of concerns raised regarding:

(a) the safety of the procedure (with several reports of anaesthesia related deaths (Dyer 1998; Brewer 1997) and reports of complications requiring prolonged hospitalisation (Seoane, Carrasco et al. 1997; Pfab, Hirtl et al. 1999; Scherbaum, Klein et al. 1998);

(b) the intensity and associated cost of service provision;

(c) studies that have examined subjective symptoms report persistent symptoms / adverse events for up to one-week post-anaesthesia (Loimer, Linzmayer et al. 1991; Scherbaum, Klein et al. 1998; Cuccia, Bertschy et al. 1996).

Given the availability of (less dramatic) alternatives, it is unlikely that ultra-rapid detoxification procedures will have a significant role for heroin detoxification outside of private treatment settings.

Summary of antagonist assisted heroin withdrawal

The safety and efficacy of antagonist-accelerated withdrawal for heroin users is yet to be established in the research literature (Tucker and Ritter 2000; O'Connor and Kosten 1998). This approach does have the advantage of inducting heroin users into a form of post-withdrawal treatment: naltrexone maintenance treatment for relapse prevention. Unfortunately, naltrexone treatment is not particularly attractive to many heroin users who may be contemplating withdrawal (Tucker and Ritter 2000; O'Brien, Greenstein et al. 1978), nor is it particularly effective in retaining heroin users in treatment compared to substitution maintenance treatment (O'Brien, Greenstein et al. 1978; Grey, Osborn et al. 1986; Osborn, Grey et al. 1986); and no better than placebo in double-blinded randomised trials (Lerner, Sigal et al. 1992; San, Pomarol et al. 1991). As such, antagonist accelerated approaches to withdrawal treatment are likely to only be indicated for individuals who are suited to longer term naltrexone treatment, such as opiate users highly motivated for abstinence and with good social support systems.

1.3.4 Summary of pharmacotherapies (other than buprenorphine)

In summary, each of the three main pharmacological approaches for heroin withdrawal reviewed thus far is well suited to particular treatment populations and clinical settings; however, they each have their limitations when the broader objectives and outcomes of withdrawal services are considered.

Methadone assisted withdrawal has been shown to be a safe, effective and acceptable approach. The initial period of stability afforded by methadone prior to the onset of significant withdrawal symptoms enables heroin users to distance themselves from daily heroin use. Methadone assisted withdrawal has an advantage in that patients are engaged in a treatment modality that can be easily continued into a longer term methadone maintenance program, thereby facilitating linkage with post withdrawal treatment. Unfortunately, methadone delays and prolongs the withdrawal syndrome, which limits its use in brief inpatient settings, and

complicates induction onto naltrexone as a post withdrawal approach for those patients considering longer term abstinence from all opiates. Methadone also carries considerable negative stigma among certain groups of heroin users, health professionals and the broader community, and in certain countries is associated with considerable regulatory control that limits the capacity for its widespread use for withdrawal. For example, only authorised medical practitioners can prescribe methadone in Australia, and fewer than 5% of general practitioners are authorised to do so.

Most research literature regarding symptomatic medication approaches has focussed upon the use of the alpha-adrenergic antagonist clonidine, and more recently lofexidine. These medications have the advantage over methadone in not prolonging the withdrawal syndrome, thereby making them well suited to brief inpatient withdrawal programs. Their use does not delay induction onto naltrexone as a post withdrawal medication, although the use of symptomatic medications for withdrawal is perhaps less likely to facilitate post withdrawal referrals into substitution maintenance treatment to the same extent as methadone assisted withdrawal treatment. The high incidence of side effects (particularly hypotension and lethargy), and their inability to relieve cravings and mood disturbances reduces their safety and effectiveness in outpatient settings. Lofexidine has a lower incidence of hypotension-related side effects, however is not registered in most countries, is considerably more expensive than clonidine, and has not been shown to significantly improve key treatment outcomes compared to clonidine.

The research evidence regarding the safety and efficacy of antagonist assisted withdrawal approaches has not been clearly established, although these approaches have gained in popularity in certain quarters, and there are clinicians with considerable experience in delivering these withdrawal techniques. Ultimately, antagonist-assisted withdrawal is likely to only be of benefit to those heroin users contemplating long term naltrexone treatment for relapse prevention, and estimates would suggest that this represents less than 10 to 20 % of heroin users presenting to conventional treatment services (Tucker and Ritter 2000).

Key issues regarding the use of these medications will be revisited in Chapter 5 when considering the tailoring of medication regimes for individual patients attempting heroin withdrawal, and include a comparison to the use of buprenorphine for this purpose (see Tables 5. 1 and 5.2). The next section in this chapter will review the literature regarding the use of buprenorphine for heroin withdrawal.

1.4. Buprenorphine in the management of heroin withdrawal

Buprenorphine is a derivative of the morphine alkaloid thebaine that was originally developed and registered as an analgesic. There has been increasing research and interest in its use as a treatment for heroin dependence since the late 1970's, and it is registered for this purpose in a number of European countries. Most research with buprenorphine has addressed issues of maintenance treatment, with several large scale randomised controlled trials demonstrating it to be of similar safety and efficacy to methadone maintenance treatment. There has also been increasing interest in its use in the management of withdrawal from heroin and other opiates. This section will examine the clinical pharmacology of buprenorphine relevant to the management of heroin withdrawal, and then consider efficacy and clinical issues in the use of buprenorphine for withdrawal.

1.4.1 Clinical pharmacology and rationale for buprenorphine in the management of heroin withdrawal

Buprenorphine is a partial agonist at the μ opiate receptor. A partial agonist is defined as a compound that "even at full saturation of the receptor system (the) effect is still less than the maximal effect obtainable with full agonists" (Ariens 1983). Buprenorphine has low intrinsic activity, only partially activating μ opiate receptors, resulting in milder, less euphoric and less sedating opiate effects than are achieved with full opioid agonists such as heroin, morphine or methadone (Jasinski, Pevnick et al. 1978; Lewis 1985). Nevertheless in adequate doses, buprenorphine effects are sufficient to diminish cravings for heroin and prevent or alleviate opiate withdrawal features in dependent heroin users, important characteristics in retaining individuals in treatment (Johnson, Cone et al. 1989).

Buprenorphine has a rapid onset of action and a long duration of action. Peak plasma concentrations are achieved one to two hours after sublingual administration, with peak effects described within one to four hours after sublingual administration (Walsh, Preston et al. 1994). The duration of action of buprenorphine is related to the dose of buprenorphine administered, with higher doses resulting in more prolonged effects than lower doses. The duration of discernible effects of buprenorphine ranges from 12 hours (at doses of 2mg) to as long as 72 hours (at higher doses of 16 or 32 mg) (Walsh, Preston et al. 1994). Buprenorphine's long duration of action allows for a once-a-day dosing regime, unlike other medications frequently used for heroin withdrawal (including clonidine, benzodiazepines, or short-acting opioids such as codeine or propoxyphene). The capacity for a once-a-day dosing regime potentially reduces

the risks of diversion or abuse of the medication in outpatient settings, and potentially reduces the cost of administration in inpatient withdrawal settings.

Buprenorphine undergoes extensive first pass metabolism when taken orally, and more potent effects are experienced through injected or sublingual routes of administration (Jasinski 1981). Contemporary preparations of buprenorphine for the treatment of heroin dependence utilise sublingual tablets, whereas injected preparations are generally reserved for the management of acute pain. Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-dealkylation (Green, Belanger et al. 1997; Iribarne, Picart et al. 1997). The metabolites to do not cross the blood brain barrier, and are excreted in the biliary system with enterohepatic cycling of buprenorphine and its metabolites (Brewster, Humphrey et al. 1981). The majority of the drug is excreted in the faeces and urine (see Walter (1997) for overview).

Rebound withdrawal

A major limitation to the use of methadone or other opiate agonists for the management of heroin withdrawal is the rebound withdrawal (increase in withdrawal features) experienced following the reduction or cessation of the prescribed opioid (see earlier discussion in Section 1.3.1). In contrast, the withdrawal syndrome following the cessation of buprenorphine appears to be milder than is typically described for other opiates. Objective withdrawal features (as measured by the Himmelsbach Scale (Himmelsbach 1941) in the 10 days following discontinuation of equivalent doses of morphine and buprenorphine were compared in some of the early buprenorphine research conducted by Jasinski and colleagues (Jasinski, Pevnick et al. 1978). Measures of withdrawal severity, including peak and total area under the curve, were considerably less for buprenorphine than morphine.

There are a number of mechanisms hypothesised for the mild rebound withdrawal seen following the reduction or cessation of buprenorphine. The most widely cited explanation is that buprenorphine has a very high affinity for and slow dissociation from mu opiate receptors, such that once bound to these receptors it is only slowly dislodged (Cowan, Lewis et al. 1977). Buprenorphine is also very lipophilic (Hambrook and Rance 1976), such that it continues to be slowly released from fat stores following the cessation of chronic dosing. These mechanisms result in the maintenance of homeostasis following its cessation, which reduces the emergence of a pronounced withdrawal syndrome (Dum, Blasig et al. 1981). The relatively low intrinsic activity of buprenorphine at the mu receptor may contribute to the milder withdrawal syndrome. However, intrinsic activity appears to be less important than the rate of dissociation (Negus and Woods 1995): other partial agonists (for example, nalbuphine) with low intrisinc

opioid activity but rapid dissociation result in more severe withdrawal syndromes (Woods and Gmerek 1985). Other authors have suggested that the slow rate of dissociation does not adequately explain the mild withdrawal syndrome, and have hypothesised that it may be related to buprenorphine's potent antagonist properties at kappa opiate receptors (Jasinski and Preston 1995).

The onset, severity and duration of rebound withdrawal symptoms appear to be related to the duration of buprenorphine treatment. Unfortunately, no study has directly examined the impact of treatment duration upon the severity of rebound withdrawal following buprenorphine's discontinuation. There are a number of methodological difficulties in comparing reports of withdrawal severity across studies that have used different instruments for measuring withdrawal severity, different study populations, and dosing regimes. Nevertheless, the published studies that have reported the emergence of withdrawal features following the cessation of buprenorphine in heroin dependent users are summarised in Table 1.3, in ascending order for duration of buprenorphine treatment. Excluded from this series are those studies that did not report withdrawal severity or had inadequate follow up time (less than 3 days) following the last dose of buprenorphine (Bickel, Stitzer et al. 1988; Nigam, Ray et al. 1993; Diamant, Fischer et al. 1998; Vignau 1998; Liu, Cai et al. 1997); those studies that introduced naltrexone prior to the possible emergence of rebound withdrawal (O'Connor, Carroll et al. 1997; Kosten and Kleber 1988; Kosten, Morgan et al. 1991); or those studies examining subjects transferred from methadone maintenance treatment (Kosten and Kleber 1988; Kosten, Morgan et al. 1991; Janiri, Mannelli et al. 1994).

The general trend of these studies suggest that the severity and duration of withdrawal features following the cessation of buprenorphine is related to the duration of buprenorphine use, with longer periods of treatment being associated with a delayed onset of peak symptoms and more prolonged withdrawal symptoms. Buprenorphine's high lipophilicity may account for this trend: following the cessation of chronic treatment, low levels of buprenorphine are slowly released from fat stores, resulting in a delay in the emergence of peak withdrawal symptoms.

Short courses of less than one week of buprenorphine appear to result in minimal, or in mild and transient symptoms that subside within two to three days after the cessation of buprenorphine. This has significant implications for withdrawal management, in that it potentially enables the use of buprenorphine in short courses to alleviate withdrawal and diminish cravings during the period of peak severity of heroin withdrawal (the first four to five days), without considerably prolonging the course of withdrawal. This potentially overcomes some of the difficulties encountered with other substitution medications such as methadone (although there is limited research examining rebound withdrawal following very short courses

of methadone – see Section 1.3.1). Longer courses of buprenorphine (for example, several weeks) are associated with a rebound withdrawal, which appears to be milder but of similar duration to rebound withdrawal seen following comparable courses of methadone (Jasinski, Boren et al. 1984; Bickel, Stitzer et al. 1988).

Blocking effects on heroin use

Buprenorphine reduces the effects of additional heroin (or other opiate) use in a dose related manner: doses of 2 mg or more are required to produce such a response, with higher buprenorphine doses (e.g. 8 mg) resulting in greater blockade effects (Bickel, Stitzer et al. 1988; Rosen, Wallace et al. 1994). The proposed mechanism of action for this 'blockade' is thought to be due to buprenorphine's high affinity for opiate receptors, which prevents heroin from occupying these receptors (Jasinski, Pevnick et al. 1978; Bickel, Stitzer et al. 1988; Rosen, Wallace et al. 1994; Johnson, Risher-Flowers et al. 1993). It has been postulated that the suppression of withdrawal symptoms and the blockade of additional heroin use are the two mechanisms responsible for reduced self-administration of heroin by patients taking buprenorphine (Mello, Mendelson et al. 1982).

Safety and side effects

The profile of side effects with buprenorphine is similar to other opiates, with constipation, headache, disturbed sleep, drowsiness, sweating and nausea the commonest reported side effects (Ling, Charuvastra et al. 1998; Lange, Fudala et al. 1990; Teoh, Mendelson et al. 1993). These authors report that buprenorphine in therapeutic doses appears to have minimal impact upon hepatic function. One potential adverse event of buprenorphine that is not seen with the use of opioid agonists is that of precipitated withdrawal (Jacobs and Bickel 1999). As indicated earlier, buprenorphine has a higher affinity for mu opiate receptors, but a lower intrinsic activity than most other agonists, including heroin. If a heroin dependent person has their first dose of buprenorphine soon after using heroin, the heroin is displaced from the mu opiate receptors and substituted with buprenorphine, which has less activity at these receptors. This process can result in a significant opiate withdrawal syndrome being precipitated, typically occurring within 1 to 2 hours after the first buprenorphine dose, and subsiding thereafter. Fortunately, heroin is a short acting drug, whose principal activity lasts for less than 4 to 6 hours, and the initial dose of buprenorphine can generally be delayed for at least 6 hours after the last use of heroin in order to avoid this adverse event. The phenomenon of precipitated withdrawal is of much greater concern for subjects transferring from long acting opiates such as methadone to buprenorphine (Schuh, Walsh et al. 1996).

Table 1.3. Summary of studies describing rebound withdrawal following buprenorphine cessation.

Study, setting, number subjects	*Dosing schedule* [a]	*Onset, duration and peak withdrawal features following cessation of buprenorphine*
Cheskin, Fudala et al. (1994) 11 subjects	*3 days* 8, 6 & 3 mg / day	No increase in mean subjective or objective withdrawal features in the 7 days after buprenorphine. Rescue medications not required.
Umbricht, Montoya et al. (1999) 28 subjects	*4 days* 12, 8, 4, 2 mg / day	4 days follow-up after last buprenorphine dose. Rebound withdrawal transient, generally peaking after 48 hours, with resolution by 72 hours after last dose. 42% subjects had clinically significant rebound withdrawal on day 6.
Mello and Mendelson (1980) 5 subjects	*5 days* < 6 mg /day	Nil withdrawal reported using objective measures
Parran, Adelman et al. (1994) 22 heroin using subjects	*6 days* 0.9 - 2.7 mg / day titrated dose (SC)	16 (73%) had no withdrawal symptoms following buprenorphine; 5 (23%) reported transient mild withdrawal; 1 (5%) had persistent mild withdrawal
Parran, Adelman et al. (1990) 8 heroin using subjects	*6 days* < 3 mg / day titrated dose (SC)	Nil rebound symptoms reported in all 5 of the 8 subjects followed up after dosing.
Schneider, Paetzold et al. (2000). n = 15 subjects, 11 had used methadone	*10 day regime* 3 mg for 7 days; 2 mg day 8; 1 mg day 9; 0.4 mg day 10. SL tablet.	Mean SOWS score on day 7< day 10 (last bup dose) < day 13 > day 16. Follow up to day 19. Peak mean withdrawal score 3 days after last bup dose.
Jasinski, Boren et al. (1984) 15 subjects	*14 days* 2mg per day. SL solution & SC	Mild objective withdrawal features observed: onset on day 2, peaking days 3 to 4, and resolved by day 7 to 10.
Fudala, Jaffe et al. (1990) 14 subjects	*37 days* 8mg per day, then abruptly ceased.	6 subjects (43%) required symptomatic medication following bup cessation. For those not requiring medications (57%), subjective withdrawal symptoms began on day 2, peaking on days 3-4, and resolved by days 8 to10. No significant increase in objective features reported.
Jasinski, Pevnick et al. (1978) 5 subjects	*57 days* 8 mg / day, then ceased. Subcutaneous (~12 mg sublingual)	Onset of objectives features on days 2 to 3, with peak severity at day 14-15.

[a] all inpatient studies; studies used buprenorphine in a sublingual solution unless otherwise stated (SL = sublingual, SC = subcutaneous)

A considerable advantage of buprenorphine over full opioid agonists derives from its safety profile. Dose response studies demonstrate that buprenorphine has 'ceiling' effects, so that high doses (16 mg or more) do not result in substantially greater respiratory depression or sedation than lower doses (8 or 12 mg) (Walsh, Preston et al. 1994). Very high doses (many times higher than normal therapeutic doses) appear to be well tolerated and do not generally result in significant respiratory depression even in non-opiate dependent individuals (Walsh, Preston et al. 1994). Although the risk of overdose from buprenorphine alone appears considerably less than other opioids such as methadone or morphine, there is the capacity for buprenorphine to contribute to sedation, respiratory depression and death from overdose in combination with high doses of other sedative drugs, such as alcohol or benzodiazepines (Reynaud, Petit et al. 1998; Tracqui, Tournoud et al. 1998).

Antagonist effects at κ opiate receptors

Buprenorphine also exhibits antagonist effects at the kappa (κ) opiate receptor (Cowan, Lewis et al. 1977). The role of kappa opiate receptors in humans remains poorly understood, however excess endogenous κ agonists are thought to be implicated in affective and psychotic conditions (Nutt, Groves et al. 1995). Buprenorphine's antagonist effects at the κ receptor are thought to result in buprenorphine having some temporary antidepressant (Emrich, Vogt et al. 1982; Kosten, Morgan et al. 1990; Mongan and Callaway 1990; Bodkin, Zornberg et al. 1995) and antipsychotic properties (Schmauss, Yassouridis et al. 1987; Groves and Nutt 1991) in certain individuals. This temporary effect upon mood may be quite beneficial during the management of heroin withdrawal, which is typically associated with dysphoria and other mood disturbances.

Transition to naltrexone

Another consideration in the use of buprenorphine as a withdrawal medication is the relative ease of transition onto opioid antagonist treatment (Kosten, Krystal et al. 1990; Rosen and Kosten 1995; O'Connor, Carroll et al. 1997; Umbricht, Montoya et al. 1999). Buprenorphine has a similar affinity for mu opioid receptors to naltrexone (Lewis 1985), and as such, naltrexone can be commenced without completely displacing buprenorphine or precipitating very severe withdrawal symptoms. The ability to commence naltrexone without considerable delays is a considerable advantage of buprenorphine over the use of other opioid agonists such as methadone for managing heroin withdrawal, where a recommended interval of 7 to 10 days between last methadone dose and first naltrexone dose is recommended (Bell, Kimber et al. 1999). A number of different approaches have been used to induct heroin users onto naltrexone

either soon after, or during buprenorphine dosing, the details of which will be reviewed later in this Chapter.

Buprenorphine can also be continued as an effective substitution maintenance medication. Given the high rates of relapse to heroin use during or immediately following withdrawal, the ability to link patients into longer-term maintenance substitution treatment is a key objective of withdrawal services. In this respect, buprenorphine has similarities to the use of methadone for the management of heroin withdrawal, and may have advantages over non-substitution approaches to heroin withdrawal (clonidine, antagonist accelerated withdrawal).

The pharmacological properties of buprenorphine with regards to its use as a withdrawal medication are summarised in Table 1.4.

Table 1.4. Properties of buprenorphine relevant for the management of heroin withdrawal

- Buprenorphine alleviates or prevents withdrawal from opiates
- Buprenorphine exerts opiate-like effects, thereby reducing cravings and increasing treatment retention.
- The withdrawal syndrome on ceasing buprenorphine appears to be less severe than heroin or morphine withdrawal. Short courses of buprenorphine appear to be associated with minimal rebound withdrawal (increase in opiate withdrawal features) upon the cessation of buprenorphine. Longer treatment periods (weeks or months) are associated with clinically significant rebound withdrawal.
- Buprenorphine diminishes the effects of heroin, thereby reducing continued heroin use during withdrawal.
- Buprenorphine is generally well tolerated by heroin users, with mild and transient side effects reported. The risk of precipitated withdrawal requires some degree of supervision. Buprenorphine exhibits ceiling opiate effects on a range of physiological and subjective measures, suggesting that it should be safer than methadone for heroin withdrawal.
- Once-a-day dosing is possible, thereby reducing risk of diversion and abuse of medication
- There are increased post-withdrawal treatment options available with buprenorphine. Naltrexone can be commenced during or soon after the cessation of buprenorphine treatment. Alternatively, buprenorphine can be continued on a long-term basis as a maintenance medication.

1.4.2 Studies examining the efficacy of buprenorphine in heroin withdrawal

Buprenorphine has a range of properties that make it a promising medication for the management of heroin withdrawal, however, as identified earlier, comparative studies with other withdrawal medications using randomised controlled designs are required to properly assess the role of a medication. The literature predating the year 2000 had recently been systematically reviewed (Gowing, Ali et al. 2000), which identified four randomised trials comparing buprenorphine to other medication regimes for heroin withdrawal (Bickel, Stitzer et al. 1988; Cheskin, Fudala et al. 1994; Nigam, Ray et al. 1993; O'Connor, Carroll et al. 1997). The Cochrane review also identified one other randomised trial comparing buprenorphine to other medications in the management of withdrawal from methadone maintenance treatment, and as such is not considered in this review (Janiri, Mannelli et al. 1994). For the purpose of achieving an up-to-date review for this thesis, the published literature was again searched (to May 2001 using Medline, Embase, Psychlit) for randomised trials using buprenorphine for heroin withdrawal published since the completion of the Cochrane review. This search identified one further study (Schneider, Paetzold et al. 2000). Hence, in total, the efficacy of buprenorphine in comparison to other medications for the management of heroin withdrawal has been examined in only five published randomised controlled trials - these are summarised in Table 1.5.

The first randomised trial conducted examined gradual withdrawal treatment regimes in an outpatient setting in the USA. Bickel, Stitzer et al. (1988) examined the efficacy of buprenorphine or methadone outpatient treatment in 45 heroin dependent individuals. Subjects were randomised to receive either seven weeks of buprenorphine (three weeks at 2mg sublingual, then gradual reductions over the subsequent four weeks), or methadone (30 mg for three weeks then gradual reductions over the next four weeks). There were no significant between group differences for mean retention in treatment (48.5 days for buprenorphine group compared with 40 days for methadone group), levels of heroin use or severity of withdrawal symptoms during the first six weeks of treatment. There was considerable drop out in both groups when doses approached zero mg, such that post-withdrawal outcomes were not reported. The authors concluded that buprenorphine was as effective as methadone, however cautioned: 'the results from both groups are poor with respect to illicit heroin use and retention. However, this is not surprising because most studies of detoxification show poor retention and relapse to opioid use during dose reduction' (ibid p.77).

Three other studies have compared buprenorphine to clonidine in short treatment regimes. In an open label study conducted in India, Nigam, Ray et al. (1993) randomised 44 heroin or opium dependent (non-injecting) users to receive ten days of either buprenorphine (maximum daily dose of 1.2mg sublingually, total dose of 10 mg) or clonidine (total dose of 7.2 mg over ten days). Ratings of opiate withdrawal were recorded over eleven days using the Subjective and Objective Opiate Withdrawal scales (Handelsman, Cochrane et al. 1987). The buprenorphine group had significantly lower withdrawal scores during days 3 to 6, significantly lower peak withdrawal scores, and fewer side effects than the clonidine group. The authors concluded that buprenorphine was superior to clonidine for the management of heroin withdrawal symptoms. However, data regarding the experience of withdrawal symptoms several days after the cessation of buprenorphine was not collected, and the possibility of (rebound) withdrawal symptoms emerging two or three days after the cessation of buprenorphine can not be discounted. The authors also cautioned that withdrawal symptoms were less severe in this group of subjects than reported in other studies, perhaps due to the short duration of dependence, non-injecting routes of administration, and opium use. The recent Cochrane review of buprenorphine in heroin withdrawal (Gowing, Ali et al. 2000) provided additional information regarding completion rates for this study: 72 subjects were recruited to the study - 38 in the clonidine group and 34 to the buprenorphine group. 19 subjects in the clonidine group completed the regime (50%), compared to 22 in the buprenorphine group (65%), indicating a non-significant trend.

Cheskin, Fudala et al. (1994) compared buprenorphine to clonidine for the management of inpatient heroin withdrawal in 25 dependent users. In a double-blind, double-dummy study, subjects were randomised to receive either a three-day regime of sublingual buprenorphine in solution (day 1: 2 mg qid; day 2: 2 mg tds; day 3: 1mg tds; total dose of 17 mg), or clonidine (2.7 mg orally over 5 days). Outcomes included objective and subjective features of opioid withdrawal and craving measures. The buprenorphine groups reported significantly lower subjective withdrawal scores and lower cravings during the first three days compared to the clonidine group. There were no significant differences beyond day three, although there was a trend for greater dysphoria over the 10-day period reported in the clonidine group. The mean total withdrawal severity over the admission (area under the curve) was reported as being 88% greater for the clonidine group. Importantly, buprenorphine did not appear to produce a rebound in withdrawal symptoms after its abrupt cessation after day three. The completion rates for withdrawal were not significantly different for the two groups (83% for buprenorphine compared to 62% for clonidine), although this may reflect the small sample size.

O'Connor, Carroll et al. (1997) comparing buprenorphine to other withdrawal medication in a randomised controlled trial conducted in an outpatient setting under double-blinded conditions with 162 heroin dependent users, although the authors commented that the blind was difficult to sustain. Three medication regimes were compared: (1) Clonidine (C) up to 1.2 mg daily for 7 days in six divided doses, followed by naltrexone 50 mg on day 8; (2) Clonidine + Naltrexone (C+N): clonidine regime as above with naltrexone doses of 12.5 mg on day 1, 25 mg day 2, then 50 mg daily for the remainder; and (3) Buprenorphine (B): Days 1-3: buprenorphine 3 mg sublingually per day for the first three days, then clonidine from day 4 onwards (as above) and naltrexone commencing at 25 mg on day 4, then 50 mg daily on days. The end point of the study was to induct heroin users onto naltrexone treatment, such that the buprenorphine group received naltrexone and clonidine from day 4 onwards. Reported outcomes for the study included withdrawal severity (total scores over 8 days; and peak withdrawal severity); completion rates represented as those receiving a 50 mg dose of naltrexone (different time frames for the three groups) and the proportion of subjects in treatment at day 8. The buprenorphine subjects reported lower total withdrawal scores and lower peak withdrawal scores than the clonidine and clonidine - naltrexone groups. Unfortunately, the report did not indicate the proportion of subjects using heroin or requiring available rescue medications, thereby confounding the interpretation of withdrawal severity as a key outcome measure. The study reported no statistically significant differences between groups regarding the proportion of subjects receiving a 50 mg naltrexone dose (65% for C; 81% for C+N; 81% for B); nor the proportion of subjects in treatment at day 8 (65% for C; 54% for C+N; 60% for B). Unfortunately, no description of post-withdrawal retention in naltrexone treatment was reported, and it is somewhat inappropriate to compare regimes requiring several doses of naltrexone (as for the C+N and B) groups to the Clonidine group who had taken their first and only dose of naltrexone at day 8. In summary, only guarded conclusions can be made from this study, which suggested that the buprenorphine regime was associated with less withdrawal severity than the other medication regimes, and that there were similar rates of induction onto naltrexone across the three groups at one week.

A recent randomised trial has compared buprenorphine and carbamazepine to oxazepam ad carbamazepine in a 21-day inpatient admission (Schneider, Paetzold et al. 2000). There were a number of limitations in this study: it was open label, had small numbers (N=27, n = 15 in buprenorphine and n = 12 in oxazepam group), and the subjects consisted of both methadone and heroin users (14 methadone only, 8 heroin only, 5 both heroin and methadone). The buprenorphine regime (using an unspecified preparation) was: 3 mg per day on days 1 to 7, 2 mg on day 8, 1 mg on day 9 and 0.4 mg on day 10 (total = 24.4 mg). The oxazepam group

received 90 mg per day on days 1 to 7, reducing to zero by day 14. All subjects received carbamazepine until day 19 in identical regimes. The findings were consistent with previously described inpatient studies: the subjects receiving buprenorphine described significantly less severe withdrawal (using the Short Opiate Withdrawal Scale (Gossop 1990)) early in the withdrawal period (during the first 7 days), and had lower scores over subsequent days (but not statistically significant). 11 of the 15 buprenorphine subjects (73%) completed the regime, compared to 7 / 12 (58%) oxazepam subjects group, which was not statistically significant.

Some cautious conclusions can be made regarding the efficacy of buprenorphine from the available evidence. Buprenorphine is associated with less withdrawal severity than clonidine (Cheskin, Fudala et al. 1994; Nigam, Srivastava et al. 1994; O'Connor, Carroll et al. 1997), clonidine - naltrexone (O'Connor, Carroll et al. 1997), and oxazepam (Schneider, Paetzold et al. 2000). Although all studies have shown a trend for greater completion rates among subjects using buprenorphine compared to clonidine, no study has demonstrated any significant advantage with buprenorphine on this outcome, which may reflect the small subject numbers enrolled in these trials. The limited evidence comparing gradual buprenorphine to methadone reductions (Bickel, Stitzer et al. 1988) suggests no substantial difference in efficacy between the two approaches. There is little information available regarding a range of other withdrawal outcomes, such as impact upon heroin use in outpatient treatment settings, adverse events, or importantly, retention in post-withdrawal treatment.

There have been several other studies examining opiate withdrawal with buprenorphine that have employed randomised controlled trial designs. Withdrawal from long-term methadone treatment was examined by in Italy (Janiri, Mannelli et al. 1994), comparing buprenorphine to the adrenergic agonists clonidine and lefetamine. Amass and colleagues (Amass, Bickel et al. 1994) examined different rates of buprenorphine dose reduction (rapid versus gradual) following maintenance buprenorphine treatment. As these studies were confined to withdrawal from maintenance treatment, they are beyond the scope of this review. Other randomised trials have examined the impact of ancillary interventions (Bickel, Amass et al. 1997); different buprenorphine dosing schedules in short inpatient withdrawal (Liu, Cai et al. 1997); and different naltrexone induction schedules following short courses of buprenorphine (Umbricht, Montoya et al. 1999). These studies will be considered in the following section examining clinical issues in the use of buprenorphine for heroin withdrawal.

Table 1.5. Summary of randomised trials of buprenorphine compared to other medications for the management of heroin withdrawal.

Study	*Design*	*Study groups (drug, dose)*	*Subjects*	*Study duration*	*Outcomes*
Bickel et al 1988	Randomised, double-blind, double-dummy, parallel group Outpatient, gradual reduction	Buprenorphine (B) S/L solution; 2 mg for 3 weeks then reducing doses over 4 weeks vs Methadone (M) 30mg orally for 3 weeks then reducing doses for 4 weeks.	N = 45 Heroin dependent Males only B = 22 M = 23	7 week treatment phase then 6 week follow up with placebo	*Completion*: Low levels of withdrawal completion for both groups, with drop out increasing as doses reduced. 9/23 M group completed 7-week regime, c/w 11/22 B group. Mean treatment duration: B group = 48.5 ± 19.4 days, M group = 40 ± 24.8 days (NS). *Drug use*: No group difference in opiate use detected on urine testing. Increased opiate use at doses reduced. *Withdrawal severity*: no significant group differences on subjective measures, although higher scores for buprenorphine group in weeks 2 to 4. *Conclusion*: Buprenorphine as effective as methadone, but authors cautioned: 'the results from both groups are poor with respect to illicit heroin use and retention. However, this is not surprising because most studies of detoxification show poor retention and relapse to opioid use during dose reduction' (p77).
Nigam et al 1993	Randomised, open label, parallel group Inpatient Short regime	Buprenorphine (B) S/L tablets 10 day regime, max dose 1.2 mg day 1, reducing thereafter, total dose = 10 mg vs Clonidine (C) 10 day regime, total dose = 7.2 mg	N = 44 Opium and/or heroin dep No injectors Males only B = 22 C = 22	11 day study (limited follow up post medication)	*Completion rates*: 3 / 22 Clon group terminated due to side effects. No other drop outs reported. NS difference b/wn groups. *Withdrawal severity*. Mean SubOWS scores significantly lower for B group on days 3 to 6 inclusive c/ w C group ($p<0.001$). Mean ObjOWS scores for B group significantly less on days 3 & 4 c/w C group ($p<0.001$). *Conclusion*: Buprenorphine superior in reducing withdrawal severity in this population. Caution: open label study; non-injecting heroin users; no follow up.
Cheskin et al 1994	Randomised, double-blind, double dummy, parallel group Inpatient Short regime	Buprenorphine (B) S/L solution Day 1: 8 mg; Day 2: 6 mg Day 3: 3 mg vs Clonidine (C) Day 1: 0.9 mg; Day 2: 0.8 mg; Day 3: 0.6 mg; Day 4: 0.3 mg; Day 5: 0.1 mg	N = 25 Heroin dependent & no med/psych conditions B = 12 C = 13	18 day inpatient admission & data collection	*Completion rates* (stayed 10 days): 10 / 12 B group completed (83%). 8 / 13 C group completed (62%). NS b/wn groups. *Severity of withdrawal*: Buprenorphine group had significantly lower withdrawal severity (objective & subjective measures) than Clonidine group during first 3 days. No significant difference thereafter. *Conclusion*: Buprenorphine superior to clonidine in reducing withdrawal severity. Caution: small study numbers, no data on drop outs (28% of total sample)

Table 1.5 continued

Study	*Design*	*Study groups (drug, dose)*	*Subjects*	*Study duration*	*Outcomes*
O'Connor et al 1997	Randomised, double-blind, double dummy, parallel group Outpatient Short regime	Clonidine (C): 0.1 to 0.2 mg 4 hrly prn for 7 days then 50 mg NTX day 8; vs Clonidine + Naltrexone (C+N): Clonidine regime as above + NTX: day 1:12.5 mg; day 2: 25 mg; day 3 - 8: 50 mg; vs Buprenorphine (B): Days 1-3: buprenorphine 3mg / day, then Clonidine as above + NTX day 4: 25 mg, days 5-8: 50mg	N=162 Opiate dependent. No major med / psych condition C = 55 C+N = 54 B+N = 53	8-day treatment regime. No subsequent follow up	*Completion*: Received 50 mg NTX dose: C (day 8) = 65%, C+N (day 3) = 81%, B (day 5) = 81%. Day 8 completion rates: C = 65%, C+N = 54%, B = 60%. (NS difference). *Drug use*: No measures of heroin use reported. Rescue medications not reported. *Withdrawal severity*: On subjective measures, B group had lower mean scores and lower peak score than C or C+N groups (significant). *Conclusion*: All 3 methods had similar treatment retention at day 8. Buprenorphine associated with less severe symptoms. Caution: blind not sustained, no heroin use measures reported, mandatory naltrexone induction limits generalisability, no reporting of naltrexone retention after day 8.
Schneider et al 2000	Randomised, open label, parallel group 21 day inpatient admission	Buprenorphine regime: days 1 to 7= 3mg; day 8 = 2 mg; day 9 = 1 mg; day 10 = 0.4 mg. Oxazepam regime: day 1 to 7 = 90 mg reducing to zero by day 13 All subjects received identical carbamazepine regime.	N=27 (14 = methadone; 5 = methadone & heroin; 8 = heroin only BPN/CBZ =15; OXA/CBZ= 12	21-day inpatient admission. No subsequent follow up reported.	*Completion (21 day admission)*: BPN/CBZ: 11 / 15 (73%) completed admission; OXA/CBZ: 7/12 completed (58%). No significant difference between groups. *Withdrawal severity*: BPN/CBZ group reported significantly less severe withdrawal (Short Opiate Withdrawal Scale Gossop 1990) during first 7 days, with lower scores (not significant) for remainder of admission. *Conclusion*: Buprenorphine & carbamazepine superior to oxazepam and carbamazepine in reducing withdrawal severity. Caution: small numbers, open label, mixed methadone and heroin withdrawal.

1.4.3 Clinical issues for withdrawal: Buprenorphine dosing regimes

The pharmacology and efficacy studies indicate that buprenorphine has considerable promise as a withdrawal medication, however there a number of outstanding issues regarding the use of buprenorphine for this purpose. Two important clinical issues warrant further consideration: (a) 'optimal' dosing regimes, and (b) optimal methods for induction onto naltrexone (Section 1.4.4). The 'optimal' dosing regime for buprenorphine has not been identified in the literature. Two issues are particularly pertinent: the duration of the reduction regime, and the buprenorphine doses used.

Duration of dosing regime

There are two broad approaches to using buprenorphine for managing heroin withdrawal: short buprenorphine regimes of several days (for example, Cheskin, Fudala et al. 1994; O'Connor, Carroll et al. 1997; Umbricht, Montoya et al. 1999), and longer or gradual reduction regimes over weeks, similar to methadone regimes for heroin withdrawal (for example, Bickel, Stitzer et al. 1988; Bickel, Amass et al. 1997; Kosten and Kleber 1988).

Only one study has been reported comparing the two approaches (Pycha, Resnick et al. 1993), with the findings failing to demonstrate any particular advantage of either approach. This single blind outpatient study compared 58 heroin dependent subjects randomised (in a 2:1 ratio) to receive either a short buprenorphine regime (n = 39, mean number of days = 9, range 7 to 13) or a gradual reduction regime (n=19, mean number of days = 28, range 22 to 37), with all subjects receiving placebo for 10 days after their last buprenorphine dose. Unfortunately, limited information is available regarding the study (for example, buprenorphine doses not described, withdrawal severity not reported). However, the primary outcome reported was completion rates, with 36% of the short regime and 21% of the gradual reduction regime completing the respective regimes. The authors commented that this difference may be attributed to the longer treatment time and increased opportunity for drop out in the gradual reduction regime. The authors noted that there was no significant difference between the two groups regarding continued heroin use (although details not provided). At three months follow up, 6 subjects (10%) were reported to be abstinent (three from each group). The authors concluded that: "outcome success was not related to rate of dose reductions and appeared limited to highly motivated individuals" (page 453).

There have been no other studies comparing short and gradual reduction regimes, and as such, the relative advantages and limitations can only be hypothesised, or extrapolated from the methadone literature. The rationale behind a short regime is to use buprenorphine for a limited

period of time to cover the period of maximal withdrawal severity (typically the first 3 to 5 days). The shorter regime has the potential advantages of avoiding significant rebound withdrawal upon the cessation of buprenorphine and thereby not significantly prolonging the duration of withdrawal discomfort (see Table 1.3). This should make it more suited to inpatient settings, and the shorter withdrawal episode should reduce costs of service delivery in outpatient settings. The shorter regime may also facilitate patients progressing beyond the withdrawal phase of treatment and engaging in post-withdrawal services (e.g. naltrexone, buprenorphine maintenance treatment, counselling), rather than remaining in 'withdrawal' for several weeks.

However, short-term regimes may be less successful in reducing heroin use during the withdrawal episode, in that some patients may be prematurely withdrawn off buprenorphine, as has been suggested in the methadone withdrawal literature (Maddux, Desmond et al. 1980). To this end, a longer reduction regime of several weeks (or months) may be advantageous. The principles behind such a regime would be to stabilise heroin users on an adequate dose of buprenorphine for 1 to 2 weeks in order to assist them to cease their heroin use. The dose can then be gradually reduced over several weeks. Whilst a longer period of time on buprenorphine is likely to provide patients with a longer period of stability, there are potential disadvantages with such an approach. Rebound withdrawal phenomena are more likely to be clinically significant, requiring specific management towards the end of buprenorphine regime, and potentially increasing relapse rates. The prolongation of the withdrawal episode may result in more patients dropping out without engaging in post-withdrawal treatment modalities, either due to relapse to heroin use (limiting naltrexone uptake), or due to some patients believing they do not need to participate in longer-term treatment after achieving a period of stability. Alternatively, the option of a more prolonged withdrawal regime may increase the proportion of patients making the transition to buprenorphine maintenance treatment.

These issues have not been systematically examined, and further research is required to address the issue of the 'optimal' duration of the reduction regime. In clinical practice, the duration of the regime is often tailored to the treatment setting (inpatient versus outpatient), resource availability, or other factors such as the patient's capacity or willingness to participate in long-term services. In the Australian treatment context, heroin withdrawal is usually conceptualised as a short-term intervention, usually limited to 6 to 10 day inpatient programs, or 1 to 2 week outpatient programs. The provision of methadone-assisted withdrawal programs using gradual dose reductions over weeks or months is uncommon (Frank and Pead 1995; NSW Health Department 1999), and the use of methadone as a withdrawal agent has not been encouraged at a national and jurisdictional policy level (National Drug Strategy 1993). In contrast, brief

withdrawal episodes using symptomatic medication have been recommended in influential clinical guidelines (Frank and Pead 1995; NSW Health Department 1999). Importantly, withdrawal services are usually funded as short-term interventions, and this appears to have become standard clinical practice.

Doses of buprenorphine

Greater attention has been given to the impact of buprenorphine doses upon withdrawal outcomes than the duration of treatment, although the dose ranging studies in this area are not conclusive, with considerable variation in the types of doses used in different withdrawal studies (see Table 1.6 for details regarding inpatient studies and Table 1.7 for outpatient studies). In part, the variation in withdrawal dosing regimes reflects two inter-related factors:

- *the era in which the research was conducted.* Early research with buprenorphine for both maintenance and withdrawal treatment used comparatively low doses - up to approximately 2 mg per day (Jasinski, Pevnick et al. 1978; Bickel, Stitzer et al. 1988). This reflected the types of doses in which buprenorphine had been routinely used as an analgesic in pain management. Subsequent research demonstrated that higher doses were safe in this population and more effective in reducing withdrawal symptoms and heroin use, producing blockade and retaining patients in treatment. This resulted in a general trend towards increased buprenorphine doses for managing heroin dependence in both withdrawal and maintenance research.
- *the buprenorphine preparations used.* Much of the early research with sublingual buprenorphine used an aqueous solution of higher bioavailability than the commercially available tablet preparation, Subutex®. Recent studies suggest that the bioavailability of the tablet is between 50% to 75% of the liquid preparation (Nath, Upton et al. 1999; Schuh and Johanson 1999; Ajir, Ling et al. 1998). These differences should be taken into consideration when comparing dosing regimes across studies, particularly for short-term regimes where the differences in bioavailability appear to be more clinically relevant. Furthermore, some of the early research with tablets employed low dose tablets (0.2 mg) available as analgesics. The use of low dose buprenorphine tablets may have restricted the use of high doses - for example, 60 x 0.2 mg tablets would be required in order to achieve a daily dose of 12 mg!

Only one study of heroin withdrawal has directly compared different short-term buprenorphine dosing regimes. Liu, Cai et al. (1997) assigned 60 heroin users (in China) according to severity of dependence to one of three regimes: low dose (maximum daily dose of 3.0 mg, mean dose of 2.0 mg); medium (maximum dose of 4.5 mg, mean dose of 2.9 mg); and high dose (maximum dose of 6.0 mg, mean dose of 3.6 mg) in a 10-day inpatient withdrawal regime. There were no

reported differences between the three groups for completion rates, cravings or withdrawal severity as measured by the CINA (Peachey and Lei 1988). The similar outcomes for the three groups may reflect that higher doses are required for individuals with higher levels of heroin use and dependence; that the differences in the three dosing regimes used were minor and inadequate to demonstrate the impact of different doses; or that there are indeed no differences in outcomes at the different buprenorphine doses used.

Several other uncontrolled studies have explored short-term heroin withdrawal using buprenorphine. In an open label single group study of 50 heroin dependent users in Austria, Diamant and colleagues (Diamant, Fischer et al. 1998) titrated buprenorphine doses according to clinical response over a 10-day outpatient withdrawal program. The study used 0.2 mg buprenorphine tablets, with a maximum daily dose of 4 mg during the first 3 days, reducing to zero over the 10 days. The authors provided no rationale for the doses used in this study; although the low dose tablets must have limited the doses used – with 20 tablets in a day required to achieve the 4 mg maximum dose. Subjects attended the clinic daily for clinical review and dose titration, with objective measures of opiate withdrawal made using the WANG scale. 35 subjects (70%) completed the program, with minimal withdrawal discomfort and minimal use of additional medications. The maximum mean daily buprenorphine dose dispensed was 2.58 ± 0.6 mg (on day 2). The authors described "no increase in withdrawal symptoms" (p.201) as the buprenorphine dose was reduced, although there was no systematic follow-up of subjects after the last dose to examine for rebound withdrawal. 24 subjects (48% of total sample) provided an opiate negative urine result on day 10.

A single group, open label, short inpatient withdrawal regime was described in 36 heroin users in France (Vignau 1998). Buprenorphine doses were individually titrated up to 8 mg per day, and reduced using a flexible regime over a 10-day period. The authors described withdrawal as mild, requiring minimal ancillary medication; however there was no systematic reporting of withdrawal severity. 21 subjects (58%) completed the 10-day withdrawal regime, and 9 subjects (25%) transferred to maintenance treatment, with only 17% of subjects not completing withdrawal or continuing in maintenance treatment.

Table 1.6. Inpatient short term buprenorphine dosing regimes

Study	*Subjects*	*S/L Preparation*	*Dosing regime*	*Equivalent total dose in S/L tablets**
Nigam et al 1993.	Opium and heroin smokers.	0.2 mg tablet	Range of daily doses = 0.6 to 1.2 mg per day over 10 days.	10 mg
Liu et al 1997	Heroin smokers.	low dose tablet	3 groups. Doses commenced at between 3 to 6 mg per day (according to severity of dependence) & titrated to 0 over 7 - 8 days.	~ 14 to 26 mg
Parran et al 1994 [a]	Heroin injectors	subcutaneous injection	Dose titrated. 0.9 to 2.7 mg / day x 2 days, 0.45 to 1.35 mg / day x 2 days; 0.2 to 0.7 mg / day x 2 days	6.6 to 20 mg
Cheskin et al 1994	Heroin injectors.	solution	Day 1 = 8 mg, day 2 = 6 mg; day 3 = 3 mg. Total dose = 17 mg	~ 24 mg
Schneider et al 2000	8 heroin users; methadone used by 19 subjects	not specified (probable tablet)	Days 1 to 7 = 3 mg per day; day 8 = 2 mg; day 9 = 1 mg; day 10 = 0.4 mg. Total dose = 24.5 mg. Carbamazepine also used over 19 days. 21 day admission.	24.5 mg
Vignau 1998	Heroin	Subutex ® tablet	Doses titrated daily. Day 1 mean = 6.1 mg (range 4.4 to 9.0); day 2 mean = 6.4 mg (range 5 to 9); day 3 mean = 5.5 mg (range 4 to 7.6); then progressively reducing to zero mg by day 12.	Total mean ~ 35 mg (data graphed)
Umbricht et al 1999	Heroin.	solution	Day 1 = 12 mg; day 2 = 8 mg; day 3 = 4 mg; day 4 = 2 mg. Total dose = 26 mg	~ 36 mg

*using a conversion of 1.4 : 1 (tablet to solution).

Table 1.7. Outpatient short-term buprenorphine dosing regimes

Study	*Subjects*	*S/L Preparation*	*Dosing regime*	*Equivalent total dose in S/L tablets*
O'Connor et al 1997	Heroin dependent (did not specify route of administration)	not specified	Fixed 3-day regime at 3 mg per day; then commenced naltrexone and symptomatic medication on day 4.	Uncertain. If solution (likely) = 12.6 mg
Diamant et al 1998	Heroin dependent	0.2 mg tablets	Doses titrated daily; mean daily doses of 2 to 3 mg per day for first 4 days, then reducing to zero mg by day 10. Total dose ~ 15 to 20 mg in tablets	Total dose ~ 15 to 20 mg tablets
Bickel et al 1988	Heroin dependent injectors	solution	2 mg daily for 3 weeks, then reduced to 0 mg over further 4 weeks	

Parran and colleagues (Parran, Adelman et al. 1994) have described using parenteral buprenorphine doses to treat individuals withdrawing from heroin (n=22) or other opioids (n=43). Buprenorphine doses were administered subcutaneously every 4 hours over a 6-day period in an inpatient setting. Dose were titrated on day 1 in the range of 0.15 mg to 0.45 mg every 4 hours (0.9 to 2.7 mg per day); and reduced over subsequent days. These doses would be approximately equivalent to 1.5 to 4 mg sublingual solution, adjusting for the different bioavailability of subcutaneous buprenorphine (Jasinski, Fudala et al. 1989). The authors reported positive withdrawal outcomes, with no withdrawal discomfort experienced by 16 (73%) subjects, 5 reported some transient withdrawal discomfort, and only one subject reported persistent withdrawal features (anxiety, restlessness and insomnia).

A range of other studies (generally examining maintenance treatment) have randomly allocated subjects to different buprenorphine doses and reported measures that are relevant to withdrawal treatment, such as severity of withdrawal features, cravings or heroin use. The relevant aspects of these studies are briefly described below.

- Kosten, Schottenfeld et al. (1993), in a double blinded RCT comparing buprenorphine 2 mg to buprenorphine 6 mg over a 24 week period of maintenance treatment. The 2mg group reported significantly more withdrawal symptoms, heroin use and cravings than the 6 mg group.
- Seow, Quigley et al. (1986) compared 2 mg to 4 mg in a randomised blinded study of 32 heroin dependent individuals over a 3-week period. The 2 mg group complained of significantly more withdrawal symptoms than the 4 mg group, with the authorsconcluding that even higher doses would be required to adequately alleviate withdrawal discomfort.
- Schottenfeld, Pakes et al. (1997) compared buprenorphine 12 mg to buprenorphine 4 mg in a double blinded randomised trial comparing retention and heroin use over a 24 week period. The higher dose was more effective in reducing heroin use than the 4 mg dose.
- Johnson, Eissenberg et al. (1995) subjects randomised 150 heroin dependent subjects to 2 weeks on either placebo (n=60), 2 mg (n=60) or 8 mg (n = 30) buprenorphine. The subjects in the 8 mg group had a higher rating of dose adequacy and less heroin use than the 2 mg group, which in turn had better outcomes than the placebo group.
- Schottenfeld, Pakes et al. (1993) examined the effects of different doses of buprenorphine in a blinded study with 15 subjects dependent to both heroin and cocaine. Doses were progressively increased every three weeks from 2, 4, 8, 12 and 16 mg daily, and then reduced every 3 weeks using the same doses. Withdrawal severity was related to dose for

both ascending and descending arms of the regimes: with greater withdrawal scores at low doses and with optimal reduction in withdrawal severity at 12 and 16 mg of buprenorphine per day (60 to 70 % of subjects reported uncomfortable withdrawal at 2 mg, 50% at 4 mg; 30% at 8 mg, 10% at 12 mg and 0% at 16mg).

- Johnson, Cone et al. (1989) in a dose induction study with 19 heroin users dosed patients on consecutive days with 2, 4 and 8 mg. Subjects reported considerably less withdrawal discomfort as the burpenorphine dose increased, although this may also be related to dose accumulation with consecutive day dosing.

- Kosten and Kleber (1988) inducted 8 heroin dependent and 8 methadone patients onto randomly assigned doses of buprenorphine: 2 mg (n=10), 4 mg (n = 4), and 8 mg (n=2). The results are difficult to interpret given the very small subject numbers, and results were grouped for both heroin and methadone patients. Nevertheless, the general finding was that the 4 mg group complained of less withdrawal than the 2 mg group.

- Kosten, Morgan et al. (1991) compared withdrawal ratings for heroin users and methadone patients randomised to different buprenorphine doses (2mg, 3 mg, 4 mg and 6 mg). Unfortunately, the grouping of data of both heroin and methadone users limits interpretation.

- Ling, Charuvastra et al. (1998) reported on measures of heroin use and cravings in over 736 heroin users randomised to 1, 4, 8 or 16 mg sublingual buprenorphine solution over a 16 week period. In general, subjects in the 16 mg group performed best, with higher treatment retention, less heroin use and lower severity of cravings than subjects on lower doses. Authors concluded that 8 mg or more of buprenorphine sublingual solution are more effective than lower doses.

It should be emphasised that these were not withdrawal studies, and that they merely report the severity of withdrawal symptoms (or other related outcomes) in heroin users on different buprenorphine doses (often in long term programs). As such, these studies are not conclusive with regard to establishing optimal dosing regimes for heroin withdrawal. Nevertheless, they suggest that buprenorphine doses of greater than 4 mg per day are more effective in suppressing withdrawal symptoms and heroin use. The optimal maximum dose appears to be in the range of 4 mg to 16 mg sublingually per day.

Whilst higher doses appear to more effectively reduce withdrawal severity, there are some concerns however, with the use of high buprenorphine doses for withdrawal management. Higher doses may result in a higher incidence of side effects, and there is evidence from three

studies that higher doses may be associated with greater rebound withdrawal following the discontinuation of buprenorphine:

- Kosten and Kleber (1988) treated 16 opioid dependent patients for one month at three doses - 2mg (n=10), 4 mg (n=4), and 8mg (n=2). Upon abrupt cessation, the 8mg group (but not the 2 or 4 mg groups) reported a marked increase in measures for opiate withdrawal, suggesting greater rebound withdrawal with higher doses, although the numbers in this study are very small.

- Seow, Quigley et al. (1986) randomly assigned 32 subjects (heroin users with a history of buprenorphine abuse) to either 2 mg or 4 mg buprenorphine (sublingual solution) daily in an outpatient setting for 2 weeks, and then abruptly transferred subjects to placebo for one week. Subjects in the 4 mg group reported less withdrawal whilst on buprenorphine, but more severe withdrawal on placebo compared to subjects in the 2 mg group. This suggests that rebound withdrawal is more severe following cessation of higher buprenorphine doses.

- Resnick, Galanter et al. (1992) titrated 29 dependent heroin users onto buprenorphine doses according to clinical response (range 1.5 to 8 mg per day) and maintained them on these doses for 4 to 12 weeks. Doses were then gradually reduced at 5 - 10% every 3 to 4 days. 28 of the 29 subjects relapsed to heroin use either during or soon after the reduction regime. Whilst systematic measures of opiate withdrawal were not reported, those individuals who required lower initial buprenorphine doses (~2 mg) did not describe relapse to heroin use or withdrawal features until after cessation of buprenorphine, whereas those on higher doses (8mg) relapsed or described withdrawal during dose reductions. The interpretation of this study is difficult due to the non-randomised assignment, the lengthy dosing regime, and it may be that those subjects prone to greater withdrawal discomfort or heroin use required higher initial doses, thereby accounting for the outcomes upon dose reduction. Nevertheless, the study suggests that the use of high doses of buprenorphine may be associated with some negative consequences following dose reduction.

In summary, the available evidence regarding optimal buprenorphine doses suggests that doses in the range of 4 to 16 mg per day may be optimal in reducing withdrawal discomfort and heroin use. Whilst most evidence points towards higher doses being more effective in reducing withdrawal symptoms and heroin use, there are some concerns regarding the use of high doses during withdrawal due to the possibility of greater side effects and rebound withdrawal phenomena.

1.4.4 Clinical issues for withdrawal: Induction onto naltrexone

There continues to be considerable interest in finding ways to successfully induct heroin users onto naltrexone without significant delays (thereby avoiding treatment drop out), and without the experience of severe withdrawal symptoms as seen with antagonist-assisted 'rapid' withdrawal procedures. This work is possible due to the comparable affinity of naltrexone and buprenorphine for mu receptors (Lewis 1985). It has been postulated that buprenorphine is not rapidly displaced after a (small) dose of naltrexone and can continue to exert some agonist effects. This avoids the severe precipitation of withdrawal that is seen with doses of naltrexone following conventional opioid agonists. Laboratory studies (Eissenberg, Greenwald et al. 1996) suggest that the severity of withdrawal precipitated by naltrexone is related to the dose of buprenorphine, and the dose of naltrexone used.

The early clinical work in this area was conducted at Yale University, with two studies reported in the literature. Kosten and Kleber (1988) reported that 7 subjects who had completed a 30-day outpatient regime of daily buprenorphine doses (2 or 4 mg) took up the offer of commencing naltrexone 24 hours after last dose of buprenorphine. The initial 1 mg dose of oral naltrexone did not precipitate withdrawal in any of the seven subjects, however only 2 of the 7 subjects continued naltrexone to doses of 50 mg, with no details provided in the report.

A similar study (Kosten, Morgan et al. 1991) was later conducted in which 39 subjects were maintained on buprenorphine doses (ranging from 2 to 6 mg daily) for 30 days, after which subjects were allowed to choose to enter naltrexone treatment. Naltrexone was commenced 24 hours after abruptly ceasing buprenorphine, with 1 mg, 6 mg, 12.5mg, 25 mg and 50 mg administered on consecutive days. 20 subjects took at least one 6 mg dose of naltrexone, although only 4 subjects were retained in naltrexone treatment for 2 weeks. The authors reported that minimal withdrawal was precipitated using this regime. Some additional data from this work was subsequently reported (Rosen and Kosten 1995) with more details regarding the use of high dose naloxone rather than low dose naltrexone as the initial opioid antagonist in 5 subjects. The high dose naloxone precipitated greater withdrawal initially, but also enabled a more rapid induction onto high doses (50 mg) of naltrexone.

The randomised trial by O'Connor and colleagues at Yale (O'Connor, Carroll et al. 1997) has been discussed in detail earlier. This study used 3mg buprenorphine daily for three days, then commenced naltrexone on day 4 at 25 mg, increasing to 50 mg thereafter, with a marked increase in withdrawal discomfort reported 24 hours later (on day 5), but unfortunately withdrawal data was not collected in the hours after each naltrexone dose, nor on days 6 and 7.

Mann and colleagues (Mann, Montoya et al. 1994) reported brief details regarding the introduction of naltrexone during a short course of buprenorphine for 45 subjects undergoing inpatient heroin withdrawal. Buprenorphine was used for only 4 days (4 mg, 6 mg, 4 mg and 2 mg daily), with comparison of the impact of introducing naltrexone (daily doses of 12.5, 25 and 50 mg) at different stages in the 8-day withdrawal episode. The introduction of naltrexone on day 5 resulted in severe opiate withdrawal; whereas the introduction of naltrexone on day 2 resulted in more tolerable features of withdrawal.

A more comprehensive randomised study from the same research group examined the timing of introduction of naltrexone in heroin users undergoing withdrawal using buprenorphine in an inpatient setting (Umbricht, Montoya et al. 1999). All subjects received a 4-day course of sublingual buprenorphine solution (12 mg, 8 mg, 4 mg and 2 mg). One group (n=32) received increasing dose of naltrexone commencing on day 2 of the admission (12.5 mg on day 2 and 3, 25mg on day 4, and 50mg daily thereafter). The other group (n=28) received placebo until day when 50 mg naltrexone was commenced. The early induction group had greater withdrawal signs early (days 2 to 5) with resolution of objective withdrawal features thereafter; whereas the buprenorphine - placebo group had a milder withdrawal early in the regime, but increased withdrawal on day 8 commencement of naltrexone. Treatment retention (day 8) was significantly greater for the late induction group than the early naltrexone group, however there was no follow up beyond day 8. The study indicated that both procedures were feasible, with early induction resulting in a more rapid resolution of withdrawal discomfort, but at the expense of greater treatment drop out.

There continues to be considerable uncertainty with regard to the optimal techniques for inducting patients onto naltrexone following courses of buprenorphine. Thus far, the studies reporting on these procedures have not specifically described the profile of precipitated withdrawal (Kosten and Kleber 1988; Kosten, Morgan et al. 1991; Mann, Montoya et al. 1994), did not collect continuous data following naltrexone administration (O'Connor, Carroll et al. 1997) or have relied exclusively on objective measures of withdrawal severity (Umbricht, Montoya et al. 1999), which are less sensitive than subjective measures. Further research overcoming these limitations, and examining different dosing regimes for naltrexone induction are required. Nevertheless, it appears that naltrexone can be safely introduced either during or soon after the cessation of buprenorphine treatment, resulting in less severe withdrawal than is typically seen in naltrexone - clonidine induction techniques.

1.5. Developing a research agenda

1.5.1 Outstanding questions regarding buprenorphine in the management of heroin withdrawal

The literature regarding the use of buprenorphine in the management of heroin withdrawal has been reviewed in this chapter. Buprenorphine has favourable pharmacological properties, and randomised clinical trials have identified that buprenorphine is more effective than clonidine in reducing withdrawal severity in inpatient settings (Nigam, Ray et al. 1993; Cheskin, Fudala et al. 1994). Completion rates for buprenorphine subjects were higher in both studies (though not statistically significant). The findings suggest that buprenorphine is safe and effective for managing inpatient heroin withdrawal.

The evidence regarding its efficacy in outpatient heroin withdrawal is less clear, and *further randomised controlled trials are required examining the efficacy of buprenorphine in outpatient withdrawal settings compared to conventional withdrawal approaches* (adrenergic agonists for short regimes, and methadone reductions for gradual reduction regimes). Bickel, Stitzer et al. (1988) compared gradual reduction regimes of methadone versus buprenorphine in a small number of subjects, with comparable but poor outcomes for both groups. The other randomised trial by O'Connor, Carroll et al. (1997) examined induction onto naltrexone following short buprenorphine, clonidine, or naltrexone and clonidine regimes. The buprenorphine group complained of less severe withdrawal symptoms than the other two groups, suggesting a possible advantage in using buprenorphine. However, measures of withdrawal severity in an outpatient study should not be the primary outcome (given the propensity for continued heroin use), and greater emphasis should be placed upon other outcome and process measures, such as rates of heroin use during (and after) the withdrawal episode, treatment retention rates, and rates of induction into post-withdrawal services (see Section 1.1.3 for discussion on evaluating withdrawal services). O'Connor, Carroll et al. (1997) did not adequately examine for these outcomes, and as such it is not possible to draw strong conclusions regarding the efficacy of buprenorphine for outpatient withdrawal. One other outpatient study has reported favourable outcomes with short buprenorphine regimes (Diamant, Fischer et al. 1998), however the absence of appropriate comparison groups in this studies limits its interpretation.

Further research is also required to examine for several important withdrawal outcomes (see Section 1.1.3) that have not been examined in either setting for buprenorphine in comparison to

other treatment approaches – most importantly, *cost effectiveness*, and *post-withdrawal outcomes (such as treatment retention, drug use, psychosocial functioning)*. Although several studies have examined induction onto naltrexone (Kosten and Kleber 1988; Kosten, Morgan et al. 1991; O'Connor, Carroll et al. 1997; Umbricht, Montoya et al. 1999), none have reported retention on naltrexone beyond the initial induction doses, and only Vignau (1998) in a single group study has reported retention in other post-withdrawal treatment options (e.g. buprenorphine maintenance treatment).

Separate to establishing the safety and efficacy of buprenorphine as a withdrawal agent are issues as to how buprenorphine should be used clinically. The evidence regarding optimal buprenorphine dosing regimes for managing heroin withdrawal is not conclusive (reviewed in Section 1.4.3). *It is important to determine buprenorphine dosing regimes that are safe, effective and can be easily implemented in routine clinical practice.* The use of doses which are too low are likely to inadequately prevent withdrawal discomfort or diminish cravings for many heroin users, with possible consequences of increased treatment drop out, and/or increased use of heroin or other drugs (such as benzodiazepines). Alternatively, doses which are too high may unnecessarily increase the severity of rebound withdrawal and prolong the duration of opiate withdrawal symptoms following the cessation of buprenorphine, increase side effects, and/or contribute to the risk of overdose in combination with other sedative drug use. As with the use of other opioids such as methadone, there is likely to be considerable individual variation in buprenorphine dosing requirements for heroin users. There is currently a poor understanding of the factors contributing to individual variation in dosing requirements for buprenorphine. *Further research is required to examine the impact of various patient characteristics upon buprenorphine doses for withdrawal - specifically, whether factors such as the amount or duration of heroin use, psychological morbidity, expectancy, or body size impact upon dosing requirements.* Finally, *a better understanding of suitable procedures for inducting and retaining patients in naltrexone treatment following buprenorphine-assisted withdrawal is required* for those patients interested in long-term antagonist treatment.

1.5.2 Overview of research conducted

In order to address the more important limitations in the current literature regarding the use of buprenorphine in managing heroin withdrawal, a series of research studies were undertaken, summarised in Table 1.8. The specific research questions for each study are presented in later chapters.

Inpatient heroin withdrawal was examined in the Inpatient Titration Study. This study addressed two issues: (a) the range of buprenorphine doses required to manage heroin

withdrawal in inpatient settings using the sublingual tablet preparation (Subutex®), and (b) the impact of patient characteristics upon dosing requirements.

Outpatient withdrawal was examined in two studies. The first study (Outpatient Titration Study) was aimed at developing a better understanding of the types of doses required to manage heroin withdrawal in a short outpatient treatment program, and to establish a suitable clinical regime for this purpose using sublingual buprenorphine tablets (Subutex®). Having developed a suitable short, outpatient dosing regime, a randomised controlled trial was conducted to examine the safety, efficacy and cost effectiveness of buprenorphine as a withdrawal agent in outpatient settings, compared to conventional symptomatic medications (including clonidine). The randomised trial examined a variety of withdrawal and post-withdrawal outcomes (as identified in Section 1.3 of this chapter).

Table 1.8. Overview of research studies

Study title	Principal aim(s) of the study	Brief description
Inpatient Titration Study (Chapter 2)	To identify range of buprenorphine doses appropriate for the management of inpatient heroin withdrawal; and to identify impact of patient characteristics upon buprenorphine doses.	Single blinded study (N = 32 completers). Maximum of 5 days of buprenorphine in an 8 to 10 day inpatient admission. Doses titrated against subjective withdrawal severity.
Outpatient Titration Study (Chapter 3)	To identify range of buprenorphine doses appropriate for the management of brief outpatient heroin withdrawal	Open label study (N=18). Buprenorphine doses titrated against clinical response in dependent heroin users attending outpatient service. Short (5 day) dosing regime examined.
Randomised trial of buprenorphine in management of outpatient heroin withdrawal. (Chapter 4)	To examine efficacy of buprenorphine compared to a symptomatic medication regime (including clonidine and benzodiazepines) across variety of withdrawal and post-withdrawal outcomes.	Randomised open label trial (N=114) comparing buprenorphine and symptomatic medications over an 8-day withdrawal episode. 4-week follow-up examining post-withdrawal outcomes, with subjects self-selecting post-withdrawal treatment.

Following a description of these trials (Chapters 2, 3 and 4), a number of issues will be explored regarding the implementation and uptake of buprenorphine for this clinical indication, particularly in the Australian context. This will be approached from two perspectives:

- An exploration of the processes involved in tailoring medications to the needs of individual patients attending for heroin withdrawal, using an evidence-based framework for clinical decision making. This will entail consideration of the relative merits and limitations of each of the four withdrawal approaches (buprenorphine, methadone, adrenergic agonists and naltrexone) with regards to factors such as safety, efficacy, resource implications and patient preferences, building on the reviews conducted in this chapter together with the evidence acquired from the research trials conducted as part of this thesis.
- An examination of some of the systemic factors likely to impact upon the uptake of buprenorphine in the management of heroin withdrawal by treatment providers and patients. This will conclude with a brief description of the development of Australian clinical guidelines regarding the use of buprenorphine and national training programs for health professionals, both of which have been based work emanating from this thesis.

CHAPTER 2: INPATIENT DOSE TITRATION STUDY

2.1. Study Objectives

This exploratory study aims to identify a suitable dosing regime of buprenorphine in inpatient treatment settings, and to identify the impact of a number of patient characteristics upon the buprenorphine doses. As described in Section 1.4.3, dosing regimes using the sublingual buprenorphine tablet preparation in the management of heroin withdrawal are not well established, with considerable variation in the types of doses and preparations previously used. There is also a very limited understanding of which factors impact upon the medication requirements of heroin users undergoing withdrawal. This is of clinical importance, in that during routine practice, medical practitioners usually prescribe a fixed medication regime at the outset of the withdrawal, which may then be modified according to the patient's response to the medication. Decisions regarding initial dosing regimes can be better tailored if there is an understanding of the impact of various patient characteristics upon the dose required to alleviate withdrawal comfortably.

Different patient characteristics are thought to impact variably upon the severity of heroin withdrawal (see Section 1.3 for discussion). Various studies have identified withdrawal severity to be significantly related to amount of opiate use (Andrews and Himmelsbach 1944; Smolka and Schmidt 1999); mode of administration (Smolka and Schmidt 1999; Strang, Griffiths et al. 1999); expectancy regarding withdrawal severity and psychological profile (Phillips, Gossop et al. 1986); whereas other factors, such as age and duration of opioid use, have consistently been found to be less important (Phillips, Gossop et al. 1986; Kosten, Jacobsen et al. 1989; Smolka and Schmidt 1999). It may be expected therefore, that similar factors may also contribute to the doses of medication required to alleviate withdrawal severity, although research is yet to examine their relative importance with regard to buprenorphine requirements. The specific study objectives were to:

- identify the range of buprenorphine doses required to comfortably alleviate withdrawal symptoms in subjects undergoing heroin withdrawal in residential withdrawal settings using a symptom-triggered titration dosing regime; and
- identify the patient characteristics that impact upon the buprenorphine dose requirements for withdrawal.

2.2. Trial Design and Methodology

2.2.1 Overview of trial design and procedures

The study was an exploratory, single-blinded case series with no comparison group using a symptom-triggered titration regime. It was conducted as a multicentre study in two inpatient withdrawal units: Depaul House, Department of Drug and Alcohol Studies, St.Vincent's Hospital, Melbourne; and the Detoxification Unit of the Canberra Hospital. Subjects underwent an inpatient admission for up to 10 days, with buprenorphine available over the first five days, corresponding to the duration of peak features of heroin withdrawal. Doses of buprenorphine were determined using a symptom-triggered titration regime against the severity of opiate withdrawal symptoms reported by patients using the Subjective Opiate Withdrawal Scale (Handelsman, Cochrane et al. 1987), with maximal doses of 16 mg per day in four divided doses. Patients were blinded to the specific dosing protocols, and to their dose of buprenorphine by the use of placebo tablets. Signs and symptoms were monitored until discharge from the unit. Other medications for the management of withdrawal were not routinely available. Conventional approaches to withdrawal counselling and support were used (Section 1.2.3).

The principal outcome measure (dependent variable) for each patient was the dose of buprenorphine required to alleviate moderate to severe opiate withdrawal symptoms. Data was collected at intake regarding key (independent) variables thought to possibly impact upon medication requirements during withdrawal: (i) amount of heroin use in the four weeks preceding intake, (ii) severity of heroin dependence, (iii) expected withdrawal severity, (iv) psychosocial functioning, (v) body weight and (vi) sex. Multiple regression analysis was conducted to identify the impact of each of these variables upon the doses of buprenorphine administered.

2.2.2 Subjects

2.2.2.1 Estimation of subject numbers

The study aimed to recruit until at least 30 to 35 subjects completed the buprenorphine dosing regime. The number of subjects was calculated on the basis of the numbers required to conduct a multiple regression analysis - it has been suggested that at least five subjects are required for each variable being entered into the regression analysis (Tabachnik and Fidell 1983). Six independent variables (describing patient characteristics at intake) were identified for this analysis; hence a target of at least 30 subjects completing the dosing regime was identified. It

was estimated that between 50 to 70 subjects would need to be recruited in order to have 35 subjects complete the regime (at an estimated completion rate of between 50 to 70%).

2.2.2.2 Selection criteria

The selection criteria, methods of assessment and their rationale are described in Table 2.1.

Table 2.1. Selection criteria

Selection criteria	Method of assessment and rationale
1. Aged 18 years or more	Proof of identity.
2. Heroin dependent and injecting as main route of administration	Assessed clinically against DSM IV 304.0 criteria. Non-injectors were excluded as route of administration has been identified as confounding the relationship between amount of heroin use and withdrawal severity (Smolka and Schmidt 1999).
3. Recent heroin use (within past 48 hours)	Assessed by self-report and positive urine test for opiates (Accusign® antibody diagnostic tests (EMIT) were used to avoid delays in confirming laboratory urine results (Wennig, Moeller et al. 1998). The rationale was to recruit subjects who had recently used heroin and had not progressed beyond the early stages of withdrawal. Peak withdrawal symptoms generally occur after opiate metabolites (morphine) are no longer present, as indicated by a negative urine test.
4. Not in methadone treatment within the past 8 weeks	Rationale was to avoid individuals who had recently ceased methadone treatment and who may be experiencing a methadone withdrawal syndrome. Assessed by self-report and confirmed with the relevant statutory government bodies responsible for issuing methadone permits in Victoria and the ACT.
5. Not dependent upon, or withdrawing from other drugs (alcohol, benzodiazepines, cannabis)	Individuals undergoing concurrent drug withdrawal may have a different profile of symptoms and often require additional withdrawal medication, thereby invalidating the titration approach used in the study. Dependence was assessed by clinical history and examination, urine drug screen, and breathalysed alcohol level where indicated.
6. Not pregnant or breastfeeding	The safety of buprenorphine in pregnancy and breastfeeding is yet to be established. Assessed by a urine bHCG level, using Answer ® dipstick tests to avoid delays in screening.
7. Able to remain in inpatient unit for duration of study	Patients unable to remain in the unit for at least 7 days were considered ineligible.
8. No active or unstable medical or psychiatric condition	Active or unstable medical or psychiatric conditions would potentially complicate the management of withdrawal and / or the interpretation of symptoms, thereby potentially invalidating dose titration.
9. Able and willing to give informed consent	Participation in the study was voluntary, and patients had alternative withdrawal and other treatment options. Capacity to give informed consent was assessed by the clinical team and research assistant prior to induction.

2.2.2.3 Recruitment

Subjects were recruited from consecutive patients presenting to the two residential units for heroin withdrawal. Participation in the study was voluntary with informed consent for the trial's clinical and research activities. Patients not wishing to participate in the study had access to routine withdrawal and other clinical services. There was no active promotion or advertising for the study in order to minimise the potential for uncharacteristic patients presenting for treatment with a new 'trial' medication.

All patients were initially screened by a nurse on presentation to the unit. Interested and potentially eligible patients were further assessed by medical staff and presented with written Plain Language Statements regarding the study. Those willing to participate had relevant urine testing for opiate use and pregnancy conducted, and had their methadone treatment status confirmed with the relevant government authority (see selection criteria Table 2.1). Eligible patients were then interviewed by the research assistant, at which time written informed consent and baseline data were collected. Study treatment procedures were then commenced.

In total, 63 subjects were recruited to the study, 32 in Melbourne and 31 in Canberra. Recruitment at the Melbourne site was conducted over a five-month period (October 1998 to February 1999). 77 patients seeking inpatient heroin withdrawal were assessed at Depaul House during this period. 36 patients (47% of those screened) were considered ineligible for the study, with reasons for exclusion shown in Table 2.2 (five patients had multiple reasons for exclusion from the study). 41/77 (53%) patients were assessed as eligible for the study – although eight patients did not enter the study: seven choosing conventional management, and one patient did not attend beyond her initial assessment. 33 subjects were recruited to the study in Melbourne, representing 43% of all patients assessed.

Table 2.2: Reasons for exclusion from study at Melbourne site

Reasons for exclusion from study	*Number*
Patient also dependent to other substance(s): alcohol (2), benzodiazepines (3), cannabis (3), pethidine (1), or multiple drugs (3)	12
Significant medical / psychiatric condition complicating withdrawal management: pregnancy (1), chronic pain condition (2), carpal tunnel syndrome (1), pelvic inflammatory disease (1), depression (2), alcohol-related brain injury (1), attention-deficit disorder (1), chronic insomnia (1), chronic intractable hiccups treated with psychotropic medication (1).	13
No heroin use in past 48 hours	6
Patient under 18 years of age	3
Patient in methadone program within past 8 weeks	3
Unable to give informed consent on admission (intoxicated)	3
Patient smoking heroin only (no history of injecting drug use)	1

The first subject recruited to the study was considered a pilot case to enable review of the clinical and research procedures. The experience of the first subject resulted in a review of the treatment procedures for the study: titrations were originally commenced on the second day of admission, however this resulted in significant withdrawal discomfort by day 2. Following this experience, the protocol was amended, with commencement of buprenorphine titration on the day of admission. Data for the first pilot subject is excluded from all subsequent analyses, and data is reported for the 32 subjects from the Melbourne site.

Thirty-one subjects were recruited at the Canberra site over a four-month period from November 1999 to February 2000. Unfortunately data regarding the number of eligible and ineligible patients, or the reasons for exclusions, was not available for this site.

2.2.3 Treatment procedures

2.2.3.1 Description and justification for the buprenorphine dosage regime

Issues regarding the parameters of a buprenorphine withdrawal regime were considered in detail in Section 1.4.3. Short courses of buprenorphine treatment were used in this study, with the duration of the buprenorphine regime dependent upon the duration of moderate or severe withdrawal discomfort, and limited to a maximum of five days from the day of admission.

Two general approaches can be used for determining the amount and duration of withdrawal medication. One approach is the titration method, where the amount of a medication is linked to the severity of withdrawal symptoms. Signs and symptoms are monitored throughout the course of treatment (using a reliable instrument or withdrawal scale), and doses of medication are administered in response to the severity of withdrawal features. An example is the titration of benzodiazepines in the management of alcohol withdrawal, where the titration approach has been shown to better match the dose and duration of withdrawal medication to individual patient requirements than fixed dose regimes (Sullivan, Swift et al. 1991; Saitz, Mayo-Smith et al. 1994).

The alternative, and more 'traditional' approach to examining different dosing regimes is to use a blinded randomised controlled study design in which subjects are randomly assigned to different fixed dosing schedules, and outcomes compared between groups of subjects at different doses. Such an approach provides information about groups of subjects, and minimises selection bias in accounting for differences in outcomes. However, there are limitations with a randomised dose design during an exploratory phase of research. A practical issue is that large numbers of subjects are often required to demonstrate statistically significant differences between groups of subjects, particularly if the response to medication is not

consistent across subjects within a group, or if several different dosing regimes need to be examined. This is a relevant issue, given the wide variety of buprenorphine doses previously reported in the research literature (Table 1.6); and the nature of withdrawal regimes (different doses are routinely used on different days of the withdrawal episode), such that several different dosing regimes would need to be explored in order to identify 'optimal' practice. Another limitation is that the evidence from randomised designs cannot automatically be applied in clinical settings, as it does not accommodate individual variation in dosing requirements. For example, a randomised study that shows that more subjects did well at a certain dose (for example, 8 mg) does not mean that all future patients should receive that particular dose. Some patients may experience side effects or other complications at this level, but may have a favourable response on a lower dose (e.g. 4 mg). Others may require higher doses to achieve their desired outcome. In clinical practice, evidence from randomised dose efficacy studies should provide a guide to dosing regimens; however, doses should be individualised according to the response to the medication, the severity of the underlying condition being treated, the emergence of adverse events, and (informed) patient preferences.

The dose titration approach was thought to be better suited to the exploratory nature of this research. Also, the second study objective was to examine the impact of various patient characteristics upon the doses of buprenorphine required to facilitate a comfortable withdrawal. The symptom-triggered titration approach was considered to be more appropriate for this objective, with regression analysis examining for the impact of key variables upon the total dose required for each subject. However, titration methods with buprenorphine have not previously been described in the published literature, and as such, the rationale and justification of the titration procedures used in this trial needs to be systematically described. The key parameters in the development of titration dosing techniques involve:

(a) the assessment and monitoring of the severity of opiate withdrawal at set intervals over the course of the withdrawal episode; and

(b) the administration of buprenorphine in response to moderate or severe withdrawal symptoms.

Measuring the severity of opiate withdrawal

In order for a titration regime to be implemented, a valid and easy to administer scale is required that scores the severity of opiate withdrawal features, with good inter-rater and test-retest reliability. The Subjective Opiate Withdrawal Scale (SOWS) and the Objective Opiate Withdrawal Scale (OOWS) (Handelsman, Cochrane et al. 1987) were ideally suited to this purpose. These instruments have good psychometric properties (Handelsman, Cochrane et al.

1987), and measure withdrawal symptoms at a particular point in time, and are therefore ideal for use in a titration regime that involves multiple dosing points each day. These scales were already routinely used at the Canberra site.

As identified in Section 1.2.3, subjective ratings of opiate withdrawal severity are considerably more sensitive than objective measures, (Turkington and Drummond 1989; Loimer, Linzmayer et al. 1991; Handelsman, Cochrane et al. 1987); are better correlated to treatment outcome and should be used to guide prescribing practices during withdrawal (Kosten, Rounsaville et al. 1985). Hence, in this study, buprenorphine doses were linked to subjective ratings of withdrawal severity using the Subjective Opiate Withdrawal Scale. This scale consists of 16 common symptoms of opiate withdrawal, with each item rated on a scale of 0 to 4, and a total score of 0 to 64. Although there is considerable variation between individuals in their rating of withdrawal severity, previous clinical experience with the SOWS had indicated that scores below the mid-teens generally reflect minimal or mild withdrawal discomfort, scores in the high-teens to low-thirties generally reflect moderate withdrawal discomfort, and score above the mid - 30's reflect severe withdrawal severity.

The collection of objective measures of withdrawal (OOWS), physiological (blood pressure, pupillary size and pulse) and behavioural parameters of intoxication (level of consciousness, speech and gait) enhanced the safety of the titration procedure, and assisted in maintaining the blind, as subjects were unaware of which of the various measures were used to determine doses.

Frequency of monitoring and dosing

The principal determinants of the time interval between reviews are the time to peak effect, and the duration of peak effect of the medication being used. Reviews should not be more frequent than the time taken for buprenorphine to reach its peak effect, or else accumulation of the medication (and over-sedation) may occur. The interval should not be less frequent than the approximate duration of peak effect, or else the patient may experience increased withdrawal symptoms prior to their next dose of medication. For buprenorphine, the time to peak effect is approximately 60 to 120 minutes, and the duration of peak agonist effect is approximately 4 hours for low buprenorphine doses (2 or 4 mg) (Walsh, Preston et al. 1994). This suggests that 4 to 6 hourly reviews should be adequate when using such buprenorphine doses at each time point. Thus, ratings of withdrawal severity for the purposes of dose titration were conducted four times a day: at 7 am, 12 midday, 5 pm and 11 pm – these times being suited to nursing routines in the units.

Buprenorphine doses dispensed

Current evidence indicates that sublingual doses of 2 mg buprenorphine solution suppress heroin withdrawal features, although higher doses have been found to be more effective in this regard, and maximal relief of withdrawal symptoms has been reported at daily doses of 16 mg (see Section 1.4.3 for review). Hence, daily doses of up to 16 mg (in 2 mg increments) were considered as appropriate upper dosing limits for the titration study (although subjects not experiencing withdrawal could receive no buprenorphine).

A dose of buprenorphine was administered if the subject reported uncomfortable (moderate or severe) features of withdrawal on the Subjective Opiate Withdrawal Scale. Based on earlier experience with the SOWS, the following titration regime was developed.

Table 2.3: Titration schedule of buprenorphine vs. withdrawal severity

SOWS score (range 0 - 64)	Buprenorphine dose administered (S/L)	Tablets administered
0 to 16	0 mg	2 x placebo tablets
17 to 32	2 mg	1 x 2 mg buprenorphine + 1 x placebo tablet
33 to 64	4 mg	2 x 2 mg buprenorphine tablets

Each subject received two tablets at each dosing time, containing either 0, 2 or 4 mg buprenorphine. Subjects were blinded to the dose of buprenorphine they received, and were not informed of the threshold scores at which buprenorphine was administered in order to discourage subjects from over-reporting symptoms to receive a dose of medication. Staff involved in dispensing medication were not blinded to the doses administered.

Individual variation in the experience of withdrawal symptoms is to be expected, and there is always the potential for some individuals to over- or under-report subjective withdrawal symptoms. Clinical staff regularly matched subjective (SOWS) with objective (OOWS) ratings of withdrawal, and significant discrepancies generally prompted a discussion with the subject regarding their scoring. For example, a subject who reported no (0) or minor (1) severity for a number of withdrawal features that were clearly observable by staff on the Objective Scale (e.g. yawning, sweating, runny nose, goose bumps) would be prompted to reconsider their score following a re-explanation of the method of scoring of the SOWS. Alternatively, subjects who rated extreme (4) or very severe (3) for items that were not observed by staff were similarly directed to reconsider their score. In this way, gross under- and over- reporting was minimised.

Dosing according to the above titration regime was commenced on the day of admission, and continued until day 4 of admission. The day 5 dose was calculated as up to half of the total day 4 dose split in two divided doses (administered at 12 noon and 11 PM). Subjects receiving 0 or 2 mg of buprenorphine on day 4 were dosed with placebo tablets only on day 5. All subjects received placebo tablets on day 6 of the admission to further enhance the blinding of subjects. Recordings of the severity of withdrawal continued throughout the period of the admission (up to ten days). The procedures are summarised in the following Table.

Table 2.4: Summary of dosing procedures

Day	*Frequency of Monitoring*	*Medication*
1–4	Four times per day 0700; 1200; 1700; 2300	No buprenorphine if SOWS score ≤16 points or intoxicated Buprenorphine 2 mg if SOWS score 17 to 32 points Buprenorphine 4 mg of SOWS score > 32 points
5	Four times per day 0700; 1200; 1700; 2300	50 per cent of the Day 4 buprenorphine dose in two divided doses (1200 and 2300).
6	Four times per day 0700; 1200; 1700; 2300	Placebo tablets at 1200 & 2300.
7–10	Four times per day 0700; 1200; 1700; 2300	No medication routinely available

Subjects were able to refuse medication at any time during the study, however continued participation in the study required participation in the data collection procedures. Subjects could voluntarily withdraw from the study at any time, and remain eligible for conventional treatment. Patients were told of the doses of buprenorphine they received on completing their participation in the study - that is, following the final discharge interview with the research assistant.

2.2.3.2 Other medications and treatment procedures

Other medications for the management of heroin withdrawal were not routinely used. The one exception was for subjects complaining of persistent insomnia, who were allowed one or two nights of low doses of diazepam (5 or 10 mg orally). Subjects were expected to participate in all individual and group counselling and case management sessions according to the usual routine within the withdrawal units. Subjects were expected to comply with the rules of the agency, and failure to comply with these rules would result in administrative discharge from the program and the study.

2.2.4 Outcome measures, data collection and management

The primary outcome for the study was the *dose of buprenorphine dispensed to each subject over the course of the withdrawal regime.* Other outcome measures included:

- *The severity of opiate withdrawal* over the course of the withdrawal episode, as measured four times a day using the SOWS and OOWS.
- *Adverse events.* Adverse events were elicited from subjects and assessed by clinicians daily.
- *Measures of patient satisfaction with buprenorphine.* Data was collected by the research assistant at a discharge interview, using both structured and semi-structured interview techniques. Subjects were asked to rate (a) *the severity of withdrawal experienced* using a Visual Analogue Scale (with 0 = no discomfort, and 100 mm = most severe discomfort ever experienced); (b) *adequacy of the buprenorphine dose* measured on a 5 point Likert scale (1 = "much too low", 2 = "too low", 3 = "about right", 4 = "too high", and 5 = "much too high"); (c) ranking of different medication regimes used for heroin withdrawal from best to worst; and (d) open ended questions regarding the *positive and negative aspects of using buprenorphine* for heroin withdrawal.

In addition to the data collected during the withdrawal episode and at the discharge interview, data was also collected at intake regarding a range of patient characteristics that were thought to possibly impact upon the severity of withdrawal, and hence upon buprenorphine dosing requirements. These variables and their operational measures are shown in Table 2.5 below.

2.2.4.1 Monitoring of Trial

The trial was externally and independently monitored by Panacea Research and Evaluation Pty Ltd, as part of the National Evaluation of Pharmacotherapies for Opioid Dependence project coordinated by the National Drug and Alcohol Research Centre in Sydney. Monitoring included independent confirmation of all subject records, and independent double entry of key data.

Table 2.5 Baseline variables potentially impacting upon dosing requirements

Variable	Measure
Quantification of recent heroin use	Measured using the Drug Use Section of the Opiate Treatment Index (Darke, Heather et al. 1991). This instrument measures frequency of heroin use within the past 4 weeks, represented as a Q score.
Severity of heroin dependence	Measured using the Leeds Dependence Questionnaire (Raistrick, Bradshaw et al. 1994). A validated, 10-item scale measuring physical, cognitive and behavioural components of dependence. Scores 0 to 30, with mild (≤ 17 points), moderate (18 - 23) to high (≥24) degree of dependence.
Expectancy regarding the severity of this withdrawal episode	Measured using a Visual Analogue Scale (0 to 100 mm) in response to the question: "How severe do you think this withdrawal episode will be? Please indicate on the following line with 0 = no discomfort, and 100 = the most severe withdrawal symptoms you have ever experienced"
Psychosocial distress	Measured using the BASIS-32 (Eisen, Dill et al. 1994), a validated 32-item scale assessing 5 parameters (subscales) of psychosocial functioning, including: relationship with self and others; depression and anxiety; functioning in daily role; impulsive and addictive behaviour, and psychosis. Average and subscale scores are represented on a 0 to 4 scale, with higher scores representing greater dysfunction or problems.
Body weight	Measured in kilograms.
Sex	Male or Female

2.2.4.2 Data handling and analysis

The principal investigator and research assistants were responsible for the security of confidential data and consent forms. All subjects received a coded number as a unique identifier. Research data forms only utilised these numerical codes, with the register linking the subject's name to the coded number and the consent forms (with both the subject's name and code number) stored in a locked filing cabinet separate from the remaining data. Data entry, and descriptive and regression analysis were conducted by the principle investigator using the program SPSS 10.1 for Windows (SPSS 2000).

Research data are held on the premises of Turning Point Alcohol and Drug Centre. Turning Point is a research, clinical and training institution with experience in storage of confidential records, and with a number of security systems for this purpose. Data will be held for at least fifteen years after the completion of the study, in keeping with the requirements of Clinical Trial Notification Scheme of the Therapeutic Goods and Administration (Therapeutic Goods Administration 1997).

2.3. Results

2.3.1 Subjects

Demographic characteristics of subjects at intake from the two sites, and for the total sample are shown in Tables 2.6 and 2.7. The majority of subjects were male (70%), unemployed (81%) and had not completed tertiary education (92%). There were no statistically significant differences for the two sites regarding sex ($\chi^2(1) = 2.37$, $p < 0.2$), education level ($\chi^2(3) = 2.64$, $p< 0.5$), or employment status ($\chi^2(4) = 5.0$, $p < 0.3$).

Table 2.6 Demographic characteristics of subjects

	Study site		Total
	Melbourne n=32 (%)	ACT n=31 (%)	N=63 (%)
Sex			
Female	13 (41)	7 (23)	20 (32)
Male	19 (59)	24 (77)	43 (68)
Highest level education completed			
7 - 10	13 (41)	17 (55)	30 (48)
11 - 12	16 (50)	11 (35)	27 (43)
Tertiary	2 (6)	3 (10)	5 (8)
Unknown	1 (3)		1 (2)
Employment status			
Full time employment	1 (3)	3 (10)	4 (6)
Part time employment	2 (6)	2 (6)	4 (6)
Home duties	1 (1)		1 (2)
Unemployed	25 (78)	26 (84)	51 (81)
Pension	3 (9)		3 (5)

Percentages may not equal 100% due to rounding off

The mean age was 27.6 ± 6.4 years (median = 26, range 18.0 to 46.7), and subjects generally described long-term dependent or regular opioid use (mean = 4.4 years, median = 2.8, range = 0.5 to 19.8 years). In general, subjects were using heroin heavily at intake, injecting on average 3.7 times a day (OTI Q score) (median = 3.25, range = 0.67 to 12), with moderate to high severity of dependence on heroin (mean LDQ of 23.5, median = 24, range = 11 to 30). The group described spending on average approximately $190 ± 142 per day on heroin (median = $160 per day, range $25 to $600).

Comparison between the two sites for these variables indicated that the only significant difference between the two sites was for 'expectancy regarding withdrawal severity', with the

Melbourne subjects having a significantly lower mean score on this measure ($t(59) = 3.37$, $p < 0.01$, 95% CI = 9 to 35). The Melbourne subjects also had a non-significant trend for higher OTI Q scores for heroin than the Canberra subjects ($t(61) = 1.98$, $p < 0.06$, 95% CI = -0.01 to 2.05).

Table 2.7. Subject characteristics at intake for total sample and each site (continuous variables)

	Melbourne (n=32) Mean ± SD	Canberra (n=31) Mean ± SD	Total (N=63) Mean ± SD
Significant ages (years)			
Age	27.4 ± 6.1	27.8 ± 6.7	27.6 ± 6.4
Age first used heroin	21.0 ± 5.3	19.6 ± 4.3	20.3 ± 4.9
Age first regular heroin use	22.6 ± 5.2	21.4 ± 5.0	22.0 ± 5.1
Duration regular heroin use (yrs)	4.1 ± 4.1	4.8 ± 4.0	4.4 ± 4.1
Measures of drug use			
Heroin OTI Q score	4.17 ± 2.40	3.17 ± 1.56	3.69 ± 2.09
Alcohol OTI Q score	0.18 ± 0.33[a]	0	0.09 ± 0.25 [a]
Cannabis OTI Q score	1.64 ± 3.08	2.91 ± 6.01	2.27 ± 4.76
Tranquilliser OTI Q score	0.66 ± 1.41[b]	0.05 ± 0.21	0.35 ± 1.05 [b]
Severity of dependence (LDQ)	23.6 ± 4.7	23.4 ± 4.3	23.5 ± 4.4
Expectancy withdrawal severity (0 - 100 VAS)	41 ± 22	62 ± 27	51 ± 27
BASIS-32 average score	1.66 ± 0.70	1.81 ± 0.76	1.73 ± 0.73
Body weight (kg)	67.6 ± 12.3	73.2 ± 13.7	69.9 ± 13.1

[a] data from 2 subjects excluded as outliers ; [b] data from 1 subject excluded as outlier

2.3.2 Completion rates and comparisons between completers and non-completers

Thirty-two of the 63 subjects (51%) completed the dosing regime, defined as reaching day 5 of the admission. Four of the non-completers discharged themselves within hours of admission, prior to the onset of withdrawal and without receiving medication. Hence, 32 of the 59 subjects (54%) commencing treatment completed the dosing regime.

There was a significant difference in completion rates between the two sites (χ^2 (1) = 5.72, $p < 0.05$). In Melbourne, 21 subjects (66%) completed the regime. Four of the 11 non-completers voluntarily discharged themselves from the inpatient unit prior to the onset of significant

withdrawal symptoms, and without receiving a dose of buprenorphine. The remaining seven non-completers discharged themselves after receiving at least one active dose of buprenorphine but before the completion of the medication regime. One of these subjects transferred directly to a methadone maintenance program.

Comparison of intake variables (age, sex, duration dependent opiate use, levels of drug use, severity of dependence, psychosocial functioning, body weight, expectancy regarding withdrawal severity) between completers and non-completers at the Melbourne site indicated that the only significant difference was that the completers had more severe psychosocial dysfunction as measured by the BASIS-32 average score (1.84 ± 0.66) compared to the non-completers (1.31 ± 0.67) ($t(30) = 2.18$, $p < 0.05$, 95% CI = 0.03 to 1.03). There was also a non-significant trend for higher completion rates among men (79% completed) than women (46% completed).

A quite different pattern was observed at the Canberra site, with 11 of the 31 subjects (35%) completing, and 20 subjects (65%) discharging prior to completion of the dosing regime. Drop-out at the Canberra site was high during the early stages of the study (for example 16 of the first 20 subjects dropped out), with most subjects discharging themselves on days 3 or 4 (11 of the first 20 subjects). In response to this high drop out rate, a concerted effort was made by staff to encourage subjects to remain in the unit until the completion of their medication regime (day 6), at which point the subject could be more confident of having completed withdrawal. This resulted in a considerable improvement in retention rates, with the majority (7 of 11) of the last subjects enrolled in the study 'completing' the titration regime.

15 of the 20 drop outs from Canberra site were followed up after discharge, with the following reasons cited by subjects for leaving the unit: n = 4 (27%) for personal or relationship issues; n = 3 (20%) due to withdrawal symptoms; n = 3 (20%) left to use heroin; n = 2 (13%) were discharged due to administrative reasons; n = 2 (13%) described the withdrawal episode as "generally unsuitable"; and n = 1 (7%) "felt fine, but bored" in the unit.

Comparison of intake variables indicated that the only significant differences between completers and non-completers at the Canberra site was for measures of heroin use at intake: specifically the mean OTI Q score was significantly higher in non-completers (3.73 ± 1.31), compared to completers (2.17 ± 1.51) ($t(29) = 2.99$, $p < 0.01$, 95% CI = 0.49 to 2.61)). In contrast, the mean severity of heroin dependence (as measured by the LDQ) was significantly lower in non-completers (22.1 ± 4.5) than completers (25.7 ± 2.6) ($t(29) = 2.5$, $p<0.05$; 95% CI = 0.7 to 6.7). These differences appear difficult to interpret, as amount of heroin use (Q score) and severity of dependence (LDQ) should be (intuitively) positively correlated. Pearson's

correlation test indicated a non-significant negative correlation between these two variables for the Canberra subjects (r = - 0.12). There was also a trend for higher completion rates among women at the Canberra site, with 5 out of 7 women enrolled (71%) completing the regime, compared to 6 out of 24 men (25%), although this was not statistically significant (Fisher's exact test, $p < 0.1$). The differences in completion rates for men and women at the two sites may be a chance occurrence due to the small subject numbers, although it does raise attention to the importance of cultural and contextual factors within an inpatient withdrawal unit upon such outcomes.

When combining the samples from the two sites (n=63), there were no significant differences at intake regarding completers and non-completers on the variables described. Table 2.8 provides summary details for the total sample, and separately for completers and non-completers. 22 of 43 men (49%), and 11 of 20 women (55%) completed the withdrawal regime.

Table 2.8 Characteristics at intake of completers and non-completers

	Completers (n=32) Mean ± SD	Non-completers (n=31) Mean ± SD
Age (yrs)	27.6 ± 7.2	27.6 ± 5.5
Age first heroin use (yrs)	20.8 ± 5.2	19.8 ± 4.5
Age first regular heroin use (yrs)	22.0 ± 5.3	22.0 ± 5.0
Duration regular heroin use (yrs)	4.1 ± 3.2	4.7 ± 4.8
Body weight (kg)	70.2 ± 13.2	69.5± 13.2
Heroin OTI Q score	3.51 ± 2.35	3.87 ± 1.79
Alcohol OTI Q score	0.14 ± 0.32 [a]	0.03 ± .13
Cannabis OTI Q score	2.28 ± 4.44	2.26 ± 5.13
Tranquilliser OTI Q score	0.59 ± 1.40	0.10 ± 0.31 [b]
Leeds Dependence Questionnaire	23.9 ± 4.4	23 .0 ± 4.5
Expectancy re: withdrawal severity	49 ± 26	54 ± 28
BASIS-32 average score	1.87 ± 0.73	1.59 ± 0.72

[a] data from 2 subjects excluded as outliers ; [b] data from 1 subject excluded as outlier

2.3.3 Buprenorphine doses administered

2.3.3.1 Completers

The key study objective was to establish the buprenorphine dosing requirements of heroin users by titrating doses according to the severity of withdrawal experienced. Dosing details are presented in Table 2.9 by site and for the entire 32 subjects completing the regime. The mean total dose was 17.4 mg over the 5 day dosing regime, ranging from 4 to 40 mg (from a total

possible dose of 72 mg). The maximum dose dispensed on any one day was 12 mg, from a possible maximum daily dose of 16 mg.

Comparison of doses between the two sites indicates a very similar pattern of dosing requirements, with no significant differences regarding total or daily doses. The Canberra site had a trend for higher doses dispensed on day 1, possibly reflecting different admission procedures between the two sites, with early morning admissions at the Canberra site, resulting in an earlier onset of withdrawal symptoms.

Table 2.9. Buprenorphine doses for subjects completing dosing protocol (n=32)

	Buprenorphine dose (mg in sublingual tablets)					
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Total*
Melbourne (n=21)						
Mean ± SD	3.1 ± 3.0	5.5 ± 3.2	4.5 ± 3.0	2.3 ± 2.6	0.9 ± 1.4	16.3 ± 9.1
Median	2	6	4	2	0	16
Range	0 - 10	0 - 10	0 - 8	0 - 8	0 - 4	4 - 36
% subjects receiving buprenorphine	67%	86%	86%	62%	32%	100%
Canberra (n=11)						
Mean ± SD	5.1 ± 2.1	6.4 ± 3.3	5.3 ± 3.8	2.4 ± 2.7	0.6 ± 1.3	19.6 ± 10.7
Median	6	6	4	2	0	20
Range	2 - 8	2 - 10	0 - 12	0 - 8	0 - 4	4 - 40
% subjects receiving buprenorphine	100%	100%	91%	64%	18%	100%
TOTAL (n=32)						
Mean ± SD	**3.8 ± 2.8**	**5.8 ± 3.2**	**4.8 ± 3.3**	**2.3 ± 2.6**	**0.8 ± 1.3**	**17.4 ± 9.7**
25th percentile	**2**	**4**	**2**	**0**	**0**	**10**
Median	**4**	**6**	**4**	**2**	**0**	**17**
75th percentile	**6**	**8**	**8**	**4**	**2**	**26**
Range	**0 - 10**	**0 - 10**	**0 - 12**	**0 - 8**	**0 - 4**	**4 - 40**
% subjects receiving buprenorphine	**78%**	**91%**	**88%**	**63%**	**28%**	**100%**

Although the dosing protocol allowed for buprenorphine doses to be administered for up to 5 days, only a minority of subjects (28%) required dosing into the fifth day of admission. The duration of buprenorphine dosing for the completers is shown in Table 2.10.

Table 2.10. Duration of buprenorphine dosing for completers (n=32)

Day	Number of subjects (%)	Cumulative % of subjects
1	1 (3)	3
2	3 (9)	13
3	7 (22)	34
4	12 (38)	72
5	9 (28)	100

2.3.3.2 Non-completers

The doses for the 27 subjects who did not complete the dosing regime are shown in the Table 2.11 (note that 4 subjects did not receive any active buprenorphine and are therefore excluded in this analysis). There were no statistically significant differences in buprenorphine doses on days 1, 2 and 4 between completers and non-completers, however the non-completers had a significantly lower mean dose on day 3 compared to the completers ($t(46) = 2.65$, $p < 0.05$, 95% CI = 0.6 to 4.4). This most likely reflects that a considerable number of subjects (12) left during day 3 prior to receiving the full amount of medication available on that day.

Table 2.11. Buprenorphine doses for subjects not completing dosing protocol (n=27)

	Buprenorphine dose (mg in sublingual tablets)				
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*
n	26	23	16	4	N/A
Mean ± SD	3.0 ± 3.4	6.3 ± 3.7	2.3 ± 2.6	0.5 ± 1.0	

2.3.3.3 Subject ranking of dose adequacy

30 subjects (27 completers, 3 non-completers) rated the adequacy of their doses of buprenorphine at the final discharge research interview using a 5-point Likert Scale (1 = much too low; 2 = too low; 3 = about right; 4 = too high; 5 = much too high), prior to being informed of the dose they had received. 87% (26 / 30) of subjects completing this interview indicated that the dose of buprenorphine was 'about right'; 10% (n=3) indicated that the dose was 'too low'; and one subject (3%) indicated that the dose was 'much too high'. The three non-completers who responded all rated their doses as 'about right'.

2.3.4 Withdrawal Severity

2.3.4.1 Subjective ratings of withdrawal severity

Data for withdrawal severity are presented in a number of ways. Table 2.12 displays the mean daily SOWS scores (mean of 0700, 1200, 1700 and 2300 scores). There were no significant differences regarding mean daily SOWS scores between the sites.

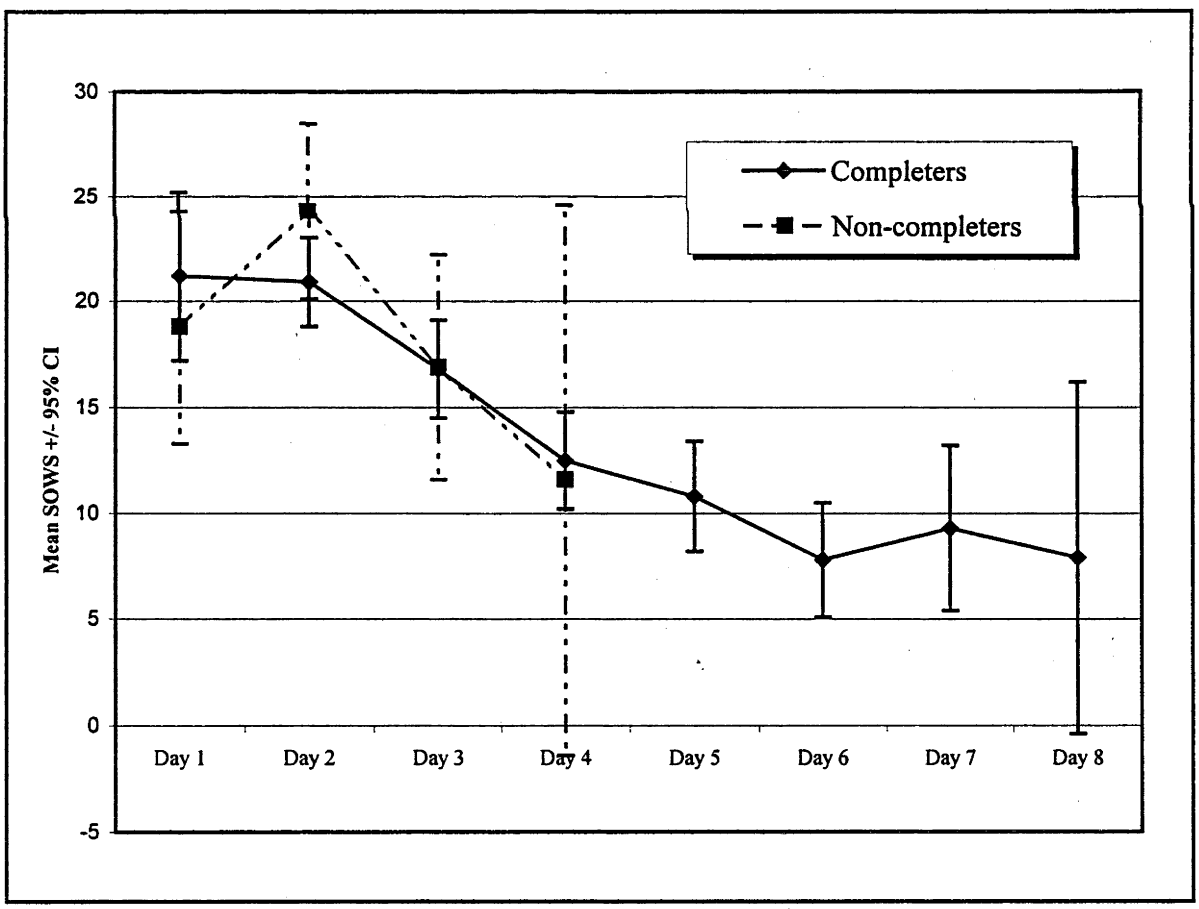
Table 2.12 Mean daily SOWS scores for completers (n=32)

	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8**
n	32	32	32	32	32	26	18	7
Mean	21.1	20.9	16.8	12.5	10.8	7.8	9.3	7.9
SD	11.2	6.0	6.3	6.3	7.2	6.7	7.9	9.0

* Day 8 data from the 5 subjects commencing naltrexone (day 7) are excluded from this analysis.

Figure 2.1 displays the range of mean daily SOWS scores (± 95%CI for means) over the first 8 days of the admission for both completers and non-completers, The small subject numbers remaining at day 4 for the non completers (n=4) and day 8 for the completers (n=7) has resulted in wide confidence intervals at these time points; nevertheless, ratings of subjective withdrawal between the two groups were generally similar.

Figure2.1: Mean Daily SubOWS scores for completers and non-completers



Withdrawal discomfort was greatest during the first 2 days of admission, with resolution of symptoms thereafter, and with minimal rebound withdrawal following the discontinuation of

buprenorphine dosing (generally days 3 to 5). There was a small increase in mean daily SOWS scores noted on day 7 (9.3) compared to day 6 (7.8). Two factors may have contributed to this increase: a degree of rebound withdrawal, (which tended to be mild (as suggested by the low SOWS scores) and transient for most subjects); and selective retention of subjects beyond day 6 (cessation of placebo dosing). Many subjects who were feeling well, with no or mild withdrawal discomfort for several days left the unit on day 6. In contrast, those subjects with greater discomfort were often more prepared to remain in an inpatient unit to manage their symptoms.

The issue of rebound withdrawal following the discontinuation of buprenorphine can also be examined by considering the number of subjects who reported a SOWS score at any time after their last buprenorphine dose (e.g. day 6 or day 7) that was higher than the SOWS score reported at the time of their last dose. This was reported by only 2 of the 32 subjects (6%).

2.3.4.2 Peak withdrawal severity

The mean peak SOWS for all subjects was 33.4 ± 11.8, consistent with moderate withdrawal severity. There was no significant difference in peak SOWS scores for completers (31.7 ± 9.7) compared to non-completers (35.3 ± 13.7). The timing of peak withdrawal symptoms for those completing withdrawal regimes are shown in the Table 2.13, emphasising that the greatest withdrawal discomfort was experienced early in the withdrawal episode, not after the cessation of buprenorphine.

Table 2.13. Time of peak withdrawal severity for completers (n=32)

Day	Number (%)	Mean SubOWS Score
Day 1	13 (41)	33.5
Day 2	14 (44)	31.9
Day 3	3 (9)	31.7
Day 4	1 (3)	25
Day 5	1 (3)	29
Day 6 or later	0	

2.3.4.3 Subject global ratings of withdrawal severity

Subjects were asked to rate the severity of withdrawal experienced on a Visual Analogue Scale, (0 mm = no withdrawal symptoms experienced, 100 mm = extreme withdrawal symptoms experienced). 29 subjects completed this section of the discharge interview (27 completers, and 2 non-completers). The mean score of global withdrawal severity experienced was 15 ± 11, median = 11, range 0 to 50. Paired t-test comparing expected with experienced withdrawal severity for the 29 subjects with complete data indicates a significant reduction from a mean

expected severity of 49 ± 25, to a mean experienced severity of 15 ± 11 ($t(28) = 6.45$, $p < 0.001$; 95% CI difference of the mean = 24 to 46).

2.3.5 Adverse events

Subjects reported any side effects or 'unusual experiences' on a daily basis during their admission, shown below. Four subjects received no active buprenorphine and are excluded from this Table. The majority of subjects reported no adverse events, and there were no serious adverse events. Headache, constipation, flushes, dry mouth, and itchiness were all anticipated adverse events, which with the exception of constipation, were generally reported early in treatment and subsided within two or three days. One subject reported continued hot flushes into the sixth day of admission, which may have been withdrawal symptoms rather than buprenorphine effects. Other adverse events reported may also have been withdrawal features rather than side effects to the medication (e.g. stomach cramps, anxiety, fatigue). One subject reported a papular skin rash that emerged during the first few days of admission. This may have been related to a concurrent viral upper respiratory tract infection, which became clinically apparent during the course of the episode. The rash subsided with no treatment required.

Table 2.14. Adverse events

Adverse event	Number of subjects reporting	% of subjects (N=59)
Nil reported	36	61
Headache	13	22
Constipation	6	10
Stomach cramps	3	5
Fatigue, tiredness	3	5
Anxiety / restlessness	3	5
Hot flushes	2	3
Dizziness after initial dose	2	3
Dry mouth	2	3
Sublingual irritation	2	3
Itchiness	1	2
Skin rash	1	2

2.3.6 Measures of Subject Satisfaction

Satisfaction with buprenorphine was elicited in a number of ways. Subjects were asked to identify the 'good things' and 'bad things' about using buprenorphine in withdrawal. Responses were recorded and coded according to themes (Table 2.15).

Table 2.15. Positive and negative experiences of buprenorphine identified by subjects (n=20)

Positives or 'good things'	%	Negative or 'bad things'	%
No or mild withdrawal discomfort	90 %	None identified when prompted	55 %
No or reduced cravings	60 %	Side effects	35 %
Clear headed / not drowsy	35 %	Taste of tablets	5 %
No or reduced anxiety / mood disturbances	25 %	Rebound withdrawal after ceasing buprenorphine	5 %
Slept well	25 %		
Felt 'normal'	20 %		
Other	35%		

Subjects were asked to rank the various medication regimes that they had previously used for withdrawal in descending order (1 = "best"). All but one subject had utilised other forms of medication during withdrawal from heroin, although few had previously attempted a naltrexone-assisted withdrawal or short-term methadone withdrawals.

Table 2.16. Ranking of medication regimes for withdrawal (n=20)

Medication for withdrawal	Mean Ranking (descending order)	Number of subjects experienced (n=20)
Buprenorphine	1	20
Naltrexone assisted	2	1
D-propoxyphene	2.8	8
Benzodiazepines	3	18
Other symptomatic	3.4	14
Codeine - paracetamol	3.5	10
Clonidine	4.8	5
Short term methadone	5	1

2.3.7 Variables impacting upon buprenorphine dose

As identified in the research objectives, the study aimed to examine the impact of a number of patient characteristics at intake upon the total dose of buprenorphine dispensed. Multiple regression analysis was conducted to examine the impact of the six baseline (independent) variables upon the total dose of buprenorphine titrated for each subject completing the dosing regime (dependent variable). The independent variables included in the analysis were described in Table 2.5, all continuous variables, with the exception of sex, which was dummy coded (0 and 1).

A considerable proportion of the variance of buprenorphine dose was accounted for by the above 6 independent variables ($R^2 = 0.513$), with significant variables being BASIS average score ($F = 10.19$, $p < .005$) (greater psychosocial dysfunction was associated with higher doses); sex ($F = 10.19$, $p < 0.05$) (women used higher doses than men); Q score for heroin use

(F = 6.46, p < 0.05), and severity of heroin dependence (LDQ) (F= 6.26, p< 0.05). The other variables (expectancy of withdrawal severity, and body weight) were not significant predictors of buprenorphine dose. Using backward stepwise regression with removal of the least significant variables resulted in a marked reduction in R^2. ·Similar findings were obtained using a forward selection stepwise regression of the 6 predicted variables. These findings are discussed in the section 4.4.

The finding that sex was significantly related to total buprenorphine dose warranted a closer examination of the doses administered to men and women. Women received a mean total dose of 22.4 ± 8.9 mg, significantly greater than the mean total dose for men of 14.9 ± 9.2 mg (t(30) = 2.22, p< 0.05, 95%CI = 0.6 to 14.4 mg).

2.4. Discussion

2.4.1 Summary of study findings

This was an exploratory study with two broad aims: to identify the dosing requirements of buprenorphine in the management of inpatient heroin withdrawal; and to identify the impact of patient characteristics upon buprenorphine dosing requirements. A number of conclusions can be drawn from the findings of the study. The similarity of doses across the two sites is encouraging from the perspective of generalising the findings to broader populations of heroin users attending inpatient services, rather than merely reflecting heroin users at a particular treatment site. Despite the wide range of doses available to subjects (up to 16 mg per day and total dose up to 72 mg), withdrawal severity was generally well contained on doses not greater than 10 mg per day. The mean total dose of buprenorphine used by subjects was 17.4 ± 9.7 mg, (median = 17 mg, range 4 to 40 mg), with 94% of subjects requiring a total dose of 30 mg or less. Higher daily doses were required during the first three days of the withdrawal: most subjects required doses between 2 and 6 mg on day one, 4 and 8 mg on day two, 2 and 8 mg on day three, and between 0 and 4 mg on day 4. Most subjects required buprenorphine for only 3 or 4 days, making the dosing regime suitable for use in inpatient withdrawal episodes of brief duration.

Subjects generally described mild and tolerable withdrawal discomfort during the withdrawal episode, with daily mean SOWS scores greatest during the first two days (and generally less than 20), and mean peak SOWS scores of 33 ± 12. Most subjects (87%) rated the adequacy of their buprenorphine doses as being 'about right', and experienced significantly less severe withdrawal than they had expected. Qualitative responses by subjects commended

buprenorphine's ability to considerably reduce withdrawal discomfort, minimise cravings, enable sleep, and to achieve these outcomes without producing significant drowsiness or sedation, as is commonly associated with other withdrawal medications (e.g. benzodiazepines, clonidine). Negative aspects when prompted were generally limited to side effects. The side effects reported were in most cases anticipated, and their incidence was consistent with earlier experiences reported in large studies with buprenorphine (Ling, Charuvastra et al. 1998; Lange, Fudala et al. 1990).

There appeared to be only minimal rebound withdrawal upon the cessation of buprenorphine dosing for the majority of subjects. No subjects report their peak withdrawal score following the discontinuation of buprenorphine dosing. Although many subjects experienced a transient increase in withdrawal severity after their last buprenorphine dose, this was generally mild (< 16 points on SOWS) and resolved within 48 to 72 hours after the last dose without the use of additional medications. The findings enhance the premise that there is minimal rebound withdrawal upon the discontinuation of short courses (several days) of buprenorphine in the management of heroin withdrawal. This is very encouraging for inpatient withdrawal services, where there is an increasing trend for admission lengths to be limited to between 6 and 8 days. The vast majority of heroin users in this study required doses for only 3 or 4 days, and experienced minimal rebound withdrawal in the 2 to 3 days after the last buprenorphine dose. Hence, buprenorphine would be ideally suited to a 7-day inpatient withdrawal episode.

2.4.2 Comparisons with earlier inpatient research

These doses are consistent with the range of doses used in most previously reported studies of short buprenorphine regimes for inpatient heroin withdrawal. As identified in Chapter 1, Section 4.3, comparison of different buprenorphine dosing regimes is complicated by a degree of uncertainty regarding the relative bioavailability of various buprenorphine preparations. Adjusting for differences in the bioavailability of the tablet and solution preparations using a conversion factor of 1.4:1 (Ajir, Ling et al. 1998), the mean total dose in this study (17.4 ± 9.7 mg) is approximately equivalent to 12.4 ± 6.9 mg of sublingual solution. The daily doses of between 2 and 10 mg (tablet) commonly used during the first three days in this study are comparable to approximately 1.5 to 8 mg of solution per day. Most subjects in the study received a total dose (tablet) of between 10 (25^{th} percentile) to 26 mg (75^{th} percentile), approximately equivalent to 7 to 19 mg of buprenorphine solution.

The doses used in this and other inpatient studies of short-term heroin withdrawal reported in the literature are compared in Table 2.17. Nigam, Ray et al. (1993) used lower doses in non-injecting opiate users; whereas Umbricht, Montoya et al. (1999) used much higher doses prior

to naltrexone induction. Similar doses to the ones identified in this study have been described by (Parran, Adelman et al. 1994; Cheskin, Fudala et al. 1994; Liu, Cai et al. 1997). Vignau (1998) is the only published short-term inpatient heroin withdrawal study using the Subutex® preparation. This study used very similar daily doses over the first 3 to 4 days of the withdrawal; however gradually reduced the buprenorphine dose over a 10 to 12 day period, such that the total dose used in the withdrawal regime was considerably greater than in the current study.

Table 2.17 Comparison of study dosing regimen with previous inpatient studies.

Study	S/L Preparation	Dosing regime	Equivalent total dose in S/L tablets
Nigam et al 1993	tablet	Range of daily doses = 0.6 to 1.2 mg per day over 10 days	10 mg
Liu et al 1997	not specified	3 groups. Doses commenced at between 3 to 6 mg per day & titrated to 0 over 7 - 8 days	~ 14 to 26 mg
Parran et al 1994 [a]	subcutaneous injection	0.9 to 2.7 mg / day x 2 days, 0.45 to 1.35 mg / day x 2 days; 0.2 to 0.7 mg / day x 2 days	6.6 to 20 mg
Current study	*tablet*	*Day 1 mean = 3.8 mg (most subjects between 2 to 8mg); day 2 mean = 5.8 mg (4 to 10mg); day 3 mean = 4.8 mg (2 to 8mg); day 4 = 2.3 mg (0 to 4 mg); day 5 = 0.8 (0 to 2 mg).*	*mean = 17.4 mg (25^{th} percentile=10 mg; 75^{th} percentile = 26 mg)*
Cheskin et al 1994	solution	Day 1 = 8 mg, day 2 = 6 mg; day 3 = 3 mg. Total dose = 17 mg	~ 24 mg
Vignau 1998	tablet	Doses titrated daily. Day 1 mean = 6.1 mg (range 4.4 to 9.0); day 2 mean = 6.4 mg (range 5 to 9); day 3 mean = 5.5 mg (range 4 to 7.6); then progressively reducing to zero mg by day 12.	Total mean ~ 35 mg (data presented graphically)
Umbricht et al 1999	solution	Day 1 = 12 mg; day 2 = 8 mg; day 3 = 4 mg; day 4 = 2 mg. Total dose = 26 mg	~ 36 mg

[a] subcutaneous injection has a bioavailability of approximately 1.5 times greater than sublingual solution (Jasinski, Fudala et al. 1989).

2.4.3 Use of low dose sublingual tablets

The majority of completers (88%) required doses greater than 4 mg. This effectively disqualifies the use of analgesic preparations of low dose buprenorphine sublingual tablets (e.g. 0.2 mg tablets registered in Australia as Temgesic®) as an effective stand-alone withdrawal medication for the majority of heroin users. Perhaps the use of low dose buprenorphine (e.g.

0.4 mg Subutex® tablets) may be appropriate in the context of a pharmacotherapy regime including symptomatic medication for heroin withdrawal (e.g. benzodiazepines, clonidine); however the use of 2 mg buprenorphine tablets should be generally preferred to achieve the doses required.

2.4.4 Factors impacting upon doses

The range of buprenorphine doses used in this study highlights the considerable variation between heroin users as to their experience of withdrawal and their medication requirements. The patient variable at intake most strongly predictive of total buprenorphine dose requirements was global psychological functioning (as measured by the BASIS-32) ($F = 10.19$, $p < 0.005$). Although this analysis was conducted examining dose requirements rather than withdrawal severity, the symptom-triggered dosing design would suggest that the same factors which contribute to withdrawal severity should also contribute to amount of medication used. In this regard, the finding is consistent with previous research linking withdrawal severity to psychological profile.

There was also a significant trend for women to have higher total buprenorphine doses ($F = 10.19$, $p < 0.005$). This finding may genuinely reflect higher buprenorphine requirements in women. Research with buprenorphine as an analgesic indicates that sex does not affect plasma concentrations, although in one study, women required less buprenorphine than men for post-operative analgesia (McQuay, Bullingham et al. 1980). Research in the addiction field has yielded contradictory findings with regards to treatment outcome, with women reporting more heroin use than men in one maintenance study (Schottenfeld, Pakes et al. 1998), but less heroin use than men in another (Johnson, Eissenberg et al. 1995). Alternatively, the gender difference may reflect a common observation that women routinely report more psychological symptoms than men (Kroenke and Spitzer 1998; van Wijk and Kolk 1997) and may have had a tendency to score themselves higher on the Subjective Opiate Withdrawal Scale, thereby receiving higher buprenorphine doses as part of the symptom-triggered titration regime employed in this study.

There was also a significant association ($F = 6.46$, $p < 0.05$) for frequency of recent heroin use (OTI Q score) and total buprenorphine dose; and severity of heroin dependence (LDQ) ($F=6.26$, $p<0.05$). This former finding is consistent with earlier work demonstrating a significant association between amount of heroin consumption and withdrawal severity (Andrews and Himmelsbach 1944; Smolka and Schmidt 1999).

2.4.5 Study limitations

There are a number of study limitations that are worth noting. The first relates to the extent that we can generalise from the findings of this study. The study was conducted on a selected sample of heroin dependent individuals seeking treatment at inpatient withdrawal units in Melbourne and Canberra. Almost half of all patients (47%) admitted to Depaul House during the conduct of the study were ineligible to participate, generally for medical or psychiatric (17%), and / or dependence to multiple substances (16%) that would have considerably altered the experience of withdrawal. The impact of such factors upon the dosing requirements of buprenorphine requires further investigation. However, it is possible to postulate that the mild withdrawal syndrome experienced with buprenorphine would be favourable for those patients with concomitant medical and psychiatric conditions, or those withdrawing from multiple substances, and buprenorphine has previously been successfully used in such populations (Parran et al 1990).

The extent to which subjects remained blinded to the titration dosing regime and their individual doses was not systematically examined. Nevertheless, the general impression gained by the principal investigator (NL) on asking subjects at the Melbourne site at the end of their participation in the study was that although subjects could identify occasions when they had been dosed with only placebo tablets, in general most subjects were unable to accurately identify the dose of buprenorphine they had received, nor the time of last active buprenorphine dosing. To this extent, the single blind design achieved its aim.

A potential limitation of this study was the use of a previously undocumented and untested titration regime. The advantages of using a symptom-triggered titration technique were discussed previously, most notably the capacity to individualise doses according to each subject's needs. Nevertheless, there is the possibility that the study regime was inadequate to accommodate a number of subjects who dropped out of treatment prior to the completion of their dosing regime. Most non-completers described mild withdrawal discomfort at the time of discharge, however 12 subjects (39% of treatment drop-outs and 19% of the entire sample) reported their final SOWS score prior to discharge at 20 points or more, and it is possible that a proportion of these subjects did not complete their withdrawal episode due to inadequate relief of withdrawal symptoms. At the Canberra site, 20% (n=3) of treatment drop-outs who were followed up after discharge indicated that withdrawal discomfort were their main reason for prematurely discharging themselves from the unit. In real clinical practice, the capacity for additional buprenorphine doses may have altered the outcome for these subjects, however the structured titration regime used for the research was less accommodating.

Nevertheless, factors other than withdrawal severity or adequacy of buprenorphine doses were most likely responsible for many of the cases of treatment drop-out. This is suggested by a number of reasons - firstly, completers and non-completers reported similar scores for withdrawal severity. Non-completers at the Canberra site generally cited reasons other than withdrawal severity for leaving the residential unit prematurely, and retention at the Canberra site improved markedly towards the end of the study, after there had been a concerted effort by staff to retain subjects until day 6, but with no change in dosing procedures. The differential drop-out rate for the two units is also suggestive that contextual factors within the treatment units impacted considerably upon treatment retention. For example, gender sensitivity within units may impact upon treatment retention: a very low proportion of women (42%) completed the regime in Melbourne (compared to 80% of men completing), whereas women had a much higher rate of completion (71%) at the Canberra site (compared to 25% of men completing). These factors are not directly attributable to inadequate doses of buprenorphine, and emphasise that outcomes for withdrawal are not confined to issues of pharmacotherapy.

Finally, whilst this study has identified a range of buprenorphine doses which were generally successful in managing inpatient heroin withdrawal in this sample of heroin users, double-blinded randomised dose efficacy studies are required in order to compare the efficacy of the doses described in this study to regimes employing lower or higher buprenorphine doses. In clinical practice, individual titration of doses is likely to lead to enhanced treatment outcomes for each patient, and the findings of this study provides a basis for the development of guidelines to assist clinical decision making.

2.4.6 Conclusion

In conclusion, this study examined dosing requirements for the management of heroin withdrawal in inpatient settings using a symptom-triggered dose titration regime. Most subjects required a total amount of buprenorphine of between 10 and 26 mg over the course of treatment. Daily doses in the range of 2 to 6 mg on day 1, 4 to 8 mg on days 2 and 3, and 2 to 4 mg on day 4 were generally sufficient to prevent or alleviate moderate to severe withdrawal discomfort, with minimal side effects, minimal rebound withdrawal upon the cessation of buprenorphine, and without the need for routine use of other symptomatic medication. Subjects expressed high levels of satisfaction with the adequacy of their buprenorphine doses, and with buprenorphine as a medication for heroin withdrawal. The range of doses used in this study is consistent with research suggesting that daily doses of 4 mg or more are generally required to comfortably alleviate heroin withdrawal, and is comparable to dosing regimes described in most previous inpatient withdrawal studies. Factors predictive of the total buprenorphine dose

for each subject were global psychological distress at intake, frequency of heroin use at intake and sex (with women requiring higher doses - although this last factor may be an artefact of the symptom-triggered titration regime employed).

The development of the relevant section in the National Clinical Guidelines (Lintzeris, Clark et al. 2001) regarding the use of buprenorphine in the management of heroin withdrawal in inpatient settings has drawn upon findings of this study, together with the review of the relevant literature in Chapter 1. The development of these guidelines is discussed in Chapter 5, and the guidelines are included as Appendix 3.

CHAPTER 3: OUTPATIENT DOSE TITRATION STUDY

3.1. Study objectives and research questions

The primary objective of this study was to identify the range of doses of buprenorphine required by heroin users to safely and comfortably complete heroin withdrawal in an outpatient treatment setting, from which a suitable dosing regime could be developed. Specifically, the primary research question for the study is: *what doses of buprenorphine are required to achieve a safe and comfortable withdrawal from heroin in an outpatient setting?*

This was an exploratory study, representing the first time buprenorphine was used for this purpose in an Australian treatment setting, the first description of a short outpatient withdrawal regime using the commercially available Subutex® tablet preparation; and among the first international descriptions of a short outpatient buprenorphine withdrawal regime (Table 1..7). Consequently, other secondary research questions related to gaining general experience from using buprenorphine for this purpose, specifically:

- What is the pattern and severity of withdrawal experienced by subjects? In particular, to what extent does buprenorphine relieve opiate withdrawal discomfort, and do subjects report a clinically significant increase (rebound) in withdrawal features on ceasing buprenorphine?
- What are the other short-term outcomes of withdrawal treatment - in particular, what are the withdrawal treatment retention rates; levels of heroin and other drug use during the treatment episode; and safety issues (adverse events and effects of additional heroin use)?
- What are the patient perspectives and levels of satisfaction with the medication?

Although the findings of the inpatient titration study provide some insights as to suitable outpatient dosing regimes, there are a number of significant differences in the delivery and context of treatment that may impact upon the dosing requirements for outpatient settings. Inpatient services can generally provide more intensive supportive care, whilst environmental triggers may increase cravings in outpatient settings. The general limitation of once-a-day supervised dosing for outpatients may also necessitate higher single doses than multiple inpatient doses. From these factors, it was hypothesized that outpatient dosing requirements may be higher than used in the inpatient setting.

3.2 Trial design and methodology

3.2.1 Overview of trial design and procedures

This was an open label, multiple case series of 18 heroin dependent subjects undergoing outpatient withdrawal, with no comparison group. The study employed a dose titration design, with buprenorphine doses (2 mg sublingual Subutex® tablets) titrated on a daily basis. The relative advantages and disadvantages of a study design employing dose titration compared to randomised fixed doses were discussed in Chapter 2.2.3. As identified in Chapter 1.1.3, treatment objectives for outpatient withdrawal management upon which doses were titrated were: (a) the comfortable alleviation of withdrawal discomfort, (b) the cessation or reduction of heroin and other drug use, (c) the minimisation of adverse events or other complications during the withdrawal episode, and (d) patient satisfaction. Systematic examination of post-withdrawal outcomes was beyond the scope of this dose-ranging study.

Subjects were reviewed daily during the 8 day withdrawal episode, with regular monitoring of withdrawal features, drug use, adverse events and subject perceptions regarding dose adequacy. Buprenorphine was available for the first 5 days of the withdrawal episode under conditions of supervised dispensing. Standard supportive counselling was provided during the treatment episode. Other medications for withdrawal were not routinely used. Subjects underwent research interviews at induction and on discharge from the study.

3.2.2 Subjects and recruitment

Subjects were recruited from patients seeking outpatient heroin withdrawal at the Clinical Services Department of Turning Point Alcohol and Drug Centre in Melbourne, over a four month period in 1998. The number of subjects required for the trial was estimated as the number at which trends regarding suitable doses would emerge. This was estimated by a number of senior and experienced medical practitioners as between 15 to 20 'completers' (i.e., not including treatment drop outs).

Recruitment to the trial was voluntary, with informed consent, and there was no active promotion or advertisement for the study. The study aimed to recruit dependent injecting heroin users with no concomitant medical or psychiatric condition, not dependent on or withdrawing from alcohol or benzodiazepines, and with no recent methadone treatment. The specific selection criteria (and their rationale) were the same as for the inpatient titration study (see Table 2.1, Chapter 2 for description), with one addition: that subjects had some form of

stable (but not necessarily drug free) accommodation - homeless patients were not considered appropriate for outpatient withdrawal (see Section 1.2.2), and were referred to inpatient services.

Thirty-four consecutive heroin users seeking outpatient heroin withdrawal were clinically screened for the study, with 28 (82%) assessed as eligible. Six patients (18% of those screened) were ineligible for the study for the following reasons: under 18 years of age (n=1); concurrent chronic pain disorder (1); active psychiatric disorder (1); concurrent benzodiazepine dependence (2), and one patient had an unstable social environment and was referred to inpatient treatment. A further ten patients (29% of those screened) were assessed as eligible but chose not to participate in the study, opting for conventional outpatient withdrawal services at the clinic (seven chose a short methadone reduction over 10 to 21 days, and three chose symptomatic medication). Eighteen subjects were recruited to the study, representing 53% of the patients screened.

3.2.3 Treatment procedures

The principal parameters of a buprenorphine withdrawal regimen, such as dose and duration of treatment, were discussed in detail in Section 1.4.3. In summary, this study examined short-term withdrawal episodes (consistent with conventional Australian withdrawal services) using buprenorphine doses within the range of 4 to 16 mg daily for four days (corresponding to the period of peak heroin withdrawal severity), followed by a dose reduction on day 5, prior to its abrupt cessation.

Careful consideration had to be given to the procedures for induction into treatment with an opioid medication, in order to minimise the risks of side effects, opioid toxicity in patients with low tolerance, and in the case of buprenorphine, to avoid precipitating withdrawal following the initiation of treatment (see Section 1.4.1). Various outpatient induction regimes have been described in the buprenorphine clinical literature, with doses in the range of 4 to 8 mg (sublingual tablets) having been reported as safe in heroin dependent individuals, and are recommended for clinical use (Bickel and Amass 1995; Ling 1999; Ling 1999). Importantly, the first dose of buprenorphine should not be administered whilst the patient is experiencing the effects of heroin use, and ideally should be delayed until the early stages of heroin withdrawal. This can be difficult to coordinate in outpatient clinical practice, but as a rule, the first dose of buprenorphine was delayed (or reduced) if the subject reported using heroin within the preceding 6 hours, or if the patient had no features of opiate withdrawal.

The maximum buprenorphine dose available on day 1 was 8 mg, and 16 mg on days 2, 3 and 4. Subjects could return to the clinic on days 1 to 3 for an additional buprenorphine dose (if considered clinically appropriate by the reviewing medical officer). Only one dose was available on days 4 and 5. The day 5 dose was pre-determined as up to half of the dose administered on day 4. Buprenorphine doses were titrated on a daily basis by the study medical officers (Drs Lintzeris and Dunlop) according to the following factors:

(i) *severity of withdrawal discomfort in preceding 24 hours*: withdrawal features were monitored at each review (prior to dosing) using the Subjective and Objective Opiate Withdrawal Scales, and questions regarding sleep (not examined in the SOWS);

(ii) *use of heroin or other drugs*: daily self-report of heroin and other drug use since last review, including subject's stated reasons for use (for example, to relieve withdrawal, for intoxication, situational factors, routine). Urine drug screens were also conducted on days 1, 5 and 7 or 8);

(iii) *adverse events during the withdrawal episode*; subjects were asked to describe any side effects or atypical occurrences daily, and these were assessed by the study doctor;

(iv) *subject perception of dose adequacy*. Subjects rated the adequacy of the previous day's buprenorphine dose using a five point Likert scale (with the options of 1 = "much too low"; 2 = "too low"; 3 = "about right"; 4 = "too high"; 5 = "much too high").

The titration dosing schedule is shown in Table 3.1. A clinical example will help demonstrate the principles used in the titration of doses. The first four subjects were dosed with 4mg on the first day. All four subjects reported experiencing withdrawal symptoms later in the evening or by the following morning, and all four reported using heroin prior to their day 2 dose – suggesting that 4 mg had been an inadequate dose. This led to a change in prescribing practice whereby subjects were dosed either 6mg buprenorphine as their first dose; or else were dosed 4 mg buprenorphine and asked to present to the clinic 3 to 4 hours later for a second dose of 2 or 4 mg. Hence, the remaining 14 subjects received a total of 6 or 8 mg buprenorphine on the first day. A considerable proportion (up to 28%) of subjects reported side effects to buprenorphine during the first day of drowsiness, dizziness or sedation. The incidence of these side effects led to caution by the medical officers in prescribing 8 mg buprenorphine as a single dose on the first day, as there was no way of predicting which subjects were to experience these side effects.

The 2 mg sublingual tablet preparation of buprenorphine (Subutex®) was used, with all doses dispensed from the clinic pharmacy under supervision. All subjects received routine case

management, supportive counselling, and written patient information as per standard practice at the clinic (Lintzeris, Dunlop et al. 1996). No other medications were routinely used.

Table 3.1. Buprenorphine outpatient titration dosing schedule

Day of program	First dose of buprenorphine (generally 9am to 12 noon)	Additional dose of buprenorphine > 3hrs after first dose	Total Possible Dose
1	4mg or 6mg	2 or 4mg	4 to 8mg
2	Severe side effects = Day 1 dose - 2 to 4mg No heroin use, withdrawal or cravings = Maintain day 1 dose Uncomfortable withdrawal / cravings = Day 1 dose + 2 to 4 mg	2 or 4mg	0 to 16mg
3	Severe side effects = Day 2 dose - 2 to 4mg No heroin use, withdrawal or cravings = Maintain day 2 dose Uncomfortable withdrawal / cravings = Day 2 dose + 2 to 4 mg	2 or 4mg (to 16 mg max /day)	0 to16mg
4	Severe side effects = Day 3 dose - 2 to 4mg No heroin use, withdrawal or cravings = Maintain day 3 dose Uncomfortable withdrawal / cravings = Day 3 dose + 2 to 4 mg	-	0 to16mg
5	Up to half of Day 4 dose	-	0 to 8mg
6 to 8	No dose	-	-

3.2.4 Data collection

In addition to the regular clinical monitoring of withdrawal severity, heroin use, adverse events and subject perception of dose adequacy (described in previous section), subjects underwent confidential research interviews on entry to the study (day 1) and on discharge (generally day 8). At intake, data was collected regarding demographic characteristics, frequency of heroin and other drug use in the preceding month using the Drug Section of the Opiate Treatment Index (Darke, Hall et al. 1992); severity of dependence on heroin in the preceding week using the Leeds Dependence Questionnaire (Raistrick, Bradshaw et al. 1994); and expected severity of withdrawal using a (0 – 100) Visual Analogue Scale (as described in Table 2.5). Data collected at the discharge research interview was similar to procedures used in the Inpatient Titration Study, including measures of severity of heroin dependence (Leeds Dependence Questionnaire), severity of withdrawal symptoms experienced (0 - 100 Visual Analogue Scale); and measures of patient satisfaction with the medication and their dosing regime (including rankings of different withdrawal medications, semi-structured 'good' and 'bad' aspects associated with buprenorphine, and a global rating of adequacy of their buprenorphine dosing regime using a 5 point Likert scale ("much too low"; "too low"; "about right"; "too high"; "much too high").

3.3 Results

3.3.1 Subject characteristics at intake

Eighteen injecting heroin users were recruited to the study. Ten subjects (56%) were male, 89% were Caucasian, average age was 25.3 years (range 21 to 37, SD = 4.5), 50% were currently employed (either part or full time), and 78% were in receipt of some social security benefits. The mean duration of opioid dependence was 3.9 ± 4.6 years (median = 2.6, range < 1 to 19 years), with a mean Leeds Dependence Questionnaire score of 23.2 ± 3.9 (range 17 to 30 out of maximum possible score of 30) representing moderate to severe dependence (Raistrick, Bradshaw et al. 1994). The mean heroin OTI Q score was 2.9 ± 1.1 (range 1.5 to 4.5), which can be interpreted as subjects having injected heroin on average 2.9 times a day in the preceding month. 17 of the 18 subjects had had previous attempts at outpatient heroin withdrawal.

3.3.2 Treatment retention rates

Fifteen of the 18 subjects (83%) completed the 5-day buprenorphine dosing regime. Two subjects (a couple) failed to attend after the third day, and one subject terminated buprenorphine treatment on day 2, transferring to a methadone maintenance program. Of the 15 subjects completing the 5-day dosing regime, one subject did not attend any further clinical or research appointments. Hence, 14 subjects (78%) completed at least 8 days of clinical follow-up and completed the research interview at discharge.

3.3.3 Buprenorphine doses

Summary data regarding the doses of buprenorphine dispensed to the 15 subjects completing the dosing schedule are shown in Table 3.2. Doses dispensed for the three non-completers were within the same ranges on any given day.

Table 3.2. Mean, standard deviation and range of daily buprenorphine doses (mg) dispensed.

	Day 1	Day 2	Day 3	Day 4	Day 5	Total
Mean	6.1	9.6	10.1	8.9	4.1	38.9
St Dev	1.2	1.7	1.9	2.0	1.5	5.8
Range	4 - 8	8 - 14	8 - 14	6 - 12	0 - 6	29 – 47

Levels of subject satisfaction with dosing regime

11 of the 14 subjects (79%) completing this interview rated the adequacy of their buprenorphine doses at discharge interview as "about right". The other three subjects (21%) rated their doses as "too low". On closer examination of these three cases, their total buprenorphine doses were above the 50th percentile for total dose (39mg, 45 mg, and 46 mg); and their peak SOWS scores were indicative of mild withdrawal severity (18, 20 and 15), and were below the mean peak SOWS (20.7 ± 11.3) reported by the other 11 subjects completing the research interview. This highlights the diversity of patient expectations regarding the role of medications in withdrawal.

3.3.4 Drug use during the withdrawal episode

In total, 13 of a possible 36 urine drug tests over the withdrawal episode were negative for opiates (36%). Four subjects (22% of total sample) provided opiate negative urine results throughout the episode. Nine subjects had a negative urine drug screen for opiates at day 5 (50% of total sample, 60% of those in treatment); 5 subjects had positive results, 3 were no longer attending, and results were 'missing' for one subject. Urine tests for opiates at day 7 or 8 revealed 4 subjects had negative results (22% of total sample, 29% of those in treatment); 6 subjects had positive results, 4 were no longer attending, and results were 'missing' for 4 subjects.

Self reported heroin use during the 8-day withdrawal episode is shown in Table 3.3. Self-report data was generally consistent with results from urine drug screens.

Table 3.3. Levels of heroin use reported by subjects during 8 day withdrawal period (n=18)

Number days used heroin during 8 day episode	Number of subjects (% of total sample)
0 days	5 (28)
1 day	5 (28)
2 days	2 (11)
3 or more days	3 (17)
Subjects did not complete	3 (17)

Subjects were asked by clinicians to describe the circumstances surrounding, and the reasons for any heroin use during the withdrawal episode. Several subjects reported heroin use in response to withdrawal discomfort prior to their day-2 dose (particularly early in the study when 4 mg doses were being used on day 1). Otherwise, all but one subject reported that their use of heroin was volitional (e.g. for intoxication, or wanting to recommence heroin use

following several days of not using) or situational (e.g. partners or friends using around them), rather than to relieve severe withdrawal discomfort. Those subjects who used heroin during the dosing period all reported that buprenorphine considerably reduced the effects of heroin, serving as a barrier to further heroin use. There appeared to be no clear relationship between the use of heroin and dose of buprenorphine dispensed. The mean total dose for those subjects not using heroin (39.8 mg) was comparable to those using heroin on one or more occasions during the withdrawal episode (38.3 mg).

3.3.5 Withdrawal severity

Subjects generally reported minimal withdrawal discomfort throughout the withdrawal episode. The interpretation of withdrawal scores is difficult for those individuals who used heroin regularly, and consequently, Table 3.4 shows data regarding withdrawal severity for those subjects (n=13) reporting no or minimal heroin use (5 self-reported nil use and 5 reported using once over 8 days; one subject reported no heroin use prior to 'dropping out' after day 5; and two subjects used heroin on days 2 and 8 but completed the withdrawal scales on day 8 prior to their heroin use that day). Data for the remaining 5 subjects is omitted here, either due to missing data (n=3) and/or due to more regular heroin use (n=2).

Table 3.4. Subjective Opiate Withdrawal Scale scores during 8 day episode

	Day 1 (n=13)	***Day 2 (n=13)***	***Day 3 (n=13)***	***Day 4 (n=13)***	***Day 5 (n=12)***	***Day 6 (n=12)***	***Day 7 (n=12)***	***Day 8 (n=11)***
Mean	15.5	14.4	7.8	7.5	7.3	9.5	9.8	9.6
St Dev	13.5	7.4	5.5	6.1	4.0	6.3	7.4	6.2
Median	11	15	7	8	7	9.5	7.5	10
Range	2 - 40	3 - 27	2 - 22	0 - 23	1 - 14	0 - 21	1 - 26	0 - 21

The peak withdrawal severity was generally experienced as mild (mean peak SOWS score = 20.2 ± 9.7), occurring during the first two days, with subsequent resolution of symptoms. There was minimal rebound withdrawal experienced: withdrawal scores generally remained low following the cessation of buprenorphine. Two subjects (out of 14 subjects for whom data was available till day 8, or 14%) reported peak withdrawal scores after day 5, although in both instances the peak SOWS scores were low (15 and 6). Six subjects (43% of subjects with data) described some mild and transient increase in withdrawal discomfort at some time during days 6 to 8 compared to scores on days 3 to 5. Only one of the 9 subjects who recommenced heroin

use after the cessation of buprenorphine stated that severity of withdrawal symptoms was the main factor in their relapse to heroin use.

Subjects rated the severity of withdrawal discomfort they expected to experience during this withdrawal episode at intake, and rated the severity of withdrawal discomfort that they had experienced on discharge, using a 100 mm Visual Analogue Scale (0 = no discomfort, and 100 = most severe discomfort experienced). The mean expected withdrawal severity at intake (n=18) was 31 ± 17, whilst the mean experienced withdrawal severity (n=14) was 16 ± 12. A paired t-test indicated that subjects' experience of discomfort was significantly less ($p<0.05$) than they had expected at the outset of the withdrawal ($t(13) = 2.29$, 95% CI = -2 to -26).

3.3.6 Adverse events

Adverse events were recorded on a daily basis, with 16 of the 18 subjects (89%) reporting some adverse events, although it was not always easy to differentiate between buprenorphine side effects and withdrawal symptoms. All adverse events were anticipated, mild, and generally resolved within several days of buprenorphine treatment. The most common adverse events reported were headache (50% of all subjects), sedation (28%), nausea, constipation and anxiety (21% each), dizziness and 'itching' (17% each).

The most commonly reported adverse event was headache. The headaches were frequently described as constant, frontal headaches, usually commencing within one or two hours of a buprenorphine dose and reducing in severity by the following morning (before the next dose). Tolerance to headaches usually occurred within one or two days, with only 2 of the 9 subjects describing headaches continuing beyond the fourth day of buprenorphine treatment. Headache has been reported previously as a common adverse event with buprenorphine (for example, 31% of subjects in a large, multicentre open label study of buprenorphine maintenance treatment (Ling, Charuvastra et al. 1998).

Sedation (28%) and dizziness (17%) were also commonly reported. Four of the five subjects reporting sedation did so in the first two days of treatment with buprenorphine, with sedation resolving by the third day, suggesting tolerance to this effect was rapidly established. 'Dizziness' included various sensations such as impaired balance or difficulties judging distances. Again these were described as mild and transient.

3.3.7 Measures of patient satisfaction

Overall there were very high levels of patient satisfaction with buprenorphine as a withdrawal agent. Subjects ranked different medications for heroin withdrawal using a card sorting

technique from 'best' (ranked as 1) to 'worst' at the discharge interview. Buprenorphine was considered the 'best' medication by 13 of the 14 respondents (mean ranking of 1.1); followed by a variety of opioid agonists, and then symptomatic medication regimes (see Table 3.5).

Subjects were asked to identify 'good things' and 'bad things' associated with the use of buprenorphine. Responses were open ended and written down by the research assistant for subsequent content analysis by the principal investigator (NL). The five most common positive responses were: (a) no, minimal or mild withdrawal symptoms experienced (79% of subjects); (b) felt 'normal' and could function in daily activities (57%); (c) reduced or no cravings for heroin use (36%); (d) blocks the effects of heroin use (36%); and (e) psychologically comfortable during withdrawal (29%). The most common negative aspects reported when prompted were (a) side effects (57% of subjects); inconvenience of daily dosing (7%); current dosing period too short (7%); and sleep disturbance (7%).

Table 3.5. Ranking of medications for the management of heroin withdrawal (n=14)

Medication	Ranking (mean)	No. subjects experienced
Buprenorphine	1.1	14
d-propoxyphene preparation (Doloxene®)	2.7	10
Codeine (30mg) - paracetamol (500mg) (Panadeine forte®)	2.9	11
Short term methadone reduction	3.0	1
Benzodiazepines	3.2	13
Other symptomatic (eg NSAIDs, antiemetics)	4.1	8
Clonidine	5	2

3.3.8 Post withdrawal outcomes

The severity of dependence to heroin in the preceding week was assessed at intake and again on discharge using the Leeds Dependence Questionnaire (LDQ). The mean LDQ score at intake (n=18) was 23.2 ± 3.9. The mean LDQ score at discharge (n=14) was 9.0 ± 7.2. This represents a significant reduction ($p<0.001$) in scores for heroin dependence over the course of the withdrawal episode ($t(13) = 8.72$, 95% CI = -11.2 to -17.9), although data for treatment non-completers is not available for this analysis, as none completed the discharge interview.

Although follow up of subjects after the withdrawal episode was not systematic, data regarding subsequent outcomes and treatment uptake was available for 16 of the 18 subjects (collected either by the subjects remaining in contact with Turning Point, or through contact with acquaintances). One subject had discontinued their withdrawal episode during the study and transferred to a short-term methadone reduction regime, which in turn became a longer-term methadone maintenance program. Two subjects (11%) entered naltrexone treatment

immediately following the completion of their buprenorphine withdrawal episode, but later ceased naltrexone and relapsed to heroin use within several weeks.

The most common outcome (n=13, 72%) was that subjects resumed regular heroin use soon after (within weeks of) the completion of the withdrawal episode. Eight of these subjects (44%) returned for further treatment at Turning Point within one month (five commenced methadone maintenance programs, and three subjects completed at least one further episode of outpatient withdrawal). Five subjects (28%) resumed heroin use soon after the study episode but it is unclear as to whether they entered treatment elsewhere.

3.4 Discussion

This was an exploratory study with two primary (and related) aims. Firstly, to examine the range of buprenorphine doses required for a comfortable withdrawal episode in an outpatient setting, with minimal heroin use or adverse events. The second broad aim was to gain experience with the use of buprenorphine for outpatient heroin withdrawal, exploring its impact upon commonly identified withdrawal outcomes such as the severity and profile of withdrawal symptoms (including the occurrence of rebound phenomena), heroin use and cravings, adverse events, completion rates, and patient perceptions regarding its use.

3.4.1 Outpatient buprenorphine dosing regime

The variation in the doses used by different subjects was not major, and a number of trends emerged during the study. The total buprenorphine dose dispensed on day 1 was usually 6 or 8 mg. The first four subjects each received 4 mg on day 1 and reported inadequate relief of withdrawal symptoms and cravings over a 24-hour period. Doses higher than 8 mg were not available as part of the study protocol; however, I would caution against the use of higher initial doses in an outpatient setting due to the emergence of adverse events (such as sedation and dizziness) in over a quarter of subjects; and the risk of precipitated withdrawal associated with higher initial buprenorphine doses (Lintzeris, Clark et al. 2001).

Higher doses were generally used during the following 3 days. Most subjects received daily doses of between 8 and 12 mg per day during days 2 (94%), 3 (94%), and 4 (80%). Despite the reduction in dose on day 5, most subjects did not report any significant increase in withdrawal discomfort the following day. This is likely due to the slow dissociation of buprenorphine from opiate receptors, such that subjects continued to feel the effects of the higher doses administered on previous days.

The majority of subjects (79%) reported at the completion of their episode that their doses of buprenorphine had been 'about right'. The three subjects who reported that their doses had been 'too low' did not experience severe withdrawal symptoms and received higher than average doses of buprenorphine - suggesting the diversity of patient expectations as to the role of medication in withdrawal.

Although the titration dose ranging study design was considered most suited to the exploratory nature of this research, dose titration studies do not provide information regarding the efficacy of different dosing regimes. Ultimately, blinded randomised controlled trials, in which subjects are assigned to different buprenorphine doses (with comparison of between groups outcomes) are required in order to identify optimal dosing regimens. Nevertheless, when compared against a variety of outcome and process measures considered important for withdrawal services (as developed in Section 1.1.3), the findings of this study are generally satisfactory: few subjects reported using heroin to alleviate withdrawal discomfort; most individuals experienced minimal withdrawal discomfort over the course of their withdrawal episode; adverse events were mild and well tolerated; most subjects completed the withdrawal regime; and there were high levels of patient satisfaction. These findings would suggest that the range of buprenorphine doses used in this study are generally satisfactory, and it is possible to recommend a buprenorphine dosing regime for outpatient heroin withdrawal. The following 5-day regime is proposed.

Table 3.6. Recommended buprenorphine dosing regime for outpatient heroin withdrawal

Day of withdrawal regime	Recommended dose of buprenorphine (sublingual tablets)
Day 1	6 mg
Day 2	8 to 10 mg
Day 3	8 to 12 mg
Day 4	6 to 10 mg
Day 5	4 mg
Total dose	32 to 42 mg

It must be emphasised that a certain degree of flexibility in withdrawal dosing regimes should be available for patients and clinicians to account for a variety of factors, such as individual variations in the effects and metabolism of buprenorphine, side effects to the medication, severity of underlying withdrawal syndrome, psychological factors (e.g. underlying anxiety conditions) and use of other drugs during the withdrawal episode. The previous Inpatient Titration Study identified that psychological state, gender, frequency of heroin use and severity

of dependence at intake, significantly impact upon buprenorphine requirements during inpatient withdrawal, and similar factors may apply in outpatient settings. Furthermore, this regimen may not be suitable for heroin users with concomitant medical or psychiatric conditions, recent methadone treatment, or individuals undergoing withdrawal from multiple drugs, conditions that were excluded from the study.

How does the proposed dosing regime arising from this study compare with previous research? The buprenorphine doses used in the outpatient setting were considerably higher than the doses used for the management of inpatient withdrawal reported in Chapter 2 (Table 2.9). The two studies had almost identical selection criteria, recruited heroin users with similar demographic characteristics, levels of heroin use, severity and duration of dependence at intake; and had similar parameters regarding buprenorphine regimes available (up to 16 mg Subutex® per day for up to 5 days); enabling a valid comparison between the two studies. The mean daily and total doses used in the two studies are shown in the Table 3.7.

Table 3.7: Comparison of buprenorphine doses used in inpatient and outpatient withdrawal

Day	Inpatient withdrawal (n=21) Mean dose ± SD (mg)	Outpatient withdrawal (n=18) Mean dose ± SD (mg)
1	3.8 ± 2.8	6.1 ± 1.2
2	5.8 ± 3.2	9.6 ± 1.7
3	4.8 ± 3.3	10.1 ± 1.9
4	2.3 ± 2.6	8.9 ± 2.0
5	0.8 ± 1.3	4.1 ± 1.5
Total	17.4 ± 9.7	38.9 ± 5.8

The general trend of these two regimes is similar, although mean daily doses utilised in the outpatient setting were approximately double the daily doses used during the first three days in an inpatient context, with even greater discrepancy on days 4 and 5. The differences can be understood by considering the different role and requirements of medication in each of the two treatment settings. In the inpatient setting, the role of medication is to primarily relieve the more severe discomfort of withdrawal, whilst the setting, with increased capacity for monitoring, supportive counselling and a drug-free environment facilitates the patient's progress through the withdrawal episode. In contrast, the outpatient is exposed to regular cues and triggers for continued heroin use. Withdrawal medication must not only relieve withdrawal symptoms, the dose should also be adequate to significantly reduce cravings for heroin use, and to block the effects of any additional heroin use, thereby reducing the positive reinforcement of heroin use during the withdrawal attempt. In many cases the outpatient has to continue to

function in their routine daily activities (such as employment, study, housework, child care, travel), and can not afford to be 'unwell' for extended periods of time, requiring the use of adequate doses to adequately alleviate withdrawal discomfort. Furthermore, medication in outpatient settings are generally dispensed once a day, hence, a higher dose of buprenorphine may be required to accomplish the goals of pharmacotherapy over a 24 hour period, compared to the inpatient context where multiple divided doses are available each day.

There have been only two descriptions of short-term buprenorphine regimens for the management of outpatient heroin withdrawal reported in the published literature (see Table 1.7 Chapter 1). The first outpatient withdrawal regime was described by (O'Connor, Carroll et al. 1997) in which 3 mg sublingual buprenorphine (preparation unspecified) was dispensed daily for 3 days prior to the initiation of naltrexone and a range of symptomatic medications (clonidine, oxazepam, ibuprofen, ketorolac, prochlorperazine) on day 4. There was no justification or rationale provided for the dosing regime used in the study, and the suitability of the regime is difficult to assess as certain key outcomes were either not reported (continued heroin use), or difficult to interpret (withdrawal severity, retention) due to the initiation of naltrexone early in the process.

Diamant, Fischer et al. (1998) reported generally positive outcomes in a short-term outpatient withdrawal regime. 0.2 mg sublingual buprenorphine tablets were clinically titrated up to a maximum of 4 mg per day (20 tablets), and then gradually reduced to zero over a 10-day period, with 70% of subjects completing the regime, and 48% had a negative urine test for opiates on day 10. The mean daily dose was reported as between 2 and 3 mg per day during the first 5 days, with a total mean dose of buprenorphine dispensed of approximately 15 to 20 mg, substantially lower than reported in this study. There were a number of differences between the studies worth noting: Diamant and colleagues used low dose (0.2 mg) sublingual tablets, the administration of buprenorphine tablets was not supervised and with multiple buprenorphine doses prescribed over the course of the day, additional symptomatic medication was used (prothipendyl and famotidine), and there was no follow up after the final day of buprenorphine dosing.

The different buprenorphine dosing regimes identified by the two outpatient studies using clinical dose titration methods (this study and the study reported by Diamant and colleagues) highlights the importance of conducting randomised trials to examine the efficacy of different dosing regimes. The findings from this study are consistent with the general trend of research literature (reviewed in Chapter 1) in which daily buprenorphine doses of 4 mg or more are more effective in reducing withdrawal discomfort, cravings and heroin use, than lower doses (Kosten, Schottenfeld et al. 1993; Seow, Quigley et al. 1986; Schottenfeld, Pakes et al. 1997;

Johnson, Eissenberg et al. 1995; Schottenfeld, Pakes et al. 1993; Kosten and Kleber 1988; Ling, Charuvastra et al. 1998). Further research is required to compare the efficacy of high daily doses (as used in this study) and low doses (as described by Diamant and colleagues) in the management of short-term outpatient heroin withdrawal, with consistency on issues such as frequency of dosing, and the use of ancillary medication and psychosocial services.

3.4.2 Outpatient withdrawal outcomes

The second aim of the study was to more broadly explore issues in the use of buprenorphine, with particular emphasis upon its impact upon key withdrawal outcomes and process measures as developed in Section 1.1.3, such as withdrawal severity, impact upon heroin use, retention rates and patient satisfaction.

Buprenorphine was effective in reducing the severity of withdrawal without considerably prolonging the duration of symptoms. Most subjects reported minimal withdrawal discomfort over the course of the withdrawal: peak withdrawal discomfort generally occurred prior to the second dose of buprenorphine, and with substantial relief of symptoms thereafter. Importantly, there appeared to be only minor and brief rebound withdrawal experienced following the cessation of buprenorphine for most subjects. However, a degree of caution should be exercised in this claim, as a considerable proportion of subjects used heroin at least once after ceasing buprenorphine, and it is possible that this was in response to rebound withdrawal, despite the claims by most subjects that their heroin use was either volitional or situational, and not as an attempt to relieve withdrawal. An argument could also be made that there was an inadequate period of follow up and that subjects may have experienced rebound withdrawal symptoms more than 3 days after ceasing buprenorphine. This is unlikely, as the day 5 buprenorphine dose (3 to 6 mg in all cases) would not be expected to exert considerable effects for more 24 to 48 hours (Walsh, Preston et al. 1994; Walsh, Preston et al. 1995), and one would expect the emergence of rebound withdrawal phenomena to occur within 72 hours of the last dose, given the short duration of the regime (see discussion in Section 1.4.3). These findings are consistent with the mild and transient rebound withdrawal described in the Inpatient Titration Study (Chapter 2).

Other short term outcomes during the withdrawal episode were generally favourable for an outpatient setting: there was good retention in withdrawal treatment - 83% of subjects completed the dosing regime, 78% were retained throughout the 8 day episode, and one subject (6%) transferred to a methadone maintenance program during the episode. Over a third (36%) of all possible urine drug screens were negative for opiates, approximately one quarter of subjects did not use heroin over the withdrawal episode (28% self report and 22% confirmed

with urine tests), and a further 28% reported using heroin only once during this time. These findings compare favourably with outcomes for patients undergoing conventional outpatient heroin withdrawal at Turning Point Alcohol and Drug Centre (Clark, Dunlop et al. 1998). However, factors other than the utility of buprenorphine may have impacted upon the findings, including a Hawthorne effect associated with the use of a new experimental treatment, and the increased monitoring and enthusiasm by the treatment staff involved in a research project. The study had no control or comparison group with which to properly evaluate outcomes, and ultimately, a randomised controlled trial comparing buprenorphine to 'gold standard' outpatient treatment is required to assess the efficacy of buprenorphine as a withdrawal medication.

3.4.3 Conclusion

This study is the first to describe a short-term outpatient heroin withdrawal regime using the commercially available sublingual tablet preparation Subutex ®. The recommended outpatient regime uses higher doses than those reported in the earlier Inpatient Titration Study, and higher doses than those described in earlier short-term outpatient withdrawal regimes (Diamant, Fischer et al. 1998; O'Connor, Carroll et al. 1997). Nevertheless, the dosing regime used in this study resulted in generally favourable outcomes, and is consistent with the general trend in the clinical research literature in which single daily buprenorphine doses of greater than 4 mg per day are more effective in reducing withdrawal discomfort, cravings and heroin use.

The early promise in the research literature of buprenorphine being an effective and safe medication for the management of heroin withdrawal has been reinforced in this study. Buprenorphine comfortably alleviated the physical and psychological discomfort associated with heroin withdrawal; it diminished cravings for heroin; blocked the effects of additional heroin use thereby enhancing patient compliance with the objectives of withdrawal treatment; and there were minimal features of a rebound withdrawal syndrome on ceasing buprenorphine. The medication was easy to use and well tolerated by subjects - the majority were treated on a once a day dosing schedule, with no take home medications, and with minimal need for additional symptomatic medications. These factors enhance the safety aspects of buprenorphine in comparison to other withdrawal medications such as benzodiazepines or clonidine. There were high levels of patient satisfaction, with almost all subjects ranking buprenorphine as their preferred medication option for heroin withdrawal.

The limitations of the study design, most notably the lack of a control group, ultimately restricts the conclusions that can be made regarding the efficacy of buprenorphine, and this issue will be examined in the following study. Nevertheless, within the context of the broader

research agenda, this exploratory study has provided sufficient basis for the development of an outpatient-dosing regime to be used in subsequent efficacy studies.

CHAPTER 4: A RANDOMISED CONTROLLED TRIAL OF BUPRENORPHINE IN THE MANAGEMENT OF OUTPATIENT HEROIN WITHDRAWAL

4.1 Study objectives and research questions

The aim of this study was to examine the clinical efficacy, safety and cost-effectiveness of buprenorphine compared to conventional pharmacotherapy for the management of short-term heroin withdrawal in outpatient specialist treatment settings. The key objectives, outcome and process measures for the evaluation of outpatient withdrawal services were examined in Section 1.1.3 (and summarised in Table 1.2), and form the framework for this study.

The principal research question for this study is: how does the use of buprenorphine compare to current 'gold standard' medication (clonidine plus other symptomatic medication) for the management of outpatient heroin withdrawal, with regard to each of the following outcomes:

- heroin (and other drug) use during and after withdrawal episode
- retention in treatment during the withdrawal episode and in the post-withdrawal period
- adverse events during the withdrawal episode and post-withdrawal period
- cost-effectiveness
- severity of opiate withdrawal symptoms during the withdrawal episode
- global measures of functioning, including severity of dependence on heroin, and measures of psychosocial functioning
- measures of patient satisfaction.

4.2 Research Design & Methods

4.2.1 Overview of Research Design

The research design was an open label randomised controlled trial in which heroin dependent individuals presenting for an 8-day outpatient withdrawal program were randomly assigned to one of two withdrawal medication regimes. The two conditions were:

- *Control Group*: a regime of conventional symptomatic pharmacotherapy for heroin withdrawal, including clonidine, benzodiazepines and other symptomatic medications;
- *Experimental Group*: a buprenorphine regime, as developed in the Outpatient Titration Study (Chapter 3).

Upon completion of the 8-day withdrawal program, subjects were able to self-select from a range of post-withdrawal treatment options. These included substitution treatment (methadone for the Control group; methadone or buprenorphine for the Experimental group); naltrexone treatment; or counselling services without pharmacotherapy. Subjects were also able to re-attempt (conventional) withdrawal services, or to seek treatment elsewhere (e.g. residential rehabilitation programs). Participation in post-withdrawal treatment services was monitored over a 4-week period following the initial withdrawal episode. Research interviews were conducted at the end of the withdrawal episode (day 8), and at the end of the 4-week follow-up period (day 35 after recruitment). All between group comparisons were conducted on an intention-to-treat basis. The design is shown in Figure 4.1.

The research was conducted across two sites: Turning Point Alcohol and Drug Centre in Fitzroy, Melbourne; and the Langton Centre in Surry Hills, Sydney. Both centres have established outpatient withdrawal programs with considerable experience in the conduct of clinical research projects.

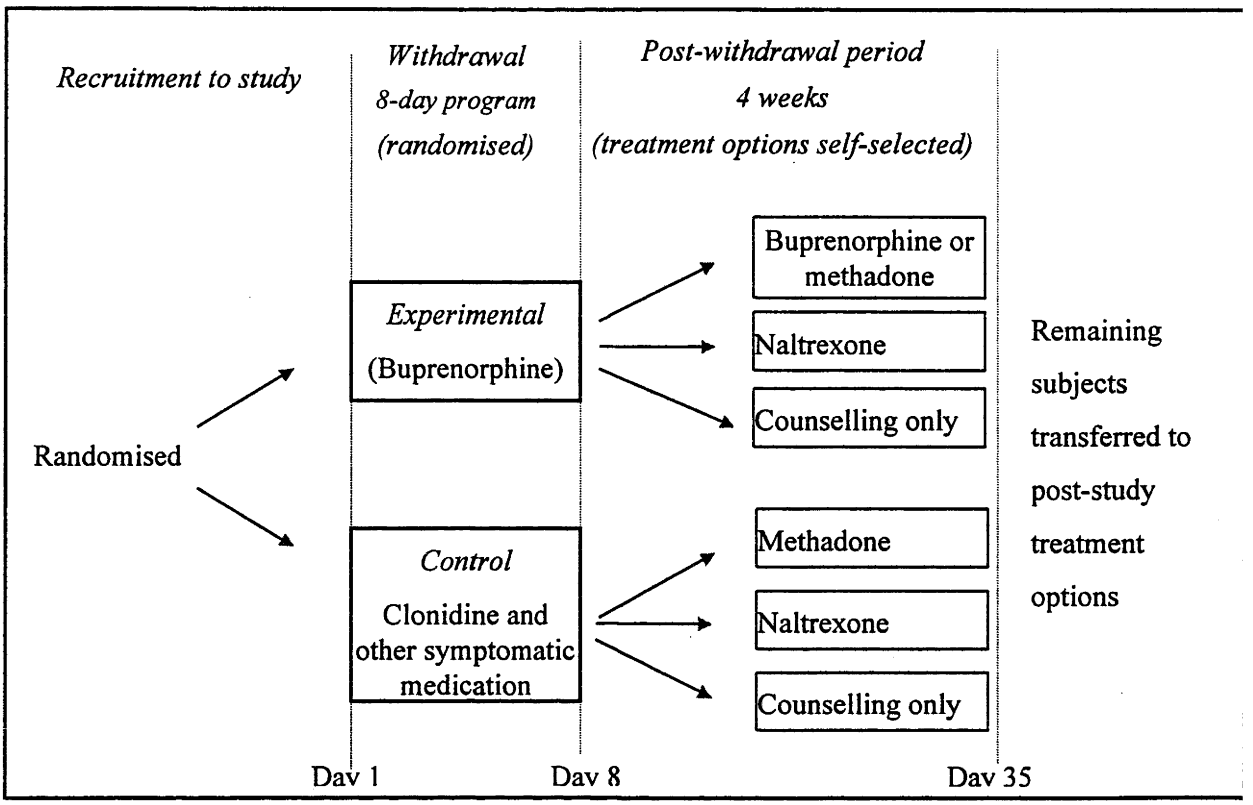


Figure 4.1. Research Design

4.2.1.1 Rationale for open-label study

Ideally, clinical research comparing different medication regimes should incorporate a double-blind design, in which treatment staff, researchers collecting data and subjects, are blinded as to Control or Experimental group allocation. This is to minimise the impact of expectancy, which can be particularly relevant when using an investigational medication in addiction research (Blaine, Ling et al. 1994). Under these circumstances, it is likely that some participants may equate 'new' with 'better', and there may be unrealistically high expectations regarding the investigational medication, and/or unnecessarily low expectations regarding the conventional medication regimes. In circumstances where two active medication regimes are used, double-dummy conditions should be employed (Blaine, Ling et al. 1994), which in this case would have required the Control subjects receiving active symptomatic medications and dummy buprenorphine tablets; whilst the Experiment subjects received active buprenorphine and dummy symptomatic medications.

However, the option of blinding research participants in this study was not feasible on two grounds. Firstly, the dosing regimes were markedly different. The Experimental group received one daily dose of buprenorphine under supervision at the clinic; whereas the Control group

were provided with a number of different medications (up to 7) which they were to take in unsupervised divided doses over a 24-hour period. Even if 'dummy' tablets had been available, most subjects would have quickly determined whether they had dummy symptomatic or active symptomatic medication (simply by taking their tablets (e.g. benzodiazepines or placebo) and seeing if there was any effect). The other main reason for not attempting a blinded study was that the pharmacological actions of the two medication regimes are substantially different, and would be quite recognisable to most subjects. For example, buprenorphine is consistently identified as an opiate by heroin users (Jasinski, Fudala et al. 1989), whereas the effects of medications such as diazepam and clonidine are substantially different. In short, blinding research participants would have been preferable, but unrealistic. Indeed the only other outpatient, randomised trial comparing buprenorphine to other withdrawal medications attempted to blind subjects, however the authors concluded that blinding had not been achieved for most subjects (O'Connor, Carroll et al. 1997). The prospect of blinding the clinical staff and outcome assessors was likewise considered unfeasible, as the patients themselves were aware of their assigned treatment.

4.2.1.2 Selecting the 'gold standard' for comparison

Medications used in the management of heroin withdrawal were reviewed in Section 1.3. This review identified that both alpha-adrenergic agonists (e.g. clonidine and lofexidine) and methadone reductions have been demonstrated to be safe and effective medications for managing heroin withdrawal, and whilst there has been no direct comparison of these medications in properly controlled studies of outpatient heroin withdrawal, they each have their role. The role of antagonist-assisted withdrawal remains unclear at this stage, and cannot be considered 'gold standard'. The decision to use symptomatic medication (principally clonidine) was due to the short time frame being considered for withdrawal services in this study. Brief methadone reduction regimes (e.g. 5 days) have not been systematically evaluated in the research literature, and as such could not be considered 'best practice' or 'gold standard'. A comparison of buprenorphine and methadone reductions over a more gradual reduction period (e.g. 10 to 21 days or even longer) is research which is required, as there has been only one such study (Bickel, Stitzer et al. 1988) with small subject numbers; however a comparison of brief buprenorphine withdrawal regime with a longer methadone reduction regime would be difficult to interpret and was not considered appropriate.

Clonidine and other symptomatic medications are routinely used in short withdrawal episodes, and were therefore considered the appropriate 'gold standard' for this trial. Whilst lofexidine has some advantages over clonidine with regards to side effects, it has not been demonstrated

to have better results for other outcomes over clonidine (Section 1.3.2). Furthermore, lofexidine is not registered in Australia, and it was considered somewhat inappropriate to compare two 'investigational' and unregistered medications.

The decision to use a variety of other symptomatic medications, including benzodiazepines, and not restrict the Control Group to clonidine was due to the common practice within Australia (including the study sites) of using such combinations of medications for heroin withdrawal (NSW Health Department 1999; Frank and Pead 1995; Lintzeris, Murray et al. 1997). To have excluded other symptomatic medications would have deterred many heroin users who have come to expect them, and may have led to criticisms of the study that 'optimal' medications had not been used for the Control group (although it should be noted that there is little research evidence regarding the value of many of these medications - see Section 1.3 for review).

4.2.1.3 Conducting a multi-site trial

There are advantages and disadvantages in single versus multi-site trials, and this study was conducted as a multi-site trial for several reasons. A practical consideration was the ability for faster rates of subject recruitment by incorporating two clinical sites, and therefore, a shorter duration for completing the research. Indeed, originally the study had been planned as a single site investigation, with projected time lines of approximately 12 to 18 months to complete the clinical component of the research. Instead, by conducting the research at two sites, the clinical component of the study was completed within 9 months at each site.

The other main reason was the greater capacity to generalise the findings of a multi-site trial. A limitation of conducting clinical research at only one site is that a number of unintended factors can impact upon the research, with the consequence that the research findings may not be able to be replicated elsewhere. For example, an unusual group of subjects may be recruited at a site due to promotional activities or 'word of mouth'; or organisational issues (such as staff changes) can impact upon service delivery; or enthusiasm (or lack thereof) of a particular key staff member can impact upon the study findings. Conducting the research at two sites reduced the potential and impact of such factors. Less important from a research design perspective, but relevant in terms of enhancing the impact of the research, conducting the study at key clinics in the two main Australian cities, Melbourne and Sydney, was also viewed as important in the dissemination and acceptance of the research findings in the alcohol and drug treatment sector (Hall 1997).

The limitations of multi-site research were also considered, and steps taken to minimise potential problems. A potential difficulty is the delivery of substantially different treatment

(and research procedures) at different sites. In this study, consistent treatment and research protocols were developed, training sessions were provided for clinical and research staff at both sites, and there was regular co-ordination of research activities across the two sites. The amount of clinician to subject contact was recorded to allow comparisons between the two sites. The principal investigator performed all data entry and analyses. Nevertheless, some discrepancies occurred with regards to baseline data collection at the two sites. Data regarding (a) demographic characteristics of current legal status, number of children (Section 4.3.1.1), and (b) reasons for exclusion of subjects was not collected at the Sydney site due to administrative errors.

Another potential problem in using sites from different cities is that there may be inherent differences in drug use patterns, such as the cost and strength of street heroin available, or routes of administration. Comparison of cost and strength of street heroin in Melbourne and Sydney during this period indicated very similar trends for the two cities (McKetin, Darke et al. 2000).

4.2.2 Subjects and recruitment

4.2.2.1 Selection criteria

The study recruited dependent heroin users presenting for outpatient heroin withdrawal, with no significant medical or psychiatric co-morbidity, or withdrawal from other drugs. Specific selection criteria for the study and their method of assessment are shown in Table 4.1. The same selection criteria were used in the two titration studies, and a more detailed rationale is provided in Table 2.1, Section 2.2.2.1. Details regarding the patients assessed and subjects enrolled are presented later in this chapter.

Regular cannabis use was not an exclusion criterion on the basis that large proportions of Australian heroin users also use cannabis regularly (McKetin, Darke et al. 2000), and to exclude them would significantly limit recruitment and the generalisability of the study findings. Furthermore, clinical experience suggests that most regular cannabis users continue to use cannabis during an outpatient heroin withdrawal episode, and therefore do not experience cannabis withdrawal symptoms; hence, cannabis use was considered unlikely to markedly hinder the interpretation of heroin withdrawal outcomes.

The selection criteria for subjects commencing naltrexone in the post-withdrawal phase as part of the study were (a) opiate negative urine drug results conducted on days 5 and 8 of the withdrawal episode (missing results were considered 'positive'); and (b) an alanine transferase level (serum liver function test) less than three times greater than the normal laboratory range.

The rationale for this arises from hepatotoxicity reported in a study of high-dose naltrexone in the treatment of obesity (Mitchell, Morley et al. 1987).

Table 4.1. Selection criteria

Selection criteria	Operational criteria
1. Aged 18 years or more	Proof of identification required.
2. Heroin dependent individuals	Assessed clinically against DSM IV 304.0 criteria
3. Recent heroin use (within past 48 hours)	Assessed by self report and positive urine test for opiates on assessment (using Accusign® diagnostic tests).
4. Not in methadone treatment within the past 8 weeks	Assessed by self report and confirmed with the relevant jurisdictional health authorities (Drugs and Poisons Unit in Victorian Department of Human Services; Pharmaceutical Services in NSW Health Department.
5. Not dependent upon or withdrawing from alcohol or benzodiazepines	Assessed by clinical history and examination, urine drug screen, and breath alcohol level where indicated.
6. Not pregnant or breastfeeding	Pregnancy was assessed by a urine bHCG test.
7. Suitable social environment for outpatient withdrawal.	The key criterion here was that the patient had some form of accommodation (but not necessarily drug-free accommodation). The presence of 'drug free' support people was not a requirement.
8. No active or unstable medical or psychiatric condition	Assessed clinically by medical officer.
9. Able to meet attendance requirements for study	Requirement was that patient could attend the clinic daily over the 8-day withdrawal period, and could engage in the 4-week post-withdrawal treatment period (e.g. no planned hospital admission, court appearance, or long term travel).
10. Able and willing to give informed consent	Participation in the study was voluntary. Capacity to give informed consent was assessed by the clinical team and research assistant.

4.2.2.2 Subject Numbers

The sample size for the study was calculated using the primary outcome measure for which greatest information was available before the trial - rates of completion of the withdrawal episode without heroin use. The sample size was determined using the following formula (Pocock 1983):

$$n = \frac{p_1 \times (100 - p_1) + p_2 \times (100 - p_2)}{(p_1 - p_2)^2} \times f(\alpha,\beta)$$

with: n = number in each group

p_1= % successes (7 days with no heroin use) expected in Control group

p_2 = % successes (7 days without heroin use) expected in Experimental group

$\alpha = 0.05$ (type I error); $\beta = 0.10$ (type II error, 90% power); $f(\alpha,\beta) = 10.5$

Various authors have estimated the successful completion rates for outpatient symptomatic heroin withdrawal to be approximately 20 per cent (see Chapter 1 for review). However, a review of computerised clinical records of outpatient withdrawal outcomes at Turning Point Clinical Services (1996-7) indicated a 20 - 25 per cent completion rate for attendance, although at least half of these patients used some heroin during their withdrawal episode. Using the criterion of one week with no heroin (or other opiate) use, a more realistic estimate of successful completion of outpatient heroin withdrawal using symptomatic medication is in the order of 5 to 10% of patients attending Turning Point Clinical Services. Similar estimates of heroin-free completion rates were independently estimated for outpatient withdrawal programs by experienced staff at the Langton Centre. The results from Outpatient Dose Titration Study (Chapter 3) conducted at Turning Point saw 28% of subjects reported completing 7 or 8 days with no heroin use. Using these estimates ($p_1 = 5\%$ completion; $p_2 = 28\%$ completion):

$$n = \frac{10 \times (100 - 10) + 22 \times (100 - 22) \times 10.5}{(10 - 22)^2} = 61 \text{ subjects}$$

From these calculations, it was estimated that 61 subjects were required in each group, and hence the proposed total number of subjects was 122. The study aimed to recruit equal numbers (approximately 60 subjects) at each site. The Turning Point site commenced and completed recruitment first, with 64 subjects randomised. Recruitment at Langton Centre was ceased after 50 subjects had been randomised. Hence, in total 114 subjects were randomised into the study.

4.2.2.3 Recruitment procedures

Subjects were recruited from heroin dependent patients presenting for outpatient heroin withdrawal at Turning Point Clinical Services in Melbourne, and at the Langton Centre in Sydney. Recruitment to the study was voluntary with informed consent for the trial's clinical and research activities. Patients not wishing to participate in the study had access to routine withdrawal and other clinical services at study sites. The emphasis was to recruit from patients presenting for outpatient withdrawal at these services, with no active advertising or promotion for the study. This was to minimise the potential for an 'atypical' group of heroin users presenting in order to try a 'new medication', with associated unrealistic expectations regarding the worth of the investigational medication.

The study recruitment procedures were different at each site. At Turning Point, all patients seeking outpatient withdrawal were screened for eligibility, and those considered broadly eligible were informed of the study, provided with written information regarding the study and the various treatment options available to them (including conventional withdrawal services). Interested patients then underwent further screening as relevant (urine testing, confirmation of

prior methadone status), were given the opportunity to read the detailed Plain Language Statement (see Appendix 1) and to ask questions of the clinical staff. Eligible subjects then underwent a confidential (~30 to 60 minute) interview with the research assistant, during which they provided written informed consent, follow-up contact details, and baseline data. On the completion of the baseline research interview, subjects were randomised into one of the two study conditions (see next section), and then referred back to the treating clinician for initiation of the treatment regime.

Limited medical resources at the Langton Centre prevented the study being offered to all potentially eligible patients presenting for outpatient heroin withdrawal. Instead, there were a limited number of study vacancies during the course of each week (usually three per week), with a 'first come, first served' approach. Recruitment procedures similar to those described at the Turning Point site were followed, with randomisation occurring following clinical assessment, and written informed consent and data collection with the research assistant. Once the allotted number of research vacancies at the Langton site had been filled each week, subsequent patients presenting for withdrawal had the option of routine access to conventional withdrawal services (using symptomatic medication), or an appointment early in the following week when vacancies for the study would be available.

4.2.2.4 Randomisation procedures

Randomisation for the study was conducted by the Randomisation Service of the NHMRC Clinical Trials Centre, an independent organisation contracted to provide this service for the study. A computerised randomisation schedule was developed by this service using the technique of dynamic balanced randomisation (Signorini, Leung et al. 1993). This method balances treatment allocation within each site and across the study as a whole (with the aim of a 1:1 ratio between Control and Experimental groups at each site). Dynamic balanced randomisation overcomes the potential for marked differences in subject allocation at different study sites, and reduces the potential for research participants to predict the group to which a particular subject may be allocated (as can occur with conventional block randomisation). Subject allocation is deterministic if certain pre-defined limits are exceeded, and random otherwise.

Upon completion of the informed consent procedures and baseline research interview, the research assistant telephoned the NHMRC Clinical Trials Centre, with summary subjects details (initials, date of birth, study site). The NHMRC Randomisation Service then provided the outcome of randomisation, initially by telephone, and with subsequent written confirmation.

58 / 114 subjects (51%) were randomised to the Experimental Group, and 56 / 114 (49%) randomised to the Control Group. At the Turning Point site, 32 / 64 (50%) subjects were randomised to each group; while at the Langton Centre site, 26 / 50 (52%) were randomised to the Experimental group, and 24 / 50 (48%) to the Control group. Details regarding subject characteristics are provided later in this Chapter.

4.2.2.5 Enrolling couples in the study

One of the advantages of outpatient withdrawal programs is that they enable couples to attempt withdrawal together, which is generally prohibited by most Australian residential withdrawal services. However, it was considered inappropriate for partners to be randomised to different treatment groups in the study, and couples undergoing treatment together (entering withdrawal within the same week) were assigned to the same treatment condition. Consequently, only one partner of each couple was enrolled into the study as a subject for analysis purposes. The partner to be enrolled as the subject was selected as the patient who initially presented to the service, or in circumstances where the couple presented simultaneously, the partner to be enrolled was randomly selected (by the research assistant tossing a coin prior to the baseline research interview and subsequent random group assignment). Full data collection and treatment procedures were followed on both partners, so that the patients (and treatment staff) were unaware as to which member of the couple had been recruited to the study. Data for the non-randomised members of couples in the study is not included in any of the intention-to-treat data analyses.

4.2.2.6 Subjects enrolled

Table 4.2 displays the number of patients seeking outpatient heroin withdrawal, the number deemed as ineligible (including reasons for ineligibility among Turning Point patients), and the number of subjects enrolled into the study at each site. The reasons for ineligibility at the Langton Centre were not systematically recorded. Data regarding subject enrolment and follow up over the study is also presented in Figure 4.2 (Section 4.2.4.3).

Thirty-five patients were potentially eligible but did not participate in the study, either due to them declining to participate, or due to limited study treatment places at the Langton Centre site (see Section 4.2.2.3). More common reasons for eligible patients voluntarily declining to participate in the study included: unwilling to attend daily during the withdrawal episode; not wanting medications for withdrawal management; unwilling to participate in a research project; or seeking to enrol in another research study (in particular a number of heroin users were keen

to enter naltrexone relapse prevention studies running at both clinic sites, and recruitment to the withdrawal study prevented enrolment in the naltrexone studies).

Table 4.2. Recruitment of subjects across the two sites

Subject Status	Turning Point n (%)	Langton Centre n (%)	Total n (%)
Total number of patients assessed	120 (100)	152 (100)	272 (100)
Total ineligible	29 (24%)	56 (37%)	85 (31%)
Medical condition	3	n/a	
Psychiatric condition	5	n/a	
Concurrent dependence to other drug	4	n/a	
Methadone treatment in prior 8 weeks	9	n/a	
Attendance difficulties	4	n/a	
Multiple reasons	4	n/a	
Total eligible	91 (76%)	96 (63%)	187 (69%)
Chose not to participate in study and/or no study places available at LC	11	35	46
Enrolled in study	80 (67%)	62 (41%)	142 (52%)
Randomised to study group	64	50	114
Non-randomised partner	16	12	28

Twenty-eight couples enrolled in the study, of which only one partner was included in data analysis (see previous discussion). Similar proportions of subjects enrolled as couples were randomised to each group, with 13 subjects randomised to the Control Group (comprising 23% of all Control subjects) and 15 randomised to the Experimental Group (26% of all Experimental subjects).

4.2.3 Treatment procedures

4.2.3.1 Withdrawal episode

The withdrawal episode required daily attendance of subjects over an 8-day period. Subjects were reviewed each day by a clinician prior to medication being dispensed. At each review, information was collected that would assist the appropriate titration of doses of medication, including (a) *withdrawal severity* using the Subjective and Objective Opiate Withdrawal Scales; (b) subject rating of the *adequacy of the dose* of the preceding day's medication; (c) any *drug use* since last presentation and the surrounding circumstances; and (d) any *adverse events.*

Supportive counselling and case management activities were provided during the course of the withdrawal episode in line with standard practice for both sites. Areas addressed included: goals of treatment, organising social environment for withdrawal, strategies for coping with withdrawal symptoms, safer injecting and prevention of overdose information where

appropriate, and linkages to post-withdrawal services. Subjects also received the written information book *Getting Through Heroin Withdrawal* (Lintzeris, Dunlop et al. 1996).

Urine drug screens were collected on days 5 and 8 of the withdrawal episode, with results available to clinicians and subjects. Subjects were reviewed at the completion of the withdrawal episode on day 8, with a discussion of the various treatment options available.

Subjects who did not attend or contact the clinic for two or more consecutive days were discharged from the study treatment procedures, although they could continue to access conventional treatment services, and were followed up for research interviews.

Medication regime for Experimental Group

The recommended dosing regime developed in the earlier Outpatient Dose Titration Study was used for the Experimental group (Table 3.6, Chapter 3). Sublingual buprenorphine tablets were dispensed once daily under supervision at the clinic pharmacy. The mean daily doses dispensed to the Experimental subjects are shown in Table 4.3.

Table 4.3 Buprenorphine doses (mg) dispensed during withdrawal episode

Day	Buprenorphine dose administered (mg) mean ± SD
Day 1	6.0 ± 0.6
Day 2	9.3 ± 1.6
Day 3	9.6 ± 3.0
Day 4	8.8 ± 2.0
Day 5	3.6 ± 1.3
Total	37.2 ± 5.3

In order to minimise the risk of precipitated withdrawal with the first dose of buprenorphine, the first dose (usually 6 mg) was only administered to those subjects who reported using heroin at least 6 hours earlier, and who did not show any features of opioid intoxication. In some circumstances this required subjects to present later in the day for their first dose, or to have a reduced first dose (e.g. 4 mg) to avoid precipitated withdrawal.

The dose of buprenorphine dispensed on days 2 to 4 was titrated according to the subject's experience of withdrawal severity, drug use, adverse events, and ratings of dose adequacy. The dosing regime allowed some flexibility to accommodate individual variation in medication requirements. For example, a subject describing uncomfortable withdrawal symptoms following day 1 without significant side effects was dispensed a 10 mg dose on day 2.

Alternatively, subjects describing mild withdrawal symptoms since the first dose of buprenorphine, and/or those experiencing (tolerable) side effects were given an 8 mg dose.

In addition to buprenorphine, benzodiazepines were prescribed for 7 of the 58 subjects (12%) at a mean total (over the 8 day withdrawal episode) dose of 20 mg (± 9 mg) oral diazepam equivalent (maximum total dose prescribed = 30 mg). Clonidine was dispensed for one subject for the management of precipitated withdrawal following the first dose of buprenorphine (see section on Adverse Events). No other symptomatic medications were prescribed to the Experimental subjects during the withdrawal episode.

Medication regimes for Control Group

The Control Group had a range of different medications available to them over the course of the withdrawal episode (see Section 4.2.1.2 for rationale). Medications were dispensed daily from the clinic pharmacy, with clear verbal and written directions for their use. The main medication was clonidine, used in a dosing regime consistent with the published literature and usual practice for both study sites. Daily doses of clonidine dispensed over the withdrawal episode are shown in Table 4.4. Subjects were instructed to miss a dose of clonidine if they experienced features of postural hypotension (feel light-headed or like fainting), and to resume clonidine with resolution of these symptoms (usually within hours).

Table 4.4. Daily and total doses of clonidine dispensed to Control Group

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total
Mean ± SD (mg, oral)	0.75 ± 0.24	0.74 ± 0.19	0.90 ± 0.83	0.71 ± 0.20	0.61 ± 0.25	0.63 ± 0.26	0.51 ± 0.23	3.11± 1.51
Maximum dose (mg)	1.2	0.9	1.2	0.9	0.9	1.2	0.9	6.3

Details regarding the total doses of other symptomatic medications dispensed over the withdrawal episode to Control subjects and approximate average daily doses are shown below.

Table 4.5 Doses of other symptomatic withdrawal medications for Control group (n =42) [a]

	Benzodiazepines (diazepam oral equivalent) (mg)	Metoclopramide (mg)	Quinine (mg)	Hyoscine butylbromide (mg)	Ibuprofen (gm)
Total dose (Mean ± SD)	101 ± 55	117 ± 50	2690 ± 1360	237 ± 125	6.55 ± 2.60
(Range)	20 to 250	30 to 210	900 to 6300	60 to 560	2.4 to 10.8
Daily dose (Mean ± SD)	14 ± 8	17 ± 7	380 ± 190	34 ± 18	0.94 ± 0.37

[a] *16 subjects did not receive any medication after the first day and are excluded from these results*

Clinician – subject contact

The number and duration of contacts with all clinical staff was recorded prospectively for each subject during the 8-day withdrawal episode. Details of these contacts are shown in Table 4.6 for those subjects who participated in treatment beyond day 1.

Table 4.6. Clinical contacts by randomised group for subjects engaged in treatment (> 1 day)

	Experimental (n= 41) Mean ± SD	Control (n = 56) Mean ± SD	
Medical staff			
number of contacts	3.5 ± 2.1	3.8 ± 1.9	NS
total time (min)	64 ± 51	71 ± 49	NS
Nursing staff			
number of contacts	3.7 ± 2.6	3.0 ± 2.5	NS
total time (min)	64 ± 57	49 ± 46	NS
Pharmacists			
number of contacts	3.2 ± 2.1	3.8 ± 2.5	NS
total time (min)	19 ± 15	37 ± 28	$p<0.01$ ($t(57)= 3.66$)
All clinical staff			
number of contacts	10.6 ± 2.5	10.7 ± 3.9	NS

There was a very similar pattern of clinician - patient contacts between the two groups, and the only statistically significant difference was that pharmacists spent more time preparing and dispensing medications for the Control group (due to daily dispensing of up to seven different medications).

4.2.3.2 Post withdrawal treatment procedures

Participation in post-withdrawal treatment services was voluntary, with subjects selecting their treatment modality. The study allowed for a number of treatment options, including naltrexone treatment, counselling (without medication), and substitution treatment. Participation in treatment services as part of the study protocol was conditional on the subjects meeting certain criteria. Subjects were informed of the post-withdrawal treatment options at the commencement of the withdrawal episode. The range of post-withdrawal treatment options available was reinforced for each subject on the final day of the withdrawal episode (day 8 of the study), and subjects provided with Plain Language Statements for post-withdrawal options (see Appendix). Those subjects who were ambivalent regarding their post withdrawal treatment options could delay their decision to enter treatment as part of the study until day 10.

Subjects also had the capacity to engage in routine clinical services that were not part of the study. Subjects could attend treatment services at other agencies, or alternatively, subjects who discontinued treatment as part of the study could commence routine clinical services available at the study sites - for example, a subject who dropped out of buprenorphine treatment after 2 weeks into the post-withdrawal period, could represent to the clinic and commence withdrawal or methadone maintenance treatment.

Buprenorphine substitution treatment

Treatment with buprenorphine was available only to subjects in the Experimental Group. To be eligible for buprenorphine treatment in the post-withdrawal phase, subjects had to have completed the withdrawal episode (satisfactory attendance record), and to have made the decision to enter buprenorphine treatment by day 10 of the study protocol. Subjects who chose not to enter buprenorphine treatment by day 10, and who presented at a later time (e.g. day 16) were ineligible to enter buprenorphine treatment (but could commence methadone or other treatment under conventional conditions).

Buprenorphine doses were generally prescribed according to maintenance treatment conditions (Lintzeris, Clark et al. 2001). Doses were individually titrated according to the needs of each subject. The starting dose was generally in the range of 4 to 8 mg, with the capacity for dose increases of up to 4 mg at a time, to a maximum daily dose of 16 mg. Buprenorphine was dispensed on a daily basis from the clinic sites, with no take home privileges allowed. Alternate day dosing with buprenorphine was not a routine option for subjects, although was accommodated in special cases of absence from the clinic (in lieu of take home doses). There were no dispensing fees for buprenorphine during the trial. Subjects were reviewed regularly by their assigned case-worker and medical staff, and had the option of more intensive counselling.

Not all subjects using buprenorphine chose to use it as a maintenance medication during the post-withdrawal phase, with a small number attempting a short course (for example, two weeks) of reducing doses of buprenorphine as another attempt at withdrawal.

Subjects who discontinued buprenorphine (missed 3 or more consecutive doses) during the post-withdrawal phase of treatment were not able to recommence buprenorphine treatment., but could enter conventional treatment options such as methadone treatment. Buprenorphine was not registered in Australia at the time the study was conducted, and as such, subjects could not access buprenorphine elsewhere. At the completion of the 4-week post-withdrawal study period, subjects on buprenorphine had the option of gradually reducing their dose and withdrawing off buprenorphine over a two to three week period, or alternatively transferring to

methadone maintenance treatment. Continued long-term maintenance treatment with buprenorphine was not an option as part of the study.

Methadone substitution treatment

Methadone treatment was available to subjects in both the Control and Experimental groups. The study protocol allowed for free methadone dispensing[1]. Methadone was generally prescribed according to standard maintenance treatment conditions as specified in the appropriate jurisdictional guidelines (Department of Health and Community Services 1995; (New South Wales Health 1999). Starting doses were generally between 20 and 30 mg per day, and titrated upwards as required to a maximum possible dose of 100 mg. Methadone was dispensed on a daily basis under supervision from the clinic sites, with no routine take home privileges allowed during the first month of treatment. Subjects were reviewed regularly by their assigned case-worker and medical staff, and had the option of more intensive counselling.

As with buprenorphine treatment, not all subjects commencing methadone were necessarily intent on using it as a maintenance medication, with some subjects attempting a brief reduction regime using low doses as another attempt at withdrawal. Subjects who discontinued methadone (missed 3 or more consecutive doses) during the 4-week post withdrawal phase of treatment were able to recommence methadone treatment under conventional conditions. At the completion of the 4-week post withdrawal study period, subjects could continue methadone treatment under conventional conditions.

Naltrexone treatment

Naltrexone treatment was available under study conditions for subjects in both randomised groups, according to the selection criteria specified earlier. Doses were dispensed daily for the first 4 days, then weekly thereafter, with a minimum frequency of review with clinical staff of once a week. Naltrexone was provided free of charge to subjects under study conditions.

Control subjects who entered naltrexone as part of the study underwent a naloxone challenge test with 0.8 mg intravenous naloxone. Measures of opiate withdrawal (SOWS and OOWS) were recorded at baseline, and again at 10 and 20 minutes after the administration of naloxone.

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[1] Subjects who had not maintained regular attendance during the withdrawal episode or who chose not to enter methadone treatment by day 10 could commence methadone under conventional treatment conditions. The only difference between conventional and study protocol conditions for methadone treatment was that subjects at Turning Point had to pay a weekly dispensing fee of $25 per week for conventional methadone; whereas there were no dispensing fees as part of the study protocol. There were no fees at the Langton Centre, and therefore, no difference between study and conventional treatment.

Subjects tolerating the naloxone challenge were then commenced on naltrexone, initially dispensed under supervision from the clinic for the first three days at 25 mg per day. The recommended dose thereafter was 50 mg per day, although some subjects reported side effects at this dose and maintained lower doses of 25 mg per day.

Induction onto naltrexone for Experimental subjects used a different procedure. Naloxone challenge tests are difficult to interpret in individuals treated with buprenorphine (Eissenberg, Greenwald et al. 1996), and as such were not used. The induction procedure used in the study entailed administering a 12.5 mg dose of naltrexone orally on day 8 (or later if so negotiated with the subject). The subject was then monitored (using SOWS and OOWS) in the clinic for up to three hours after the naltrexone dose, during which time any severe withdrawal response should have become apparent (Eissenberg, Greenwald et al. 1996). Subjects complaining of withdrawal discomfort had access to a range of symptomatic medications (see Table 4.7 below). Subjects were allowed home after the period of monitoring (with symptomatic medications as required). The study doctor reviewed the subjects the following day. The naltrexone dose was maintained at 12.5 mg if the subject reported considerable withdrawal discomfort, or increased to 25 mg if the initial dose had been tolerated. The naltrexone dose was generally increased to 50 mg per day by the fourth day, although some subjects reported side effects at this dose and maintained lower doses of 25 mg per day.

A number of subjects were ineligible for naltrexone as part of the study protocol (due to heroin use during the withdrawal period), but nevertheless over the course of the 4-week post-withdrawal period were able to complete opiate withdrawal and commence naltrexone treatment under conventional conditions (Bell, Kimber et al. 1999). Subjects had to pay the standard cost of the naltrexone medication (approximately $5 per 50 mg tablet) under these conditions.

Table 4.7. Medication available for Experimental Group subjects commencing naltrexone.

Medication	Dose
Clonidine	100 mcg 3 - 4 hourly for subjects <65 kg body weight; 150 mcg 3 - 4 hourly for subjects >65 kg body weight
Diazepam	5mg 3 - 4 hourly as required
Metoclopramide	10mg 6 hourly as required
Ibuprofen	400mg 4 to 6 hourly as required
Hyoscine butylromide	20 mg 6 hourly as required

Counselling services

Subjects could choose to enter counselling only services (without the use of substitution medications or naltrexone). The extent and content of counselling was determined by

negotiation between the subject and counsellors in keeping with routine counselling services at each site. The content generally addressed relapse prevention, motivational interviewing and other post-withdrawal issues. Counselling sessions were usually scheduled as 60 minute appointments, one to two times per week over the 4-week period.

Withdrawal programs

A number of subjects had further attempts at withdrawal treatment during the 4-week follow-up period. Those subjects attempting withdrawal at the study sites were provided with conventional symptomatic medication regime similar to that described for the Control Group withdrawal. As described in the earlier section, a small number of subjects attempted to use short courses of reducing doses of buprenorphine or methadone as withdrawal medications.

Treatment at sites not involved in the study.

There were a number of cases (n = 16) where subjects engaged in treatment at agencies not involved in the study - 5 subjects entered conventional methadone programs elsewhere, 5 entered withdrawal programs, 2 entered counselling, 3 entered naltrexone and 2 entered other forms of treatment). Limited data regarding these treatment episodes is available. For those subjects lost to follow up at day 35 (n=23), participation in methadone treatment was determined by contacting the relevant jurisdictional health departments to see if a permit had been issued for the 'missing' subjects during the 4-week follow-up period. There was no way of identifying participation in other treatment modalities (e.g. withdrawal, naltrexone) by subjects 'lost' to the day 35 research interview.

4.2.4 Outcomes, measures and data management.

4.2.4.1 Outcomes and measures

The framework for the evaluation of withdrawal services in this study was developed in Chapter 1.1. The primary outcomes and related measures for this outpatient study were:

1. *Use of heroin and other drugs during the withdrawal episode and in the post-withdrawal period.* Data regarding heroin and other drug use in the preceding month was collected at baseline using the modified Drug Use Section of the Opiate Treatment Index (OTI) (Darke, Heather et al. 1991). The modifications included questions regarding the number of days used heroin in the preceding 28 days, and the average daily cost of heroin when used. Drug use during the withdrawal episode was measured by (a) self report to clinical staff, recalling any heroin use, amount and reasons for use; (b) self report at the day 8 research interview recalling the number of times and the number of days that the subject used heroin since

commencing the withdrawal episode; and (c) urine drug screens collected on days 1, 5, and 8. Drug use in the post-withdrawal period was assessed using the modified Drug Use Section of the OTI at day 35.

2. *Retention in withdrawal treatment.* Retention in treatment was measured as the number of days each subject participated in withdrawal treatment. Subjects were deemed to have completed the withdrawal episode if they did not miss 2 or more consecutive days during the 8-day episode.

3. *Participation in post-withdrawal treatment.* This was measured as (a) the number of subjects entering post-withdrawal treatment options during the 4-week follow-up period; (b) the number of days subjects were enrolled in any treatment during the 4 week follow-up period; and (c) the number of subjects retained in post-withdrawal treatment (enrolled in some form of drug treatment at day 35).

4. *Cost-effectiveness.* Cost effectiveness was calculated by comparing the incremental costs of all health services utilised by subjects during the 8-day withdrawal episode, against various outcome measures. Incremental costs refer to costs that are inherently different between the two groups (such as staffing, medications, treatment of adverse events), without including costs considered to be essentially the same across subjects in the two groups, including 'overhead' costs to the organisations providing the services (including heating, power, rent, clinic administration and support (e.g. receptionists, filing), and services standard to both (including pre-randomisation assessment and recruitment expenses, research costs not related to clinical activity). The cost of health services utilised by subjects during the withdrawal episode was calculated from clinic records (e.g. medication charts), prospective data collection by clinic staff of the duration of contacts with subjects, and self-report by subjects at the day 8 research interview of other health services and medications used in the preceding week. The two outcome measures for use in the economic evaluation were (a) the number of self-report heroin-free days during the withdrawal episode, and (b) the proportion of subjects completing the 8-day withdrawal episode without any heroin use on urinalysis.

The secondary outcomes and related measures for the study are:

1. *Severity of withdrawal features.* Withdrawal severity was a secondary outcome for this study as it is difficult to interpret data regarding the severity of withdrawal symptoms during outpatient withdrawal where some subjects continue to use heroin. Subjects rated the severity of opiate withdrawal on a daily basis using the Subjective Opiate Withdrawal Scale, completed prior to dosing during days 1 to 8. Objective features of opiate withdrawal were assessed daily using the Objective Opiate Withdrawal Scale by trained clinicians prior to

dosing during the withdrawal episode. At the day 8 research interview, subjects rated the global severity of withdrawal experienced during the withdrawal episode using a Visual Analogue Scale with 0 = "No withdrawal discomfort experienced" and 100 = "Most severe withdrawal discomfort experienced".

2. *Side effects and adverse events*. Subjects were asked to record any adverse events that occurred during the first week of withdrawal treatment (daily reporting). The treating medical officer assessed any adverse events, with an interpretation of the extent to which the adverse event was related to the study medication.

3. *Measures of psycho-social functioning*. Severity of dependence to heroin was measured using the Leeds Dependence Questionnaire (Raistrick, Bradshaw et al. 1994) at baseline, at day 8 and at day 35. The Leeds Dependence Questionnaire assesses physical, psychological and behavioural aspects of dependence within the past week, and is therefore well suited to detecting changes in the severity of dependence following short-term interventions such as withdrawal. Social functioning and psychological well-being were assessed at baseline, at day 8 and at day 35 using the BASIS-32 (Eisen, Dill et al. 1994). The BASIS-32 is a self-completed 32-item questionnaire assessing five parameters of psychosocial functioning within the past week, thereby making it suitable to detect any changes following a short withdrawal episode. An additional measure of psycho-social functioning examining a longer time frame (one month), the SF-36 (Ware, Snow et al. 1993) was used at baseline and day 35.

4. *Subject perceptions of satisfaction with withdrawal medications and goal attainment.* Subjects were asked at the day 8 research interview to rate their satisfaction with their withdrawal medication (using a Visual Analogue Scale with 0 = very unsatisfied to 100 = very satisfied); and to rate the adequacy of the doses used (using a 5 point Likert scale). Subjects were also asked open-ended questions to identify the "good" and "bad" aspects associated with the medication regime to which they had been randomised.

   Subjects were asked at intake to rate the importance of various goals regarding their drug use and treatment (see Appendix) using Visual Analogue Scales (0 = not important to 100 = very important). The goals used in the questionnaire had been identified as key reasons for presentation for withdrawal in an earlier qualitative study of outpatient heroin withdrawal at Turning Point (Dunlop, Koutroulis et al. 1996). Subjects were then asked at the completion of the withdrawal episode (day 8) and at the day 35 follow up interview whether they achieved their goals for withdrawal treatment (using VAS with 0 = no goals achieved and 100 = all goals achieved).

Data was also collected at intake regarding the following variables:

- *demographics* (age, employment status, legal status, accommodation status, drug use status of partner, and drug use in place of accommodation);
- *locater information* to assist in tracking subjects for follow up research interviews;
- *previous participation in drug treatment services.*
- *expected severity of heroin withdrawal.* Subjects rated the severity of withdrawal they expected to experience using a Visual Analog Scale (0 mm = no withdrawal discomfort to 100 mm = extreme withdrawal discomfort).

The interview schedules, questionnaires, Plain Language Statements and other Case Record Forms for this study are included in Appendix 1.

4.2.4.2 Data collection

Earlier sections have described the outcome measures and data collection procedures during the baseline, day 8 and day 35 research interviews, and as part of clinical service delivery during the initial assessment, withdrawal and post-withdrawal interventions. The schedule of data collection for each subject is shown in Table 4.8. Subjects were reimbursed (at $20 per interview) to cover the costs of participation in the research interviews on days 8 and 35.

4.2.4.3 Rates of follow-up of subjects for research interviews

A trial profile diagram is shown in Figure 4.2. 114 subjects were recruited to the study, with 58 (51%) randomised to the Experimental Group, and 56 (49%) randomised to the Control Group.

101 of the 114 subjects recruited to the study (89%) completed the day 8 research interview with the research assistant, with similar follow up rates for the two groups: 91% (53 / 58) for the Experimental Group compared to the 86% (48 / 56) for the Control group.

91 of the 114 subjects (80%) completed the day 35 research interview, with comparable follow-up rates for the two groups: 83% (43 / 58) of the Experimental group compared to the 77% (43 / 56) of the Control group.

It is generally considered that an acceptable loss to follow-up for an intention to treat analysis is in the order of up to 20 % of subjects - beyond this proportion, it is difficult to generalise and make conclusions from the available data (Sackett, Richardson et al. 1997). The follow up rates of 89% at day 8 and 80% at day 35 are adequate to enable between group comparisons on an intention-to-treat basis.

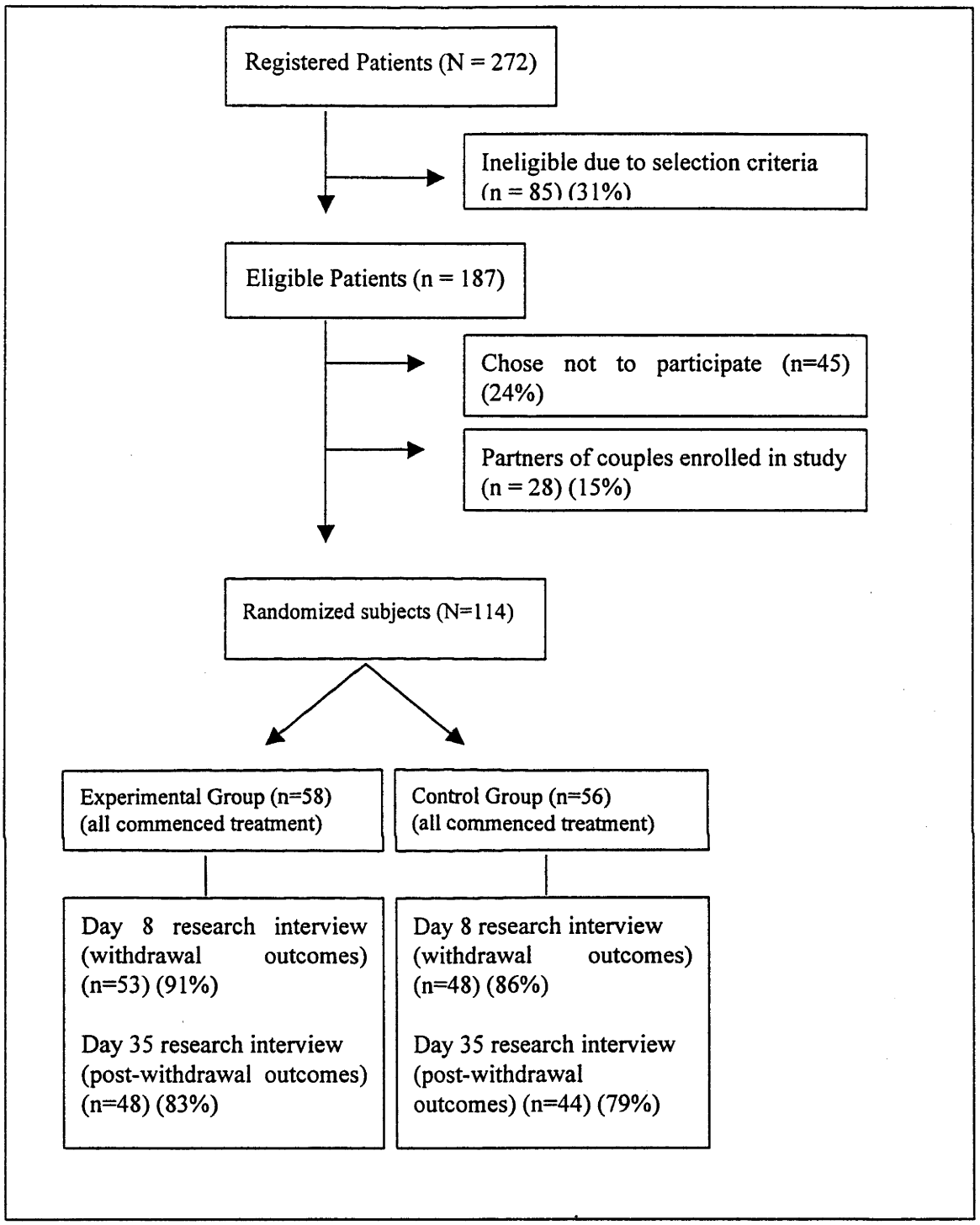

Figure 4.2. Progress of subjects through trial

Table 4.8. Summary of trial procedures for each subject

Procedure	Week 1							Week 2							Weeks 3 & 4							Week 5							Ongoing
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14								29	30	31	32	33	34	35	
Clinical admission	■																												
Research admission	■																												
Withdrawal episode (case management, counselling, data collection)	■	■	■	■	■	■	■																						
• Experimental	■	■	■	■	■																								
• Control	■	■	■	■	■	■	■																						
Informed consent & induction to post-withdrawal treatment								■	■	■																			
Post-withdrawal treatment								■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Urine drug screen	■				■			■																					
Research interview	■							■																				■	

4.2.4.4 Data handling and storage

Data collected by clinical staff as part of the delivery of study clinical services was subject to the clinic policies regarding confidentiality of clinical records. These identify that details regarding treatment and the contents of the clinical records are to remain confidential, with information provided to others only with the consent of the patient, or where there is a responsibility of duty of care (e.g. transferring treatment, management of severe adverse event). Data and information provided to research assistants was not available to clinical staff, except in one case where the research assistant had concerns regarding the safety of a subject who had expressed suicidal ideation during the baseline interview. The research assistant relayed this information to the treating staff (who assessed the patient as being at low risk of harm).

The principal investigator (NL) was involved in providing clinical services to subjects at the Turning Point site, and was responsible for all data entry and analysis. The potential for the principal investigator to have (inappropriate) access to confidential research data during the delivery of clinical services to subjects was minimised by: (a) a research assistant conducted all research interviews, (b) all information identifying the subject was removed from research files; and (c) data entry into computer data bases until the completion of treatment services.

All records of subject research data are securely stored and only available to study researchers. Information linking the subject to the research data (e.g. consent forms, follow-up forms) is securely stored separately from the remaining files, and only available to study researchers. The data will be retained for 15 years as required for studies under the Clinical Trials Notification scheme (Therapeutic Goods Administration 1991).

4.2.4.5 Data Monitoring

The project was independently monitored as part of the National Evaluation of Pharmacotherapies for Opioid Dependence coordinated by the National Drug and Alcohol Research Centre and the National Centre for Epidemiology and Population Health. Monitoring was conducted by Panacea Inc., which included an audit of all data collected for a random sample of 10 % of subjects, and confirmation of the existence of all clinical and research files.

4.2.4.6 Data Analysis

Data was entered into and analysed using SPSS for Windows 10.1 software package. Key outcomes were analysed for between-group differences on an intention-to-treat basis using Pearson chi-square tests for categorical data and Student t-tests for continuous data. Where significant differences were identified between groups for key outcomes, estimations of the effect size of the between-groups differences are presented using Numbers Needed to Treat (NNT) with 95% confidence intervals (95% CI) for categorical outcomes, and 95% CI for

difference of the means for continuous variables. Multiple regression analysis was conducted to examine for predictors of key withdrawal and post withdrawal outcomes.

4.3. Results

4.3.1 Baseline Data

This section presents baseline data for all subjects recruited, and by each randomised group to examine for differences in potential confounding variables.

4.3.1.1 Demographic characteristics of subjects

74 subjects (65%) were male, with similar proportions in each group (69% Experimental, 61% Control). Other demographic characteristics are shown in Table 4.9. There were no significant group differences with regards to these measures.

Table 4.9. Subject demographic characteristics

	Experimental (n=58)		Control (n=56)		Total (N=114)	
	n	%	n	%	n	%
Country of Birth						
Australia	52	90	42	75	94	83
Oceania	1	2	4	7	5	4
Asia	2	3	3	5	5	4
Europe	3	5	7	13	10	9
Aboriginal						
Yes	6	10	1	2	7	6
No	52	90	55	98	107	94
Highest Education Completed						
Grades 1 - 6	2	3	1	2	3	3
Grades 7 - 10	13	22	12	21	25	22
Grades 11 - 12	28	48	29	52	57	50
Completed tertiary	9	16	10	18	19	17
Missing	6	10	4	7	10	9
Marital status						
Never married	36	62	33	59	69	61
Married / defacto	14	24	15	27	29	25
Divorced / separated	6	10	6	11	12	11
Missing	1	2	2	4	3	3
Employment status						
Student	8	14	7	13	15	13
Employed (full / part time, self employed)	24	41	21	38	45	39
Unemployed / pension	26	45	28	50	54	47

Certain data was only available for the 64 subjects from the Turning Point site (see Section 4.2.1.3). Thirteen subjects (20%) reported having any children, (7 Control (22 %) and 6 (19%) Experimental subjects), although only six subjects (9%) reported currently living with their children (2 Control and 4 Experimental subjects). Participation in the study was voluntary; nevertheless, three subjects (5%) had court sentences pending, and three subjects (5%) were serving non-custodial sentences; 56 of 64 (88%) subjects reported no current legal status, and data was missing for two subjects (3%).

4.3.1.2 History of drug use and participation in drug treatment services

Significant ages regarding heroin use and study enrolment

The mean (± standard deviation) age of subjects at recruitment was 29.7 years ± 7.8 (range 18 to 49). Subjects were asked to recall the age they first used heroin and the age of first regular heroin use (Table 4.10). On average, there was a two to three year delay between first and regular heroin use, and subjects enrolled in this study on average more than six years after commencing regular heroin use. There were no significant differences between the two groups on these measures.

Table 4.10. Significant ages regarding lifetime history of heroin use

	Experimental (mean ± SD)	Control (mean ± SD)	Total (mean ± SD)
Age first used heroin	21.5 ± 5.6 (n=55)	20.4 ± 5.7 (n=51)	21.0 ± 5.7 (n=106)
Age first regular heroin use	23.6 ± 6.3 (n=54)	23.1 ± 6.4 (n=51)	23.3 ± 6.3 (n=105)
Age at study enrolment	30.1 ± 7.8 (n=58)	29.3 ± 7.8 (n=56)	29.7 ± 7.8 (N=114)

Lifetime treatment history

Subjects reported the number of times they had participated in various drug treatment modalities during their lifetime (Table 4.11). Most subjects (n=100, 88%) had prior treatment experience, with no significant between group differences. Withdrawal episodes accounted for over 60% of all prior attempts. Sixty nine percent of all withdrawal attempts had been in outpatient settings, inpatient withdrawal accounted for 29%, and 'rapid' opiate withdrawal using opioid antagonists accounted for only 2% of all withdrawal attempts (reflecting its limited availability in Australia at the time of the study).

Table 4.11. Lifetime history of drug treatment participation by randomised group

	Experimental (n=58)	Control (n=56)	Total (N=114)
All treatment modalities			
Mean ± SD	7.0 ± 8.8	6.8 ± 8.5	6.9 ± 8.6
Median	4	4	4
No prior attempt	n = 9 (16%)	n = 5 (9%)	n = 14 (12%)
Withdrawal services			
Mean ± SD	4.4 ± 6.1	4.4 ± 6.8	4.4 ± 6.4
Median	2	2	2
No prior attempt	n = 16 (28%)	n = 9 (16%)	n = 25 (22%)
Other treatment services			
Mean ± SD	2.9 ± 4.5	2.6 ± 3.3	2.8 ± 3.9
Median	1	2	1.5
No prior attempt	n=19 (33%)	n=16 (29%)	n=35 (31%)

Details regarding lifetime participation in treatment services other than withdrawal are shown in Table 4.12. Although more subjects had participated in methadone maintenance than any other treatment modality, outpatient counselling accounted for 42% of all non-withdrawal treatment episodes, methadone maintenance for 34%, other (usually 12-step self help programs) 12%, residential rehabilitation 7%, and naltrexone 4%.

Table 4.12. Proportion of subjects having ever participated in non-withdrawal treatment

Treatment modality	Experimental (n=58)		Control (n=56)		Total (N=114)	
	n	(%)	n	%	n	%
Methadone maintenance	29	(50)	27	(49)	56	(49)
Buprenorphine maintenance [a]	3	(5)	0	(0)	3	(3)
Naltrexone treatment	7	(12)	6	(11)	13	(11)
Outpatient counselling	24	(41)	22	(39)	46	(40)
Residential rehabilitation	10	(17)	6	(11)	16	(14)
Other (usually self help)	3	(5)	6	(11)	9	(8)

[a] 3 subjects had participated in a prior clinical research trial of buprenorphine maintenance in Sydney.

Treatment past 12 months

Most subjects (n=80, 70%) had participated in some form of treatment within the past 12 months. Overall, subjects reported a mean of 2.6 (± 4.0) treatment attempts in the past year (Experimental Group = 2.7 ± 4.8, Control Group = 2.5 ± 2.8, with no significant between-group

differences (t (112) = 0.37, p = 0.71). Most treatment attempts in the past year were for withdrawal (62%), outpatient counselling (17%) and methadone (10%).

Unassisted withdrawal attempts ('cold turkey')

Subjects were asked to estimate the number of times they had attempted 'cold turkey', defined as a withdrawal attempt without assistance or support from a health professional (Table 4.13). Most subjects (n=104, 91%) reported having attempted cold turkey before, with approximately two thirds (n=77, 68%) having done so within the past year.

Table 4.13 Previous attempts at unassisted withdrawal ('cold turkey')

	Experimental n = 58	Control n = 56	Total n = 112
Lifetime			
Mean ± SD	10.2 ± 16.9 [a]	6.1 ± 8.7	8.1 ± 13.6
Median	3	3	3
Range	0 - 100	0 - 50	0 - 80
Past 12 months			
Mean ± SD	2.9 ± 5.1 [b]	1.9 ± 2.5	2.4 ± 4.0
Median	1	1	1
Range	0 - 50	0 - 12	0 - 30

a: 2 subjects (each reporting 100 attempts) are excluded from calculation of the mean and SD (> 5 times SD)

b: 3 subjects (reporting 40, 50 & 50 attempts) are excluded from calculation of the mean & SD (> 5 times SD)

Several subjects reported numerous cold turkey attempts such that the distribution of the data is skewed, and the means are not representative of the majority of subjects (even with the exclusion of extreme (> 5 SD) 'outliers'). Most subjects (70%) reported 5 or less attempts at cold turkey during their lifetime, and 69% of subjects reported 2 or less attempts at cold turkey within the past year. A square root transformation of the data was performed to accommodate for the skewed distribution and to facilitate comparison between the two groups. There was no significant difference between the groups for lifetime cold turkey attempts ($t(92)=1.88$, $p> 0.05$) or for attempts within the past year ($t(87)=1.69$, $p > 0.05$).

4.3.1.3 Measures of drug use at enrolment

Heroin Use

Measures describing heroin use at baseline are presented in Table 4.14. On average, subjects reported using heroin three to four times a day (OTI Q score) on most days in the past month, spending approximately $100 per day. There were no significant group differences.

Table 4.14. Measures of heroin use at baseline by randomised group.

	Experimental (n=58) mean ± SD	Control (n=56) mean ± SD	Total (N=114) mean ± SD
Frequency / quantity measures			
Q score (OTI)	3.51 ± 2.34	3.20 ± 1.83	3.36 ± 2.10
# days used in past 28	26.3 ± 2.9	25.3 ± 4.5	25.8 ± 3.8
Average daily cost of heroin ($)	95.90 ± 71.80	100.60 ± 74.20	98.20 ± 72.70
Measures of dependence			
DSM-IV criteria (out of 7)	6.3 ± 1.0	6.4 ± 0.9	6.4 ± 0.9
Leeds Dependence Questionnaire	20.2 ± 6.0	20.4 ± 5.3	20.3 ± 5.6

Comparison of injectors and non-injectors

103 / 114 (90%) subjects reported routinely injecting heroin, with 11 subjects (10%) describing non-injecting routes (smoking in 10 / 11 cases). Four of the non-injectors were randomised to the Experimental, and seven to the Control Group ($\chi^2(1) = 1.03$, $p = 0.31$). The non-injectors were significantly younger (mean = 21.5 ± 4.2) than the injecting heroin users (mean = 30.6 ± 7.5) ($t(17.8) = 6.20$, $p < 0.001$), reported significantly more frequent heroin use (mean OTI Q score = 6.80 ± 3.78) than injectors (mean = 3.0 ± 1.44) ($t(10.3) = 3.32$, $p < 0.01$); however had similar average daily cost of heroin, LDQ scores and psychosocial functioning (BASIS-32).

Measures of other drug use

The proportion of subjects reporting the use drugs other than heroin in the preceding month is shown in Table 4.15. There were no significant differences between groups in mean OTI Q scores, or the proportions of subjects using any particular drug class. For those subjects reporting any use in the past month, the mean Q score (± SD) for alcohol use was 0.98 standard drinks (± 1.64); for cannabis 3.90 (± 5.39) at an average daily cost of $13.60 (± 16.20); and 1.44 tablets (± 2.25) for benzodiazepines. The mean daily cigarette consumption was 20 (± 10).

Table 4.15. Proportion of subjects reporting use of other drugs in the past month at intake

	Experimental (n=56)		Control (n=58)		Total (N=114)	
	n	%	n	%	n	%
Other opiates	8	14	10	18	18	16
Alcohol	27	47	26	46	53	47
Cannabis	31	53	31	55	62	54
Benzodiazepines	22	38	22	39	44	39
Amphetamines	5	9	4	7	9	8
Cocaine	5	9	3	5	8	7
Hallucinogens	2	3	2	4	4	4
Tobacco	54	93	55	98	109	96

4.3.1.4 Measures of psychosocial functioning

Details regarding employment status, marital status, and psychosocial measures of heroin dependence have been presented earlier (Section 4.3.1.1). Data was collected regarding drug use by the subject's partner, and drug use in the subject's place of accommodation, both variables thought to possibly impact upon outcomes for outpatient withdrawal (Table 4.16). There was no statistically significant difference between the groups with regard to partner's drug use status ($\chi^2(2) = 5.20$, $p = 0.074$), or for heroin use in the subject's place of residence ($\chi^2(3) = 2.38$, $p = 0.97$).

Table 4.16. Drug use status of partner and place of residence

	Experimental (n=58)		Control (n=56)		Total (N=114)	
	n	%	n	%	n	%
Partner's drug use						
No current partner	32	55	19	34	51	45
Partner does not use heroin	9	16	13	23	22	19
Partner uses heroin	17	29	24	43	41	36
Heroin use in residence						
Lives alone	7	12	6	11	13	11
Majority do not use heroin	30	52	28	50	58	51
Majority use heroin	21	36	21	37	42	37
Missing data	0	0	1	2	1	1

Psychosocial functioning in the week prior to enrolment was measured using the BASIS-32 (Eisen, Dill et al. 1994). Data for each of the five subscales and Average BASIS-32 score are shown in Table 4.17. Each subscale has a maximum score of 4.0, with lower scores signifying better functioning. There were no significant differences between the two groups.

Table 4.17. BASIS-32 scores at intake

	Experimental (n=58) mean ± SD	Control (n=56) mean ± SD	Total (N=114) mean ± SD
Relation to self / others	1.97 ± 0.92	2.02 ± 0.90	1.99 ±0.91
Depression / anxiety	2.02 ± 0.97	1.96 ± 0.87	1.99 ± 0.92
Daily living / role functioning	2.16 ± 0.93	2.14 ± 0.87	2.14 ± 0.90
Impulsive / addictive behaviour	1.29 ± 0.81	1.15 ± 0.66	1.22 ± 0.74
Psychosis	0.70 ± 0.79	0.55 ± 0.61	0.63 ± 0.71
Average	1.68 ± 0.72	1.61 ± 0.62	1.64 ± 0.67

Psychosocial functioning in the preceding month was measured using the SF-36 (Ware, Snow et al. 1993). Data for the two groups for each of the subscales is shown in Table 4.18. There were no significant between group differences. Included in this table is the percentile of the

total study sample for each subscale compared to SF -36 scores for the general adult population in the United States (Ware, Kosinski et al. 1994). The study population were performing poorly in comparison - scoring below the 30th percentile for each subscale.

Table 4.18. SF-36 scores at intake (mean± SD)

	Experimental (n=58)	Control (n=56)	Total (N=114)	Percentile
Physical functioning	82.7 ± 17.4	78.6 ± 21.3	80.7 ± 19.4	28%
Role - physical	32.3 ± 38.9	32.6 ± 37.5	32.5 ± 38.1	16%
Bodily pain	52.9 ± 26.3	53.5 ± 23.8	53.2 ± 25.0	20%
General health	49.4 ± 19.7	46.7 ± 20.3	48.1 ± 19.9	14%
Vitality	39.2 ± 17.6	36.9 ± 15.9	38.1 ± 16.8	17%
Social functioning	40.1 ± 23.4	47.1 ± 22.5	44.0 ± 23.1	12%
Role - emotional	35.1 ± 43.0	34.5 ± 40.7	34.8 ± 41.7	18%
Mental Health	51.6 ± 20.1	52.1 ± 16.5	51.8 ± 18.3	13%

4.3.1.5 Goals and expectancy regarding withdrawal treatment

'Expected withdrawal severity' was rated by subjects at intake using a 0 to 100 mm Visual Analogue Scale (0 = "no withdrawal discomfort", and 100 = "most severe withdrawal experienced"). The total sample had a mean score of 68 ± 22.7. The scores of the two groups were similar: the Control Group reported a mean of 66 ± 23, and the Experimental Group a mean of 70 ± 23 ($t(112) = 0.83$, $p = 0.41$).

Subjects rated the importance of a number of goals regarding their heroin use and treatment participation using Visual Analogue Scales with 0 = "not important" and 100 = "very important" (Table 4.19). Whilst not shown, the mean scores for the two randomised groups were similar for all measures, with no statistical differences between groups.

Almost all subjects identified that ceasing heroin use during withdrawal was a very important goal, and indeed the majority (88%) indicated that continued abstinence in the post-withdrawal period was very important for them (VAS score > 80 points). Interestingly, despite indicating abstinence as an important goal, most subjects also rated the goal of reducing their heroin use as just as important for them. A minority of subjects (28%) indicated that reducing (as opposed to stopping) their heroin use during the withdrawal episode was a low priority for them (VAS score < 40 points), and an even smaller proportion (21%) indicated that reduced heroin use in the post withdrawal period was a low priority. These results suggest that most subjects have multiple goals regarding their heroin use when approaching withdrawal services, with both abstinence and reduced use being considered important. Most subjects (81%) indicated that

participation in treatment in the post withdrawal phase was important for them (VAS score > 60).

Table 4.19. Subject ratings regarding treatment goals at intake

Level of importance (VAS Score)	To cease heroin use throughout the withdrawal episode (%)	To reduce heroin use during the withdrawal episode (%)	To participate in ongoing treatment after 8 day withdrawal episode (%)	To cease heroin use for at least 1 month after withdrawal episode (%)	To reduce heroin use for at least 1 month after withdrawal episode (%)
0 - 20	0	27	5	5	19
21 - 40	0	1	2	0	2
41 - 60	3	5	12	4	3
61 - 80	4	5	7	3	7
81 - 100	93	61	74	88	69
Mean ± SD	94 ± 9	71 ± 39	83 ± 25	89 ± 22	75 ± 37

4. 3.1.6 Baseline data by study site

The data has been thus far presented according to Control and Experiment study groups. This section will briefly review the baseline characteristics of subjects enrolled at each of the study sites (Turning Point = TP; Langton Centre = LC). Overall, subjects recruited at the two sites were remarkably similar on most measures.

There were no significant differences between the two sites regarding subject demographic characteristics or measures of psychosocial functioning. The mean age (TP mean = 29.9 ± 8.0; LC mean = 29.5 ± 7.5) and sex (64% of TP subjects and 66% of LC subjects were male) at the two sites were very similar. There were no significant differences between the two sites regarding subject's country of birth, highest educational level achieved, marital status or employment status. Subjects at each of the two sites had very similar measures of psychosocial functioning, with no significant differences regarding heroin-use status of their partner or place of residence, BASIS-32 or SF-36 scores.

One of the few areas in which there were differences between subjects at the two sites was their history of previous drug treatment. The mean number of total prior treatment episodes for subjects at the TP site was 8.0 ± 9.6, compared to 5.5 ± 7.1 times for subjects at the LC site. The TP group reported a significantly greater number of withdrawal episodes (mean = 5.7 ± 7.6) compared to the LC group (mean = 2.8 ± 3.9); representing a greater number of outpatient withdrawal episodes among TP subjects (there was no difference in prior inpatient withdrawal participation). In contrast, although not statistically significant, the LC subjects had participated in more non-withdrawal episodes (mean = 3.1 ± 4.5) than TP subjects (mean = 2.5 ± 3.5), with

more Langton Centre subjects having attempted methadone treatment (58%) and naltrexone treatment (16%) than at the TP site (42% and 8% respectively). A similar proportion of subjects (13 % at TP, 12% at LC) were presenting for their first ever treatment episode, and subjects at both sites reported a similar number of treatment attempts within the past year.

Measures of heroin use and dependence were also very similar for subjects at the two sites. TP subjects reported a mean Q score of 3.29 ± 1.74, had used heroin on average 26 days out of the past 28 at $98.52 ± 77.86 per day. LC subjects reported an average OTI Q score of 3.45 ± 2.50, using heroin on 26 of the previous 28 days at an average daily cost of $97.81 ± 66.15. Mean scores for the measures of dependence (DSM-IV and LDQ) were almost identical for subjects at the two sites. There were no significant differences regarding OTI Q scores for other drugs (alcohol, benzodiazepines, cannabis, psychostimulants) across the two sites.

The LC group had a higher mean score regarding expected severity of withdrawal (mean = 72 ± 21) compared to the TP group (mean = 65 ± 24), although the difference was not statistically significant ($t(112) = 1.83$, $p = 0.07$; 95% CI = -1 to 16). Subjects at the two sites had similar ratings regarding the importance of each of the various treatment goals.

4.3.1.7 Summary of baseline data

114 subjects were recruited at the two study sites, with 58 randomised to the Experimental condition and 56 to the Control condition. Two thirds of subjects were male, with an average age of approximately 30 years, and almost half reported no current employment or engagement in study. Most subjects (90%) were injecting heroin, spending on average approximately $100 per day, and using heroin approximately 3 to 4 times a day. Subjects enrolled in the study approximately six years (on average) after commencing regular heroin use. The majority of subjects had sought treatment several times previously, with withdrawal the most common prior treatment modality, followed by outpatient counselling and methadone maintenance treatment. 70% had sought treatment in the previous 12 months. Approximately one third of subjects had a heroin-using partner, and over one third (37%) of subjects lived in a household where the majority of other residents used heroin. Almost all subjects identified that cessation of heroin use during and after the withdrawal episode were very important goals, however, three quarters of subjects also indicated that a reduction in heroin use during (and after) the withdrawal were also important goals for them. The similar scores on most measures at baseline suggests that the two study sites recruited very similar subjects.

Importantly, there were no significant differences at baseline between the two randomised groups for any of the key variables that may impact upon treatment outcomes (confounders). To this extent, the randomisation produced two similar groups of subjects, enabling

comparisons between the randomised conditions without the concern of significant baseline differences.

4.3.2 Findings during withdrawal episode

4.3.2.1 Rates of retention in withdrawal services

Completion of the withdrawal episode was recorded for all subjects as a categorical measure, and refers to retention in treatment during the withdrawal episode, without incorporating any measure of heroin use. 50 of the 58 subjects (86%) in the Experimental group completed the withdrawal episode according to protocol, compared to 32 of 56 Control subjects (57%). A Pearson chi-square test indicates a significant difference between the two groups ($\chi^2(1) = 11.92$, $p = 0.001$). The relative risk (RR) regarding withdrawal retention is 1.5, and the Number Needed to Treat (NNT) for this outcome is 3.4 (rounded up to 4) (95% CI for NNT = 2.2 to 7.5 patients (rounded up to 3 to 8)).

Treatment retention was also recorded by the number of days that subjects remained in withdrawal treatment (Table 4.20 and Figure 4.3 on following page). This was calculated as the last day of attendance or contact with clinic staff. The Experimental group remained in withdrawal treatment for a mean of 7.3 ± 1.9 days, whereas the Control group participated for a mean of 5.6 ± 3.1 days. The differences in mean retention between the groups were statistically significant (t (91.4) = 3.59, p = 0.001, 95% CI for difference of the means = 0.8 to 2.7 days). Kaplan Meier estimates of mean retention times were compared by the Mantel-Cox log rank test, indicating a significant difference between the groups (log rank= 12.25, p = 0.0005).

Table 4.20. Retention in withdrawal treatment

Days retained in withdrawal treatment	Experimental (n=58)		Control (n=56)	
	n	%	n	%
Day 1	58	100	56	100
Day 2	55	95	42	75
Day 3	53	91	41	73
Day 4	53	91	38	68
Day 5	53	91	35	63
Day 6	51	88	34	61
Day 7	51	88	34	61
Day 8	50	86	32	57

A limitation of the study was that the participants were not blinded to the treatment condition. Consequently, it is possible that a number of subjects (particularly from the Control group) were disenchanted with the outcome of the randomisation and 'dropped out' after being

informed of their allocated treatment. Assuming this was relevant for subjects who did not attend after day 1 (and excluding their data), it is possible to recalculate the proportion of subjects completing the withdrawal episode. 42 Control subjects attended beyond day 1, with 32 (76%) of these subjects completing the withdrawal episode. 55 subjects in the Experimental group attended beyond day 1, with 50 (91%) completing the withdrawal episode. A chi - square test indicates that the differences between the two groups remains statistically significant (χ^2 (1) = 3.95, $p < 0.05$), indicating greater completion rates for subjects in the Experimental condition.

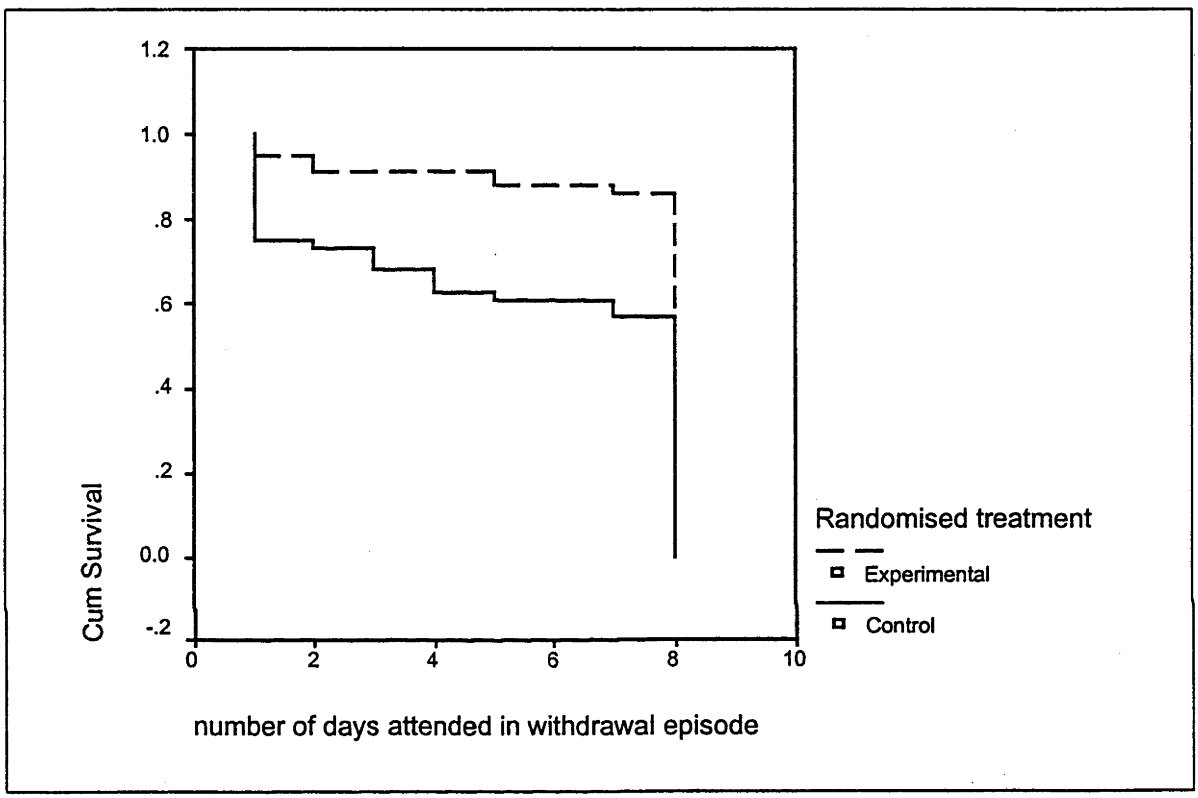

Figure 4.3 Retention in withdrawal episode by randomised group

4.3.2.2 Drug Use During Withdrawal Episode

Heroin use during the withdrawal episode was measured by self-report (independently to clinicians during treatment and to the research assistant at the day 8 interview), and by urine drug tests collected at day 5 and day 8.

Heroin use – urine drug test results

Urine drug test results can be presented several ways. Data regarding opiate urine results for subjects participating in treatment are shown in Table 4.21. Pearson chi-square tests indicate significant differences between the two groups at both day 5 (χ^2 (1) = 11.53, $p = 0.01$) and at day 8 (χ^2 (1) = 4.73, $p = 0.03$). Significantly fewer Control subjects (2/32 or 6%) were retained

in treatment and provided negative opiate urine results on both days 5 and 8; compared to 12/50 (24%) of Experimental subjects ($\chi^2(1) = 4.34$, $p < 0.05$).

Table 4.21. Opiate urine test results during withdrawal for subjects in treatment

Negative opiate urine result	Experimental	Control
Day 5	20 / 53 (38%)	2 / 35 (6%)
Day 8	17 / 50 (34%)	4 / 32 (13%)
All urines	37 / 103 (36%)	6 / 67 (9%)

As determined in the original study protocol, a 'worse-case scenario' approach for missing urine results was employed, with all missing urine specimens considered as 'positive' for opiates. Table 4.22 details the combined urine results for subjects using the 'worse case scenario' for missing data. The Experimental group had a significantly greater number of subjects remaining abstinent (day 5 and day 8 negative urines) during the withdrawal episode ($\chi^2(1) = 7.75$, $p = 0.005$; NNT = 6; 95% CI for NNT = 4 to 18). 25 Experimental subjects (43%) provided at least one negative urine result during the episode, compared to only 4 Control subjects (7%) ($\chi^2(1) = 19.4$, $p < 0.001$, NNT = 3, 95% CI for NNT= 2 to 5).

Table 4.22 Combined opiate urine drug test results

Urine opiate results	*Experimental (n=58)*	*Control (n=56)*
Both urine tests negative	12 (21%)	2 (4%)
One urine test negative	13 (22%)	2 (4%)
No urine test negative	33 (57%)	52 (93%)

Heroin use- self report

Subjects were asked about their heroin use during the withdrawal episode at the day-8 research interview. Experimental subjects (n=53) reported using heroin on significantly fewer days (mean = 2.6 ± 2.5) compared to the 48 Control group subjects completing the interview (mean = 4.5 ± 2.3 days) ($t(99) = 3.95$, $p < 0.001$, 95% CI = 1.0 to 2.5 days). From a clinical perspective, it is possible to categorise subjects' reduction in heroin during the withdrawal episode as marked reduction (using heroin on 0, 1 or 2 days during the withdrawal episode), moderate reduction (using heroin on 3, 4 or 5 days), or minor / no reduction (using heroin on 6, 7 or 8 days). Table 4.23 presents these findings. There is a statistically significant difference between the two randomised groups ($\chi^2(2) = 13.0$, $p < 0.01$). The relative risk for subjects having a marked reduction in heroin use between the two groups is 2.3, with a NNT of 2.84 (or 3) (95% CI for NNT = 2 to 6).

Table 4.23. Patterns of heroin use during the withdrawal episode

	Experimental (n=53)		Control (n=48)	
	n	(%)	n	(%)
Marked reduction in heroin use	33	(62)	13	(27)
Moderate reduction in heroin use	11	(21)	16	(33)
Minor / no reduction in heroin use	9	(17)	19	(40)

A 'worse case scenario' approach was also used to account for the 13 cases not completing the day-8 research interview. This calculation incorporated data collected by clinical staff regarding heroin use during the withdrawal episode. The number of days used was calculated as [8 - (the number of 'clean' days reported to clinical staff during the withdrawal episode)]. For example, a subject attended the clinic for 5 days, reporting no heroin use on 2 days (but then had no further clinical or research contact); the number of heroin days = (8 - 2) = 6). Findings are shown in Table 4.24. There is a significant difference between groups ($t(112) = 4.37$, $p < 0.001$, 95% CI = 1.2 to 3.1).

Table 4.24. Self report number of days used heroin during withdrawal episode

	Experimental (n=58)		Control (n=56)	
	n	(%)	n	(%)
Number of days used heroin				
0	13	(22)	2	(4)
1	6	(10)	3	(5)
2	14	(24)	8	(14)
3	7	(12)	8	(14)
4	4	(7)	4	(7)
5	2	(3)	4	(7)
6	3	(5)	2	(4)
7	4	(7)	10	(18)
8	5	(9)	15	(27)
Mean ± SD	2.9 ± 2.6		5.0 ± 2.6	
Median	2.0		5.0	

It should be noted that there was a discrepancy between the self-reported heroin use and findings from urine drug screens. 12 Experimental subjects had negative urine tests for opiates at day 5 and day 8, whilst 13 subjects reported no heroin use during the same period. The difference is accounted for by one subject who provided a day 5 urine test positive for amphetamines and morphine. On informing the subject of the positive urine result, he adamantly denied using heroin, but admitted to using 'ecstasy' early in the withdrawal episode. He brought samples of the 'ecstasy' tablets that he had used (4 different varieties) for drug

analysis. Laboratory analysis indicated that all 4 varieties of 'ecstasy' contained heroin (and amphetamines), thereby accounting for the discrepancy between self-report and urine results.

Subjects also reported in the research interview the number of occasions (rather than number of days) they had used heroin during the withdrawal episode. Results are presented in Table 4.25, with data missing for 13 subjects. As for the other measures of heroin use, there was a significant difference between the two groups ($t(99) = 2.66$, $p < 0.01$, 95% CI = 1.3 to 8.9).

Table 4.25. Number of times used heroin during the withdrawal episode

	Experimental (n = 53)	Control (n = 48)
Mean ± SD	4.6 ± 6.3	9.6 ± 12.3
Mode	0 and 2	2
Median	2	5

In order to compare the level of heroin use in the period prior to treatment (measured as an OTI Q score) and level of heroin use during the withdrawal period, data regarding number of times used during the withdrawal episode was transformed into a modified OTI Q score (modified Q score = number of times used heroin during withdrawal episode divided by 7, the number of days). Change in Q scores from baseline to day 8 was calculated as $Q_{day\ 8} - Q_{day\ 1}$. The Experimental group (n=53) had a mean change in Q score of -2.77 ± 2.33, compared to the Control group's mean change of -1.76 ± 1.63 (n=48); this difference was highly significant ($t(99) = 2.51$, $p = 0.01$, 95%CI = -0.21 to -1.82).

Severity of dependence on heroin

Severity of heroin dependence in the preceding week was assessed at day-8 using the Leeds Dependence Questionnaire (LDQ). The Control subjects (n=48) reported a mean score of 14.8 ± 7.0, whereas the Experimental subjects (n=54) reported a significantly lower mean score of 9.1 ± 6.8 ($t(100) = 4.12$, $p < 0.001$, 95% CI = 2.9 to 8.4).

Both groups had a significant reduction in their day-8 LDQ scores compared to baseline (paired t-test, $p<0.001$); however the reduction in Experimental LDQ scores (mean = -11.1 ± 6.9) was significantly greater than the Control group reduction (mean = -5.9 ± 6.2) ($t(100) = 3.94$, $p < 0.001$, 95% CI for difference of means = 2.6 to 7.8).

Use of other drugs

Subjects were asked at the day-8 interview about the use of various drugs during the withdrawal episode - the more commonly reported drugs are shown in Table 4.26. The proportion of subjects reporting any use of these drugs is comparable to the baseline reports (see Table 4.15). Chi-square tests indicate no significant differences between the groups.

Table 4.26. Proportion of subjects reporting use of other drugs during the episode

	Experimental (n=54) n (%)	Control (n=48) n (%)
Cannabis	34 (63)	26 (54)
Alcohol	24 (44)	18 (38)
Other opiates	7 (13)	8 (17)

The use of benzodiazepines is omitted from this table. All Control subjects were prescribed benzodiazepines, and 3 / 48 Control subjects (6%) also reported using additional benzodiazepines. In comparison, 7 Experimental subjects (12%) were prescribed benzodiazepines as part of the study (see Section 4.2.3.1). 17 / 54 Experimental subjects (31%) reported using (non-study) benzodiazepines during the withdrawal episode. The majority of these subjects reported using only small amounts of benzodiazepines: 5 subjects reported using only one tablet over the 8 day period, 5 reported using between 2 to 5 tablets, 3 reported using between 6 to 10 tablets, and 4 subjects reported using more than 10 tablets over the course of the withdrawal. Four of the 17 subjects reporting non-study benzodiazepines use were also prescribed benzodiazepines by the study doctors. Hence, in total, 20 Experimental subjects (34%) reported any benzodiazepine use during the episode (including study and non-study medications), with relatively low doses reported by most.

4.3.2.3 Withdrawal severity

The interpretation of withdrawal scores in an outpatient context is compromised by the use of heroin and other drugs by subjects during the withdrawal episode, and hence withdrawal severity was identified as a secondary outcome for this study. As described in Section 1.1.3, several approaches should be used to compare withdrawal severity between the two groups: daily withdrawal scores, total 'area under the curve' scores, and peak withdrawal scores.

Daily subjective withdrawal severity

There were too few Control subjects (n=2) reporting no heroin use to enable comparison of withdrawal data for 'abstinent' subjects in the two randomised groups. Hence, data was examined for subjects who described heroin use on 2 days or less (as such limited heroin use was less likely to dramatically alter the profile of withdrawal severity over the 8 day period). The mean daily SOWS scores (± SD) are shown in Table 4.27 for these 45 subjects (n = 12 Control group, n = 33 Experimental group). Student t-tests indicate that Experimental subjects scored significantly less than the Control subjects on days 4 and 5, with non-significant trends

on days 3 and 6 (which may be due to small numbers in the Control group (Type II error)). Figure 4.4 represents mean daily SOWS scores (± 95% CI) by randomised group.

Table 4.27. Daily SOWS scores for subjects reporting heroin use on 2 or less days

	Experimental mean ± SD (n)	Control mean ± SD (n)	
Day 1	16.7 ± 10.2 (32)	13.9 ± 11.4 (12)	NS
Day 2	17.5 ± 13.2 (33)	22.4 ± 11.3 (10)	NS
Day 3	14.2 ± 12.5 (32)	24.0 ± 17.9 (10)	p = 0.06, t(40) = 1.94
Day 4	10.1 ± 8.1 (33)	27.5 ± 18.3 (10)	p = 0.02, t(10) = 2.93
Day 5	7.8 ± 7.9 (31)	21.0 ± 15.7 (8)	p = 0.05, t(7.9) = 2.30
Day 6	8.5 ± 7.4 (22)	19.5 ± 15.0 (8)	p = 0.08, t(8.3) = 1.99
Day 7	8.0 ± 9.1 (25)	14.1 ± 11.3 (7)	NS
Day 8	8.7 ± 8.0 (29)	11.4 ± 11.9 (7)	NS

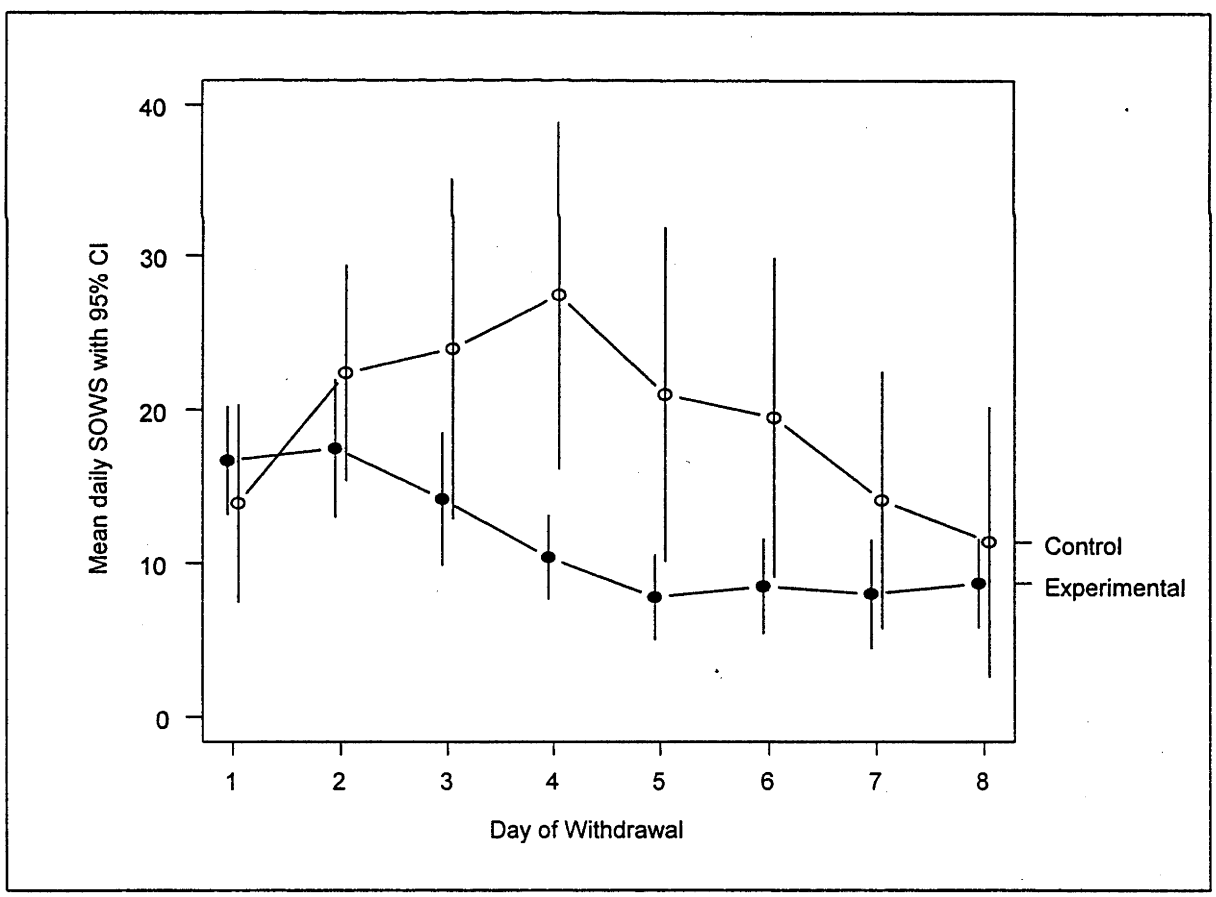

Figure 4.4 Subjective withdrawal severity by randomised group for subjects using heroin on 0,1 or 2 days during withdrawal episode (n=33 Experimental, n = 12 Control subjects).

A repeated measures analysis for those subjects reporting minimal heroin use (≤ 2 days) was conducted for those subjects with minimal heroin use. SOWS scores for days with missing data were imputed as half way between the SOWS scores of the previous and subsequent days (for example, day 4 SOWS = 20, day 5 SOWS is missing, day 6 SOWS = 12, the day 5 SOWS score was assigned a value of 16 points). The Experimental group reported significantly less total withdrawal symptoms than the Control subjects ($F = 9.17$, $p < 0.01$).

Peak withdrawal severity

Another important measure of withdrawal severity is the peak withdrawal severity reported by subjects during the withdrawal episode. For this analysis, only subjects who reported 2 or more SOWS scores after baseline (day 1) were included. The mean peak SOWS score for the Control group (n=35) was 29.7 ± 15.0, whereas the mean peak score for the Experimental group (n=53) was 19.9 ± 11.7. The peak withdrawal score was significantly lower for the Experimental group ($t(86) = 3.40$, $p = 0.001$, 95% CI = 4.0 to 15.4). The magnitude of the difference suggests this to be of clinical as well as statistical significance. The day at which peak withdrawal symptoms was reported (excluding baseline pre-treatment scores) is shown in Table 4.28, with the majority of subjects in both groups describing peak symptoms during the first 3 days of the withdrawal episode.

Table 4.28. Day of peak withdrawal severity

	Experimental (n = 53)	Control (n = 34)
Day 2	30 (57%)	10 (30%)
Day 3	6 (11%)	8 (24%)
Day 4	4 (8%)	7 (21%)
Day 5	2 (4%)	4 (12%)
Day 6	5 (9%)	1 (3%)
Day 7	5 (9%)	2 (6%)
Day 8	1 (2%)	2 (6%)
Mean ± SD	3.3 ± 1.9 days	3.8 ± 1.8 days

Rebound withdrawal in Experimental subjects

11 of 53 subjects (21%) in the Experimental group reported a peak SOWS score on days 6,7 or 8. This is after the cessation of buprenorphine and possibly indicates a degree of rebound withdrawal. The data is difficult to interpret for two subjects who used heroin on at least half of the days during the treatment episode and therefore the profile of the withdrawal syndrome for these subjects will have been altered considerably. The remaining 9 subjects (17%) reported using heroin on three days or less, and therefore the possibility of rebound withdrawal must be considered. Of these 9 cases, 5 subjects (9%) had mild rebound withdrawal severity (≤5 point

increase in SOWS score compared to scores from days 2 to 5) and/or transient withdrawal (resolution of peak severity by day 8). In four cases (of 53 subjects, or 8%) moderate rebound withdrawal was experienced (increase in SOWS >5 points compared to day 2 to day 5 scores), or SOWS scores remained elevated at day 8.

Global subject ratings of withdrawal severity

Another approach in estimating withdrawal severity employed a more global measure at the day-8 research interview in order to include the experience of those individuals who continued to use heroin. Subjects rated the general withdrawal discomfort experienced using a 0 to 100 VAS, with 0 = no withdrawal discomfort, and 100 = most severe withdrawal discomfort ever experienced. The Control group (n=44) reported a mean score of 63 ± 26, significantly higher than the Experimental (n=54) mean of 32 ± 28, ($t(96)= 5.65$, $p < 0.001$, 95% CI = 20 to 42).

4.3.2.4 Adverse events

Adverse events (Table 4.29) were reported daily by subjects during the withdrawal episode, and assessed by the treating clinician. Excluded from the Table are symptoms that were assessed as clearly being part of the underlying withdrawal syndrome (for example, withdrawal symptoms considered by the subject as being usual or typical for them in both severity and onset), or adverse events considered to be definitely unrelated to the medication or the condition being treated. Data was missing for 13 Control and 3 Experimental subjects who did not attend clinical appointments beyond the first day.

Table 4.29. Adverse events during withdrawal episode

Adverse event	Experimental (n=55)	Control (n=43)
Headache	15 (27%)	2 (5%)
Precipitated withdrawal symptoms	7 (13%)	-
Nausea	5 (9%)	-
Sweating	5 (9%)	-
Drowsiness	4 (7%)	6 (14%)
Vomiting	3 (5%)	-
Lethargy / tiredness	3 (5%)	12 (28%)
Paraesthesia / sensory disturbances	3 (5%)	-
Dry mouth	2 (4%)	7 (16%)
Significant rebound withdrawal on ceasing medication	2 (4%)	-
Constipation	2 (4%)	-
Significant mood disturbance (agitation, dysphoria)	2 (4%)	3 (7%)
Light-headed / dizziness / hypotension	1 (2%)	15 (35%)
Sleep disturbance	-	3 (7%)
Other (each reported by one subject only)	6 (11%)	2 (5%)
None reported	16 (29%)	13 (30%)

Similar proportions of subjects in each group reported no adverse events. The profile of adverse events reported in each group is consistent with previous reports for these medications: the Control subjects predominantly complained of anticipated side effects to clonidine (lethargy, light headedness, dry mouth, drowsiness) (Washton and Resnick 1981). The subjects receiving buprenorphine predominantly complained of headache, nausea, sweating and drowsiness, typically following the first few doses of buprenorphine, and subsiding thereafter.

Seven Experimental subjects (13%) reported some degree of precipitated withdrawal upon commencement of buprenorphine. This was despite efforts to ensure that subjects were not given a dose of buprenorphine within 6 hours of recent heroin use (see Section 2.3.1). In most cases the precipitated withdrawal was mild in severity, and of short duration (up to six hours). Only one case of precipitated withdrawal was of sufficient severity to warrant management with ancillary medications (clonidine, metoclopramide and diazepam). One subject continued to use heroin throughout the withdrawal episode and continued to experience a degree of precipitated withdrawal following each buprenorphine dose, resulting in the subject refusing buprenorphine doses on days 4 and 5. Two subjects who experienced precipitated withdrawal were subsequently administered split doses of buprenorphine on the following day as a precaution (i.e., a small dose was administered in the morning and the subject presented four hours later for the remainder of the day's dose).

4.3.2.5 Measures of psychosocial functioning

The BASIS-32 was administered at day 8 to assess various aspects of psychosocial functioning during the course of the one-week withdrawal episode (Table 4.30). Whereas subjects from the two groups reported similar BASIS-32 scores at baseline, the subjects in the Experimental group reported a significantly higher level of psychosocial functioning (lower scores) during the withdrawal episode for the combined Average score, and for all subscales with the exception of the Psychosis subscale.

Table 4.30. BASIS-32 scores at day-8 by randomised group

	Experimental (n=53) mean ± SD	Control (n=48) mean ± SD	
Relation to self / others	1.21 ± 0.81	1.76 ± 0.88	p=0.001, t(100)=3.28, 95%CI =0.22 to 0.8
Depression / anxiety	1.15 ± 0.72	1.89 ± 0.92	p<0.001, t(89)=4.50, 95%CI = 0.41 to 1.0
Daily living / role functioning	1.32 ± 0.81	1.92 ± 0.95	p=0.001, t(100)=3.44, 95%CI= 0.25 to 0.9
Impulsive / addictive behaviour	0.65 ± 0.59	0.94 ± 0.55	p< 0.05, t(100)=2.54, 95%CI = 0.06 to 0.5
Psychosis	0.31 ± 0.45	0.45 ± 0.51	NS
Average	0.96 ± 0.56	1.45 ± 0.66	p<0.001, t(100)=3.98, 95%CI= 0.24 to 0.7

Within-subject change in BASIS-32 scores was assessed for the Average and the five subscales (BASIS score $_{day\ 8}$ - BASIS score $_{day\ 1}$). The Experimental group had a significantly greater reduction in BASIS Average score, Depression, Addiction and Daily Living subscales ($p<0.01$), and Relationship and Psychosis subscales ($p<0.05$), compared to the Control group.

4.3.2.6 Measures of patient satisfaction

The adequacy of medication dosing regimes can influence treatment outcomes. To examine for this potential confounder, subjects were asked at the day-8 research interview to rate the adequacy of the doses of medication prescribed during the withdrawal regime using a 1 to 5 Likert scale (see Appendix 1). Findings are presented in Table 4.31. Most subjects in both groups indicated that their doses had been 'about right', although approximately one quarter of subjects indicated that their dose had been inadequate. There were no significant differences between groups on this measure.

Table 4.31. Ratings of dose adequacy of withdrawal medications.

	Experimental (n=53) n (%)	Control (n=44) n (%)
Much too low = 1	4 (8)	3 (7)
Too low = 2	10 (19)	9 (20)
About right = 3	38 (72)	31 (70)
Too high = 4	1 (2)	1 (2)
Much too high = 5	0	0

General satisfaction with the withdrawal medication was elicited at the day-8 research interview using a Visual Analogue Scale, with 0 = 'not satisfied' and 100 = 'very satisfied'. The mean score for the Control group (n=46) was 36 ± 31, whereas the mean score for the Experimental Group (n=54) was 81 ± 24, representing a statistically significant difference between the groups ($t(98) = 8.26$, $p < 0.001$, 95% CI = 34 to 56).

Subjects were asked in an open-ended question to identify the 'good' or 'positive' aspects and the 'bad' or 'negative' aspects associated with their prescribed medication. Common positives regarding buprenorphine included: the alleviation of withdrawal discomfort (reported by 91% of subjects), reduction of cravings (51%), enabling subjects to function with normal daily activities (28%), improved sleep (19%) and the ability to remain 'clear headed' during the withdrawal (13%). Less common positives included the 'blocking' of the effects of heroin use (6%) and the convenience of the dosing regime (6%). The more common negative aspects included: side effects (25%) and taste of the medication (13%), whilst only a small proportion reported that buprenorphine did not adequately relieve withdrawal discomfort (6%),

precipitated withdrawal (4%) or described significant rebound withdrawal following its cessation (9% - a similar proportion as identified earlier in Section 4.3.2.3).

Positive aspects reported by subjects using symptomatic medication included: reduction in withdrawal discomfort (57%), improved sleep (20%), reduction in cravings (13%), heavy sedation (as a positive - 9%), and the avoidance of a prolonged withdrawal (7%). Negative aspects regarding symptomatic medication included: heavy sedation (56%), other side effects (43%), inadequate relief of withdrawal symptoms (28%); and poor daily functioning (15%).

21 of 48 Control subjects (44%) indicated that they would use symptomatic medication again if required for heroin withdrawal, 15 (31%) indicated they would not, and 12 (25%) were undecided. In comparison, 52 of the 54 Experimental subjects (96%) indicated that they would use buprenorphine again, one subject (2%) responded negatively, and one (2%) was undecided. There was a significantly different distribution of responses between the two groups ($\chi^2(2) = 34.49$, $p < 0.001$).

Another measure of treatment satisfaction included subjects rating the extent to which they had achieved the goals they had identified at the outset of the withdrawal episode. Experimental subjects (n=54) reported a significantly higher degree of goal attainment (mean = 66 ± 28) than Control subjects (n = 47, mean = 41 ± 29) ($t(99) = 4.47$, $p < 0.001$, 95% CI = 14 to 36).

4.3.2.7 Cost effectiveness of withdrawal interventions

Cost effectiveness was determined by comparing the incremental cost of all health services utilised during the withdrawal episode, against measures of withdrawal outcome, on an intention-to-treat basis.

Calculation of incremental health costs during the withdrawal episode

The cost of all health services utilised during the withdrawal episode includes services related and unrelated to the withdrawal episode. These were calculated as follows:

> Costs related to withdrawal episode = Trial staffing costs + Trial medication costs + Cost of other health services (related to withdrawal) + Cost of other medications (related to withdrawal)
>
> Costs unrelated to withdrawal = Cost of other services (not related to withdrawal) + Cost of other medications (not related to withdrawal)

A prospective record was maintained of all contacts (following randomisation and recruitment to the study) between trial clinicians and subjects during the withdrawal episode. A comparison of the mean number of clinical contacts and total contact time with each profession is presented

in the Table 4.32[2]. Subjects in the Experimental group had a significantly greater number of overall clinical contacts, and in particular nursing contacts, however utilised less pharmacist time than the Control group subjects.

Trial staff costs were calculated for each subject according to the following formula:

> [Total contact hours $_{\text{medical staff}}$ x average hourly cost $_{\text{medical staff}}$] + [Total contact hours $_{\text{nursing staff}}$ x average hourly cost $_{\text{nursing staff}}$] + [Total contact hours $_{\text{pharmacists}}$ x average hourly cost $_{\text{pharmacists}}$] + [Total contact hours $_{\text{other staff}}$ x average hourly cost $_{\text{other staff}}$]

Oncosts were estimated at approximately 16% of salaries. The mean hourly rate for each professional group at the two sites is provided in Appendix 2.

Table 4.32. Clinical contacts by randomised group for all subjects

	Experimental (n = 58) Mean ± SD	Control (n = 56) Mean ± SD	
Medical staff			
number of contacts	3.5 ± 2.1	3.0 ± 2.0	NS
total time (min)	62 ± 51	56 ± 50	NS
Nursing staff			
number of contacts	3.6 ± 2.7	2.4 ± 2.3	$p < 0.05$ ($t(85.5) = 2.54$)
total time (min)	62 ± 57	40 ± 42	$p < 0.05$ ($t(105.1) = 2.43$)
Pharmacists			
number of contacts	3.1 ± 2.1	3.1 ± 2.5	NS
total time (min)	19 ± 15	29 ± 27	$p < 0.05$ ($t(85.5) = 2.54$)
Other staff			
number of contacts	2.0 ± 0	1.0 ± 0	NS
total time (min)	50 ± 10 (n = 2)	28 ± 8 (n=4)	NS
All clinical staff			
number of contacts	10.3 ± 2.9	8.6 ± 4.9	$p < 0.05$ ($t(88.3) = 2.29$) 95% CI = 0.2 to 3.2

Details regarding trial medications administered during the withdrawal episode were collected from clinical records and were presented in Section 4.2.3.1. Costs for all medications were assigned at pharmacy wholesale prices as at April 1999 (Schedule of Pharmaceutical Benefits, April 1999), with the exception of buprenorphine, which was not registered at the time of the

[2] Note: Table 4.32 describes contacts for all subjects enrolled in the study for calculating total costs. This is in contrast to Table 4.6, which only included data for those subjects who attended 2 or more days during the withdrawal episode (n=97).

study. The wholesale price of buprenorphine (2 mg Subutex®) in Australia was provided by Reckitt & Benkiser at $1.54 per 2 mg tablet (personal communication, August 2000).

Details regarding the utilisation of health services and medications from other service providers (not from study sites) were ascertained at the day-8 research interview, including whether services were related or unrelated to the withdrawal episode (from subject's perspective). Data was available for 100 subjects (46 in Control group, 54 in Experimental group). The majority of subjects did not utilise medications or services outside of the study (see Table 4.33). The health services related to the withdrawal episode were consultations with general practitioners (5 subjects), counsellors (2 subjects) and other health professionals (acupuncture, masseuse) by 3 subjects. There were no significant differences between groups in the number of subjects utilising external services.

Medications used outside of the study were costed in the same manner as described for trial medications. The Centre for Economic Health Evaluation provided estimates for the cost of health services utilised outside of the study (see Appendix 2 for details).

Table 4.33. Utilisation of external health services during the withdrawal period

	Experimental (n=54) n (%)	Control (n= 46) n (%)
Related to withdrawal episode		
Number subjects using other health services	3 (6)	7 (15)
Number subjects using other medications	7 (13)	4 (9)
Not related to withdrawal episode		
Number subjects using other health services	4 (7)	3 (7)
Number subjects using other medications	4 (7)	5 (11)

The costs of health services incurred during the withdrawal episode are shown in Table 4.34 for the two randomised groups. There were no significant differences between the two randomised groups with regards to the cost of health services related to the withdrawal episode, nor for the total cost of all health services utilised during the withdrawal episode. The only item which was significantly different between the two randomised groups was the cost of the trial withdrawal medications, with the Experimental group having a significantly greater cost than the Control group ($t(112) = 8.52$, $p < 0.001$).

Table 4.34. Cost of all health services utilised during the withdrawal episode.

	Experimental Group (mean ± SD)	Control Group (mean ± SD)
Costs related to withdrawal episode		
Trial staffing costs [a]	$75.55 ± 33.32	$66.99 ± 41.71
Trial medication costs [a]	$26.85 ± 9.80	$11.94 ± 8.84
Other medications	$0.59 ± 3.37	$0.13 ± 0.83
Other health services	$4.82 ± 26.51	$13.75 ± 60.55
Total related costs	*$110.48 ± 47.07*	*$101.36 ± 76.25*
Costs not related to withdrawal episode		
Other medications	$0.26 ± 1.25	$0.90 ± 3.40
Other health services	$3.96 ± 16.78	$7.07 ± 26.26
Total unrelated costs	*$4.22 ± 16.77*	*$7.97 ± 26.71*
Total cost of health services provided during withdrawal episode	*$114.70 ± 48.78*	*$109.33 ± 83.70*

[a] data available for all 114 subjects. Data on other variables are restricted to those subjects (n=100, 88%) completing day-8 research interview

Cost effectiveness

Two outcomes for outpatient withdrawal services were considered to be most relevant for a cost effectiveness analysis:

(i) The number heroin-free of days achieved during the withdrawal episode, in which cost effectiveness for the withdrawal episode was calculated for each subject using the equation:

Cost effectiveness = total (incremental) cost of health services / number heroin free days[3]

Using this equation, the mean incremental cost for subjects to achieve one heroin-free day for the Experimental group (n=53) was $30.03 ± 32.14, and for the Control group (n=46) was $52.47 ± 72.14, which can be interpreted as the Experimental condition achieves on average, 1.75 times more heroin free days for the same cost. Statistical comparison between the two groups indicates this to be a non-significant trend (t(58.4) = 1.84, p = 0.07, 95% CI = -$1.98 to $46.85). Given that this data is not distributed normally, the non-parametric tests comparing the two groups indicates a non-significant difference (Mann Whitney U = 992, p = 0.11).

[3] Subjects reporting no heroin-free days during the withdrawal episode were assigned a value of 1 heroin-free day in order to avoid zero as a denominator.

(ii) The proportion of subjects completing the withdrawal episode with no heroin use. Cost effectiveness with this outcome was calculated as:

> Cost effectiveness per group = total (incremental) cost of health services for all subjects in group / proportion completing the withdrawal episode with no heroin use

With this outcome measure, the cost to achieve one completed withdrawal episode without heroin use was $554.10 for the Experimental condition, and $3,036.94 for the Control condition, representing a incremental cost effectiveness ratio of 5.48 (Experimental) to 1 (Control).

4.3.2.8 Predictors of withdrawal outcomes

Multiple regression analysis was conducted to examine which subject variables at baseline were independently related to the two primary short-term withdrawal outcomes: days used heroin during withdrawal episode, and number of days retained in withdrawal treatment. Given the significant impact of the randomised treatment condition upon the withdrawal outcomes, regression analysis was conducted separately for the Experimental group and Control groups. The baseline characteristics initially entered into the univariate regression analysis were: sex (dummy variable); age; years since commenced regular heroin use; number of prior treatment attempts; partner's heroin use (dummy variable); route of administration (dummy variable); average daily cost of heroin in past 4 weeks; number of days used heroin in past 4 weeks; heroin OTI Q score; Leeds Dependence Questionnaire; BASIS Average score; alcohol Q score; cannabis Q score; tranquilliser Q score; expectancy regarding severity of withdrawal; and treatment goals at intake. Stepwise backwards regression was employed, with non-significant variables removed sequentially from the equation until the removal of variables considerably reduced R^2.

Three intake variables were significant predictors of the number of days heroin was used during the withdrawal episode by the Experimental subjects ($R^2 = 0.36$): age at entry to study ($F = 7.41$, $p < 0.01$), average daily cost of heroin use in preceding 4 weeks ($F = 6.02$, $p < 0.05$), and having a heroin-using partner ($F = 4.95$, $p < 0.05$). The only significant predictors of heroin use during withdrawal for the Control subjects ($R^2 = 0.44$) were average daily cost of heroin use in preceding 4 weeks ($F = 6.95$, $p < 0.05$), and severity of dependence on heroin ($F = 6.37$, $p < 0.05$).

Regression analysis was also conducted with the number of days retained in withdrawal treatment as the dependent variable. Increased severity of dependence on heroin (LDQ) at baseline ($F=7.63$, $p < 0.01$) and general psychosocial dysfunction (BASIS-32 Average) ($F =$

4.58, $p < 0.05$) were significant predictors of increased duration in withdrawal treatment for the Experimental subjects ($R^2 = 0.33$). Intake OTI heroin Q score was the only significant variable ($F = 5.10$, $p < 0.05$) for the Control group ($R^2 = 0.35$).

4.3.2.9 Comparison of withdrawal outcomes by site

A similar pattern of withdrawal outcomes was replicated at each of the two study sites. There was a significant difference between the two sites in that a greater proportion of all Turning Point subjects completed the withdrawal regime (51 / 64 or 80%) than at the Langton Centre (31 / 50 or 62%) (χ^2 (1) = 4.35, $p < 0.05$). The Experimental group had a significantly ($p<0.05$) greater rate of completion than the Control group at each site.

Levels of heroin use during the withdrawal episode were very similar across the two sites, with no significant differences between sites. A significantly greater proportion of Experimental subjects had an opiate negative urine test than Control subjects within each site, and the Experimental group reported using heroin on significantly fewer days than the Control group ($p < 0.01$). A similar pattern was seen regarding other treatment outcomes, with the Experimental group at each site reporting significantly lower severity of dependence ($p < 0.05$), lower global withdrawal symptom severity ($p<0.01$), and higher subject-rated global medication satisfaction scores ($p<0.01$).

4.3.2.10 Summary of findings during withdrawal episode

Subjects from both randomised groups described significant reductions in their heroin use during the withdrawal episode. Whereas subjects reported using heroin (on average) 3 to 4 times a day prior to enrolment, the mean level of heroin use during the withdrawal episode was approximately once a day. Similarly, subjects reported significant improvements in measures of dependence and psychosocial functioning during the withdrawal episode compared to baseline.

The primary short-term outcomes for outpatient withdrawal services (reduction in heroin use and retention in withdrawal treatment) were significantly enhanced for the Experimental subjects compared to the Control subjects. The extent of the difference between the groups was considerable, with small Numbers Needed to Treat, suggesting a clinical as well as a statistical advantage in using buprenorphine during withdrawal.

The study examined incremental cost effectiveness (and did not include overhead expenses similar to both groups). The cost of delivering health services for subjects during the withdrawal episode was similar for both groups. When considering heroin-free days during the withdrawal episode as the primary treatment outcome, the Experimental condition achieved

1.75 times more heroin-free days for the same cost as the Control condition, although this was not statistically significant (p = 0.07, 95% CI for difference of means = -$1.98 to $46.85). The incremental cost-effectiveness ratio for the outcome of 'completing withdrawal without heroin use' was 5.5 to 1.

Secondary short-term outcomes were also enhanced for the Experimental group. Despite the difficulties in interpreting withdrawal severity scores during outpatient withdrawal, the available data suggests that Experimental subjects experienced less severe withdrawal symptoms than Control subjects. The peak withdrawal severity for subjects in both groups was generally described early in the withdrawal episode (prior to the day 3 dose for most subjects). A minority of Experimental subjects described peak withdrawal symptoms in the days following the cessation of buprenorphine: five subjects (9%) had mild and transient rebound withdrawal symptoms, and four subjects (8%) described moderate or persistent rebound withdrawal.

Measures of psychosocial functioning (BASIS-32 and severity of dependence) indicated significantly better levels of functioning during the withdrawal episode among the Experimental group. There were significantly higher levels of satisfaction with the withdrawal medication reported by the Experimental subjects. Adverse events were generally anticipated for the study medications. A similar proportion of subjects from both groups reported no adverse events, with no severe adverse events during the withdrawal episodes.

4.3.3 Post-Withdrawal Outcomes

4.3.3.1 Participation in post withdrawal treatment services

The principal outcome in the post-withdrawal period was the extent to which subjects participated in treatment services, serving as a measure of the capacity for withdrawal services to facilitate linkages to ongoing treatment. The number of subjects entering and being retained in post-withdrawal treatment at day 35 for the two groups is shown in Table 4.35. There was a significant difference in the distribution of subjects from the two groups ($\chi^2(2)= 6.10$, $p<0.05$)[4].

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[4] 22 subjects (10 Experimental, 12 Control) did not complete day 35 research interviews and hence complete data regarding post-withdrawal treatment is missing. Clinic records and jurisidictional records regarding state-wide methadone treatment were reviewed for these subjects and evidence of ongoing treatment is included in this table; however, it is possible that some subjects entered other forms of treatment elsewhere. The data presented has used a 'worse case scenario' and assigned 'missing data' as having not participated in treatment.

Table 4.35: Summary of post-withdrawal treatment participation by randomised group.

	Experimental (n=58)	*Control (n=56)*	*Total (N=114)*
Subject did not enter any treatment	11 (19%)	19 (34%)	30 (26%)
Subject entered treatment but not retained in treatment at day 35	11 (19%)	15 (27%)	26 (23%)
Subject in treatment at day 35	36 (62%)	22 (39%)	58 (51%)

A high proportion of subjects from both groups participated in some form of treatment in the post withdrawal period (66% of Control and 81% of Experimental group, $\chi^2(1) = 2.80$, p= 0.09). A significantly higher proportion of Experimental subjects were retained in some form of treatment at day 35 compared to Control subjects ($\chi^2(1) = 5.50$, $p < 0.05$, NNT = 4.4 or 5, 95% CI for NNT = 3 to 25).

The Experimental subjects participated in treatment for significantly more days in the 28-day post-withdrawal interval (mean = 19.0 ± 11.2) compared to the Control group (11.0 ± 11.0) ($t(112) = 3.83$, $p < 0.001$, 95% CI = 3.8 to 12.1).

Table 4.36 examines the patterns of participation in different treatment modalities during the post-withdrawal period. Approximately a third of the Control subjects (36%) attempted another withdrawal episode during the 4-week follow up period. These were predominantly outpatient withdrawal or 'cold turkey' attempts, although two subjects did report attempting rapid opioid withdrawal with naltrexone at a private clinic. Few Experimental subjects (3%) attempted another withdrawal episode.

Table 4.36 Participation in treatment modalities in the post-withdrawal period

	Experimental (n=58)		Control (n=56)	
	Entered	In treatment at day 35	Entered	In treatment at day 35
Withdrawal treatment	2 (3%)	0	20 (36%)	3 (5%)
Outpatient	1	0	11	2
Residential	0	0	3	0
'Cold turkey'	2	0	8	1
Substitution treatment	39 (67%)	30 (52%)	20 (36%)	15 (27%)
Methadone	5	5	20	15
Buprenorphine	34	25	N/A	N/A
Naltrexone treatment	9 (16%)	3 (5%)	7 (13%)	5 (9%)
Outpatient counselling	5 (9%)	5 (9%)	2 (4%)	0
Other	0	0	1 (2%)	0

Significantly more Experimental subjects entered substitution treatment in the post-withdrawal period ($\chi^2(1) = 11.3$, $p < 0.005$) and significantly more were in substitution treatment at day 35 ($\chi^2(1) = 7.42$, $p < 0.01$) compared to Control subjects. The high proportion of Experimental subjects who continued with buprenorphine treatment may be related to the high levels of patient satisfaction with buprenorphine as a medication, but may also be related to the limited availability of buprenorphine outside of the study. The rate of retention in substitution treatment at day 35 was similar in both groups (75% of Control and 77 % of Experimental subjects who entered substitution treatment were still in treatment at day 35). Retention rates were similar for subjects entering methadone (20/25, 80%) and buprenorphine (25/34, 74%).

Similar proportions attempted naltrexone treatment (13% of Control subjects, 16% of Experimental subjects). 5 / 7 (71%) Control subjects who commenced naltrexone were still in treatment at day 35, compared 3 / 9 (33%) of Experimental subjects (statistically not significant). The Experimental subjects generally commenced naltrexone earlier in the follow up period: 7 Experimental subjects and only 2 Control subjects initiated naltrexone treatment under trial conditions by day 11 of the study, which may account for the different proportions in naltrexone treatment at day 35.

4.3.3.2 Post-withdrawal outcomes by randomised group (intention to treat)

The various post-withdrawal outcome measures are reported and analysed in this section for the total sample and by randomised group on an intention-to-treat basis. It should be emphasised that participation in treatment in the post-withdrawal period was self-selected by subjects, and the outcomes at day 35 may be related to a range of factors in the post-withdrawal period (such as the efficacy of any treatment program in which the subject is engaged in), and cannot be entirely attributed to the impact of the withdrawal episode.

Heroin Use

Measures of heroin use (modified OTI and Leeds Dependence Questionnaire) at the day-35 interview are shown in Table 4.37. There was considerable individual variation in heroin use, and hence the data regarding frequency of use is presented in categories to assist interpretation.

Overall, subjects from the Experimental group reported significantly less heroin use in the past month than Control subjects as measured by the OTI Q score ($t(89) = 2.48$, $p < 0.02$, 95% CI = 0.11 to 0.96), and the number of days used heroin ($t(89) = 2.94$, $p < 0.01$, 95%CI = 1.8 to 9.4 days). There was a non-significant trend for severity of dependence (LDQ) ($t(90) = 1.95$, $p = 0.054$, 95% CI = -0.1 to 6.4).

Table 4.37. Measures of heroin use in post-withdrawal period by randomised group

	Experimental (n=58) n (%)	Control (n =56) n (%)	Total (n=114) n (%)
Q score for heroin (OTI)			
0	5 (9)	1 (2)	6 (5)
0.04 (used once only)	4 (7)	3 (5)	7 (6)
0.05 - 0.14 (< than weekly)	11 (19)	4 (7)	15 (13)
0.15 - 0.99 (less than daily)	15 (26)	13 (23)	28 (25)
1.0 or more (daily)	14 (24)	23 (41)	37 (35)
Missing	9 (16)	12 (21)	21(18)
Mean ± SD [a, b]	0.68 ± 0.92	1.21 ± 1.13	0.93 ± 1.05
Median Q score [a]	0.38	1.0	0.50
# days used in past 28 days			
0	5 (9)	1 (2)	6 (5)
1 - 7	22 (38)	13 (23)	35 (31)
8 - 14	8 (14)	8 (14)	16 (14)
14 - 21	8 (14)	9 (16)	17 (15)
21 - 28	4 (7)	12 (21)	16 (14)
Missing	9 (16)	12 (21)	21 (18)
Mean ± SD [a]	9.0 ± 8.2	14.6 ±10.0	11.6 ± 9.5
Average daily cost of heroin mean ± SD ($)[a]	50.91 ± 41.77	53.21 ± 66.18	52.03 ± 54.74
Mean LDQ score ± SD [a]	9.6 ± 7.4	12.8 ± 8.1	11.1 ± 7.8

[a] Mean and median scores for 93 subjects with complete data (49 Experimental and 44 Control group)

[b] Two outliers are excluded from this analysis: (1 Control, Q = 10.0) & (1 Experimental, Q = 20.0)

Within-subject changes in heroin use between day 35 and day 8 were examined for both heroin OTI Q ($Q_{day\ 35} - Q_{day8}$) and LDQ scores ($LDQ_{day\ 35} - LDQ_{day\ 8}$). These findings indicate that the main reductions in OTI Q and LDQ scores had occurred in the initial withdrawal period for most subjects, and these changes had generally been sustained over the follow up period. Overall there was little change in Heroin Q scores from day 8 to day 35 for either group (Experimental mean = -0.01 ± 0.88; Control mean = 0.10 ± 1.13), with no significant between group differences, although some subjects made considerable changes as suggested by the large standard deviations Similarly, there was minimal within-subject change in severity of dependence from day 8 to 35 (Experimental mean = 0.8 ± 6.9; Control mean = -.9 ± 8.1), with no significant between group differences.

The average daily cost of heroin for those subjects reporting heroin use in the follow up period was compared to their reported average cost at baseline. There was a significant reduction in

the average daily cost of heroin use (paired t-test, t (84) = 6.83, p <0.001), with similar reductions reported by subjects in both groups.

Other Drug Use

The proportion of subjects reporting use of other drugs in the preceding 4 weeks (as measured at the day 35 interview with the OTI), are shown in Table 4.38. Data was missing for 22 subjects.

Table 4.38. Use of other drugs in the post-withdrawal period

	Experimental (n=48)		Control (n=44)		Total (n=92)	
	n	(%)	n	(%)	n	(%)
Other opiates	4	(8)	5	(11)	9	(10)
Alcohol	32	(67)	22	(50)	54	(59)
Cannabis	32	(67)	26	(59)	58	(63)
Benzodiazepines	12	(25)	13	(30)	25	(27)
Amphetamines	0	(0)	3	(7)	3	(3)
Cocaine	4	(8)	2	(5)	6	(7)
Hallucinogens	6	(13)	4	(9)	10	(11)
Tobacco	43	(90)	42	(95)	85	(92)

There were no significant between-group differences in the OTI Q scores, nor in the proportion of subjects using these drugs. Cannabis consumption remained high, with 63% of individuals reporting some use in the preceding month, compared to 54% at baseline. There was considerable variation in the Q scores for cannabis, with several subjects reporting scores of greater than 10. The mean Q score for those individuals using cannabis was 4.35 ± 7.18 (median = 1.63, maximum = 40).

A similar proportion (59%) reported some alcohol use in the preceding month, although most individuals using alcohol reported moderate consumption levels (mean = 1.1 standard drinks ± 1.8, median = 0.4, maximum = 11). At baseline, 47% of subjects had reported any alcohol use in the preceding month (see section 4.3.1.3, Table 4.15). Fewer subjects reported using benzodiazepines (27%) compared to baseline (39%). Benzodiazepine users reported a mean OTI Q score of 1.0 ± 1.2 (median = 0.5, maximum = 4). Tobacco use remained high, with 92% smoking at the mean rate of 17 ± 10 cigarettes per day.

Paired t-tests compared OTI Q scores for alcohol, cannabis and tranquillisers at day 35 with baseline (day 1) scores. The Experimental group reported a statistically significant increase in alcohol Q scores ($t(47)=2.90$, $p < 0.01$), but no significant changes in cannabis or tranquilliser scores. However, the extent of the increased mean Q score for alcohol consumption over this

time corresponds to 0.27 standards drinks of alcohol per day, and is unlikely to be of major clinical significance. The Control group reported no significant changes in Q scores for these drug classes over the study period.

Measures of Psychosocial Functioning

Psychosocial functioning was measured using the BASIS-32 (preceding week) and SF-36 (preceding month) at day 35. Results are shown in following Tables.

Table 4.39. BASIS scores at day 35 by randomised group

	Experimental (n=48) mean ± SD	Control (n=44) mean ± SD
Relation to self / others	1.23 ± 0.78	1.35 ± 0.90
Depression / anxiety	1.11 ± 0.82	1.36 ± 0.83
Daily living / role functioning	1.24 ± 0.84	1.44 ± 0.92
Impulsive / addictive behaviour	0.73 ± 0.56	0.73 ± 0.58
Psychosis	0.32 ± 0.41	0.31 ± 0.42
Total Average	0.96 ± 0.59	1.08 ± 0.66

Although the Experimental group had lower mean scores (signifying better functioning) for most subscales and for the global Average score, the differences between the two groups were not significant for any of the measures. Examination of within-subject changes in BASIS scores from day 8 (Table 4.30) to day 35 revealed that the Control group made significant improvements ($p<0.05$) in the Average score and most subscales (all except for Psychosis) during the post-withdrawal period. In contrast, the BASIS scores for the Experimental subjects did not differ significantly during this time. Hence, the main improvements for Experimental subjects had occurred during the withdrawal episode, and these were generally sustained thereafter, whereas the Control subjects had made fewer initial improvements during the withdrawal episode, but made considerable advances by the fifth week.

SF-36 scores indicated that there were significant differences in favour of the Experimental group at day 35 on the subscales of Bodily Pain ($t(90) = 3.40$, 95% CI= 6.5 to 24.5), Vitality ($t(90) = 2.40$, 95% CI= 1.6 to 16.4), Social Functioning ($t(90) = 3.19$, 95% CI = 5.6 to 24.1) and Mental Health ($t(90) = 2.11$, 95% CI = 0.5 to 15.6). Paired student t-tests from baseline (Table 4.18) to day 35 for subjects from both groups (n=92) indicated a statistically significant improvement ($p<0.05$) for all subscales with the exception of Physical Functioning. However, subjects continued to perform poorly on these subscales compared to scores for adults from the general population. For example, the subjects in the Experimental group (who generally were performing better than the Control subjects) were between the 18th and 35th percentile for the

various subscales (Ware, Kosinski et al. 1994). By comparison, subjects at baseline tended to be between the 12th and 28th percentile for the various subscales (Table 4.18).

Table 4.40. SF-36 scores at day 35 by randomised group.

	Experimental (n=48) mean ± SD	Control (n=44) mean ± SD		Percentile*
Physical functioning	85.5 ± 18.0	83.3 ± 19.5	NS	35%
Role - physical	51.0 ± 40.3	40.9 ± 38.5	NS	21%
Bodily pain	67.3 ± 20.8	51.8 ± 22.7	p<0.02	33%
General health	53.4 ± 22.6	54.7 ± 25.9	NS	18%
Vitality	50.9 ± 18.6	41.9 ± 17.0	p<0.02	32%
Social functioning	67.7 ± 22.5	52.8 ± 22.2	p<0.01	25%
Role - emotional	43.8 ± 41.3	41.7 ± 40.1	NS	18%
Mental Health	63.9 ± 19.1	55.9 ± 17.2	p<0.05	26%

* refers to percentile for Experimental subjects at day 35 compared to US adult general population data

Goal Attainment

Subjects were asked the extent to which they had attained their treatment goals using a 0 (no goals attained) to 100 (all goals attained) Visual Analogue Scale. The Control subjects reported a significantly lower mean score (50 ± 31), compared to the Experimental mean score of 63 ± 31 ($t(90) = 2.12$, $p < 0.05$, 95% CI = 1 to 26).

4.3.3.3 Outcomes by post-withdrawal treatment status

This section examines the various outcome measures according to the treatment status of subjects in the post-withdrawal period, in order to examine the impact of post-withdrawal treatment upon key outcomes. Data is analysed according to whether subjects entered and/or were retained in post withdrawal treatment, and not by the (randomly allocated) group status, as in the previous section.

Heroin and other drug use

Measures of heroin use are presented according to the treatment status of subjects at day 35 in Table 4.41. Data is available for only 93 subjects (82%).

As a group, subjects-in-treatment at day 35 reported significantly less heroin use on all measures compared to those subjects not in treatment at day 35: Q score: ($t(49.8) = 5.03$, $p < 0.001$, 95% CI = 0.64 to 1.50); days used heroin: ($t(69.9) = 4.17$, $p < 0.001$, 95% CI = 4.1 to 11.7); average daily cost of heroin ($t(42.0) = 2.93$, $p < 0.01$, 95% CI = $11.21 to 60.63); and LDQ score ($t(70.9) = 4.94$, $p < 0.001$, 95% CI = 4.5 to 10.5).

Table 4.41. Heroin use by treatment status at day 35

	In treatment at day 35 (n=52)	Not in treatment at day 35 (n=41)
Q score		
0	4 (8%)	2 (5%)
0.04 (used once only)	4 (8%)	3 (7%)
0.05 - 0.14 (< than weekly)	14 (27%)	1 (2%)
0.15 - 0.99 (less than daily)	21 (40%)	7 (17%)
1.0 or more (daily)	9 (17%)	28 (68%)
Mean ± SD [a]	0.47 ± 0.56	1.54 ± 1.24
Median Q score	0.22	1.33
Number of days used in past 28 days (mean ± SD)	8.1 ± 7.5	16.1 ± 10.0
Average daily cost of heroin ($AUS) (mean ± SD)	35.74 ± 18.71	71.67 ± 74.54
LDQ score (mean ± SD)	7.9 ± 6.1	15.3 ± 7.9

[a] The mean score excludes n= 2 outliers (neither in treatment at day 35) with Q score = 10.0 and 20.0

On examining the Q scores more closely, it is apparent that a similar proportion of subjects in both groups reported no heroin use or use on only one occasion (12% in the 'not in treatment' group, 16% in the 'treatment' group). The main difference between the two groups appears to be that the majority of subjects (68%) in the 'not in treatment' group had relapsed to regular heroin use (Q scores ≥ 1.0), with only a small proportion (19%) sustaining irregular heroin use (Q score between 0.05 and 0.99). In contrast, only a minority (17%) of those in treatment had relapsed to regular use (Q score ≥ 1.0), whereas the majority (67%) sustained irregular heroin use (Q score between 0.05 and 0.99). The difference in average daily cost of heroin for those describing heroin use between the two groups is further evidence of the treatment group being better able to limit or control their use of heroin.

Within-subject changes in heroin use were examined according to treatment status. The 'in treatment' subjects (n=52) reported an overall reduction in the heroin Q score from day 8 to 35 (mean = - 0.21 ± 0.83), whereas the 'not in treatment' group (n=41) reported an increase in their Q score (mean = 0.39 ± 1.12); representing a significant difference between groups ($t(62.5) = 2.76$, $p < 0.01$, 95% CI = 0.17 to 1.04).

Use of other drugs did not appear related to day 35 treatment status, with no significant group differences for the more commonly used drugs (alcohol, cannabis, benzodiazepines, other opiates).

The data indicates that the group of subjects who were retained in treatment at day 35 were using less heroin, and were less dependent on heroin than the group of subjects not retained in treatment. Interestingly, a considerable proportion of subjects (n = 26 or 23% of the total sample) entered some form of treatment in the post-withdrawal period, but were not retained in treatment at day 35. A separate series of analyses (one way ANOVA) was conducted examining heroin use outcomes for three groups of subjects (Table 4.42):

- subjects retained in treatment at day 35 (data available for 52 / 58 subjects (90%));
- subjects who entered, but dropped out of post withdrawal treatment (data available for 25 / 26 subjects (96%)); and
- subjects not entering any post-withdrawal treatment (data available for 16 / 30 subjects (53%)).

The three groups differed significantly across all measures of heroin use. Tukey's post-hoc analyses indicate that the enhanced outcomes were seen in those individuals who were retained in treatment at day 35. With regards to OTI Q score, the 'in-treatment' group used significantly less heroin than the 'treatment drop out' group ($p < 0.001$, 95 % CI = 0.50 to 1.56), and significantly less than the 'no treatment' group ($p < 0.001$, 95% CI = 0.48 to 1.80). The Q scores for the treatment drop out and no treatment groups were not significantly different ($p = 0.93$)

Table 4.42. Heroin use in post withdrawal period by treatment status

	In treatment at day 35 (n=52)	Post-withdrawal treatment drop out (n = 25)	No post w/d treatment (n= 16)	
OTI Q score				
mean ± SD	0.47 ± 0.56	1.50 ± 1.34	1.61[a] ± 1.06	F (2, 90) = 15.23
median	0.25	1.33	1.41	p < 0.001
Days used heroin in past 28				
mean ± SD	8.1 ± 7.5	14.2 ± 9.6	18.8 ± 10.3	F (2, 90) = 10.89 p < 0.001
Ave daily cost of heroin ($AUS)				
mean ± SD	$35.74 ± 18.71	$62.17 ± 51.94	$85.31 ± 98.90	F (2, 85) = 6.08
median	$30	$50	$50	p< 0.005
LDQ score (mean ± SD)	7.9 ± 6.1	15.6 ± 8.0	14.9 ± 8.2	F (2, 91) = 12.98 p < 0.001

[a] The data for 2 subjects who were outliers (Q = 20.0 and 10.0) were excluded from the analysis of Q scores.

Post-hoc analyses indicate that subjects in treatment at day 35 used heroin on significantly fewer days than subjects who dropped out of treatment ($p < 0.05$, 95% CI = 1.0 to 11.1 days), and subjects who did not enter treatment ($p < 0.001$, 95% CI = 4.8 to 16.5 days). The 'no treatment' and 'treatment drop out' groups were not significantly different on this measure.

Similar findings were seen with regard to severity of dependence on heroin as measured by the LDQ. The 'in-treatment' group had significantly lower scores than the 'treatment drop out' group ($p < 0.001$, 95% CI = 3.7 to 11.9) and the 'no treatment' group ($p < 0.01$, 95% CI = 2.3 to 11.8). There was no statistically significant difference between the 'no treatment' and 'treatment drop out' groups.

Subjects in treatment reported spending significantly less on heroin when they did use, compared to subjects in the 'no treatment' group ($p < 0.01$, 95% CI = \$13.83 to \$85.30); and there was a non-significant trend compared to the 'treatment drop out' subjects ($p= 0.12$, 95 % CI = -\$5.00 to \$57.85). The 'no treatment' and 'treatment drop out' groups were not significantly different on this measure.

Finally, data regarding heroin use is presented in Table 4.43 for those subjects who remained in treatment at day 35 according to their treatment modality (buprenorphine, methadone, naltrexone or counselling). Statistical comparisons have not been made given the small numbers and the similarity of scores for heroin use measures across the four treatment modalities. The exception is the naltrexone group, who reported very low levels of heroin use, although data is missing on many (38%) of these subjects, limiting the capacity to draw conclusions.

Table 4.43. Measures of heroin use at day 35 by treatment modality

Treatment modality	# subjects with data / # subjects in treatment (%)	OTI Q score (mean ± SD)	Days heroin use in past month (mean ± SD)	LDQ score (mean ± SD)
Substitution treatment	39 / 45 (87%)	0.44 ± 0.51	8.1 ± 7.0	8.1 ± 6.1
Buprenorphine	25 / 25 (100%)	0.34 ± 0.47	6.3 ± 6.3	7.4 ± 6.4
Methadone	14 / 20 (70%)	0.63 ± 0.53	11.2 ± 7.2	9.5 ± 5.6
Naltrexone	5 / 8 (63%)	0.03 ± 0.05	0.4 ± 0.6	1.8 ± 2.4
Counselling	4 / 5 (80%)	0.44 ± 0.32	11.7 ± 10.4	10.0 ± 6.9

Psychosocial measures

One possible explanation for some subjects not seeking treatment is that they were functioning quite well (regardless of their heroin use) and were not in need of ongoing treatment. To

examine for this possibility, BASIS-32 data is presented in Table 4.44 according to whether subjects were enrolled in treatment at day 35.

Table 4.44. Day 35 BASIS-32 data according to post-withdrawal treatment status

	In treatment (n=52) mean ± SD	Not in treatment (n=40) mean ± SD	
Relation to self / others	0.98 ± 0.63	1.69 ± 0.90	$p < 0.001$ ($t(66.5) = 4.20$)
Depression / anxiety	0.87 ± 0.65	1.69 ± 0.82	$p < 0.001$ ($t(90) = 5.37$)
Daily living / role functioning	0.96 ± 0.64	1.82 ± 0.91	$p< 0.001$ ($t(66.5) = 5.07$)
Impulsive / addictive behaviour	0.55 ± 0.41	0.96 ± 0.65	$p < 0.001$ ($t(62.3) = 3.47$)
Psychosis	0.22 ± 0.34	0.44 ± 0.48	$p< 0.01$ ($t(67.4) = 2.44$)
Total Average	0.75 ± 0.44	1.37 ± 0.65	$p< 0.001$ ($t(65.7) = 5.22$)

The group of subjects not in treatment at day 35 had significantly higher psychosocial dysfunction on all subscales and for the mean Average score. Within-subject changes in BASIS scores for the post-withdrawal period indicates that overall, both groups reported marginal improvements at day 35 compared to day 8 on all subscales, although there was considerable variation among subjects and no significant between group differences.

There were marked differences on most of the SF-36 subscales for those subjects in treatment at day 35 compared to those not engaged in treatment (see Table 4.45). Despite the subjects in treatment reporting significantly better outcomes on most subscales, they continued to rate poorly in comparison to general population data (Ware, Kosinski et al. 1994), scoring in the 18th to 35th percentiles for the different subscales.

Table 4.45. SF-36 scores at day 35 according to post withdrawal treatment status

	In treatment (n=52)	Percentile*	Not in treatment (n=40)	
Physical functioning	86.2 ± 18.1	35%	82.3 ± 19.4	NS
Role - physical	53.4 ± 39.0	21%	36.9 ± 38.8	$p<0.05$
Bodily pain	66.5 ± 20.8	33%	51.2 ± 23.1	$p<0.01$
General health	62.9 ± 18.5	29%	42.4 ± 25.8	$p<0.01$
Vitality	52.2 ± 18.9	32%	39.4 ± 14.9	$p<0.01$
Social functioning	67.5 ± 21.6	25%	51.6 ± 22.9	$p<0.01$
Role - emotional	46.8 ± 41.4	18%	37.5 ± 39.4	NS
Mental Health	67.2 ± 16.4	28%	50.8 ± 17.1	$p<0.01$

* refers to percentile compared to US adult general population data

Goal attainment

The subjects in treatment at day 35 indicated (on a Visual Analogue Scale) that they had achieved a greater proportion of their treatment goals (mean = 68 ± 28) compared to those

subjects not in treatment at day 35 (mean = 43 ± 30). The difference between the two groups was statistically significant (t (90) = 4.20, p <0.001, 95% CI = 13 to 37).

4.3.3.4 Predictors of post-withdrawal outcomes

Multiple regression analysis was conducted to examine the impact of a number of variables at baseline and during the withdrawal episode upon the two primary outcomes in the post withdrawal period: *participation in post-withdrawal treatment* and *heroin use* (number of days used in past 28). Separate analyses were conducted for the Control and Experimental Groups, given the importance of Group upon both dependent variables. Independent variables included baseline characteristics (identical to those described for earlier regression analysis in Section 3.2.8); and withdrawal episode variables, including: number of times used heroin during withdrawal episode; number of days used heroin in withdrawal episode; abstinence from heroin during withdrawal (dummy variable); day 8 LDQ score; withdrawal severity experienced (global VAS score); number of days retained in treatment during withdrawal episode; day 8 BASIS-32 Average score; satisfaction with withdrawal medication (VAS score); goal attainment in withdrawal (VAS score).

With regards to days attended in post withdrawal treatment, the significant variables for the Experimental group ($R^2 = 0.40$) were average daily cost of heroin at intake ($F = 9.94$, $p < 0.01$) and number of days participated in the initial withdrawal episode ($F = 9.24$, $p < 0.01$). Two variables were significant for the Control group ($R^2 = 0.40$): average daily cost of heroin at intake ($F = 6.90$, $p < 0.05$) and importance of reduced heroin use in the post withdrawal period treatment as a treatment goal at baseline ($F = 7.19$, $p < 0.05$). Interestingly, amount of heroin use in the withdrawal episode was not predictive of post-withdrawal treatment participation for either group of subjects.

Variables which were predictive of the number of days of heroin use in the post-withdrawal period for the Experimental group ($R^2 = 0.52$) were: average daily cost of heroin use at intake ($F=13.7$, $p < 0.01$), number of days used heroin in withdrawal episode ($F = 6.0$, $p < 0.05$), number of previous treatment attempts in the past year ($F = 7.4$, $p < 0.05$), and number of lifetime attempts at non-withdrawal treatment modalities ($F = 7.5$, $p < 0.01$). For the Control group, number of days in which heroin was used during the withdrawal episode ($F = 6.3$, $p < 0.05$) was the only significant predictor of days heroin use in the post withdrawal period ($R^2 = 0.42$).

4.3.3.5 Induction onto naltrexone following buprenorphine treatment

This section examines the experience of induction onto naltrexone soon after a short buprenorphine withdrawal. Nine subjects who underwent buprenorphine assisted withdrawal commenced treatment with naltrexone during the 4 week post-withdrawal period. Of these, 4 subjects commenced on day 8 (three days after their last dose of buprenorphine (4 mg) on day 5); two subjects commenced on day 10; and one on day 11. The remaining 2 subjects commenced naltrexone at least 7 days after the last dose of buprenorphine, and they will not be further considered in this section as they underwent a conventional induction onto naltrexone. Furthermore, one subject (commencing at day 10) initiated naltrexone at home without clinical monitoring, and without clinical review for three days. Data for this subject is therefore unavailable and cannot be included in this description. Hence, data is presented on six subjects initiating naltrexone treatment following buprenorphine-assisted withdrawal.

The procedures for induction onto naltrexone following buprenorphine withdrawal were described in Section 4.2.3.2 in detail. Recapping, subjects were administered an initial 12.5 mg oral dose of naltrexone, 25 mg the following day, and if tolerated, 50 mg daily thereafter. Subjects were monitored using the Subjective and Objective Withdrawal Scales at baseline (prior to the initial naltrexone dose), for 3 hours after the initial dose (where possible), and on subsequent days (immediately prior to dosing). Symptomatic medications were available to subjects. The Subjective Opiate Withdrawal Scales for the four subjects who commenced naltrexone on day 8 are shown in Figure 4.5.

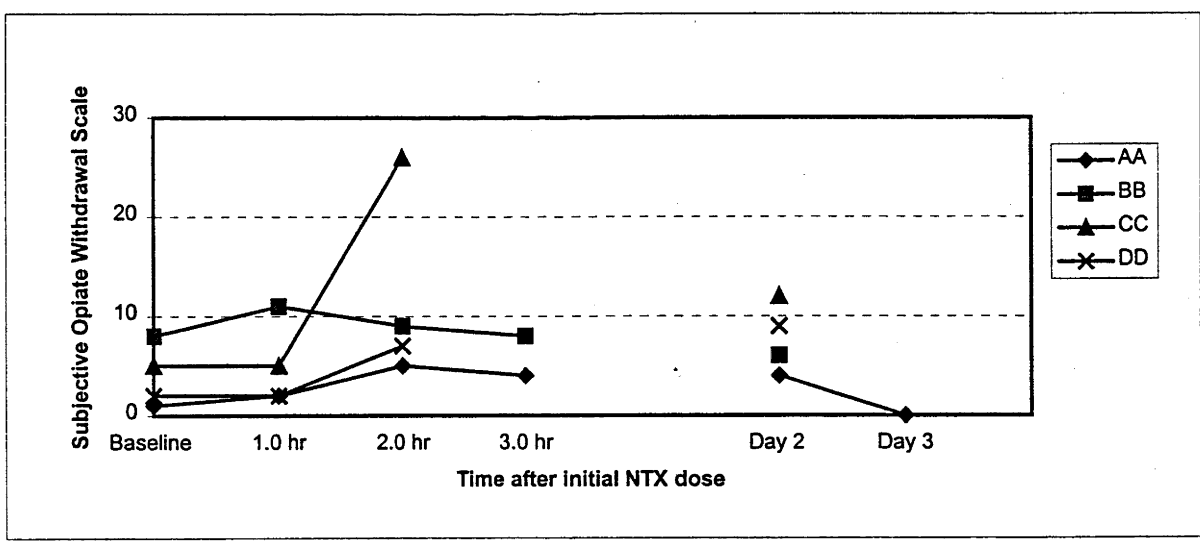

Figure 4.5: SOWS scores following naltrexone induction

The SOWS data presents only a limited picture of the response to naltrexone due to the brief period of monitoring of withdrawal after the initial naltrexone dose. Consequently, a short

clinical summary is presented for each of these subjects, and for the two subjects inducted on days 10 and 11.

Subject AA. 26 year old woman. AA described no withdrawal discomfort at baseline (SOWS = 1, OOWS = 1). She described mild withdrawal symptoms during the clinical observation period, peaking in severity at 2 hours after the naltrexone dose (SOWS = 5, OOWS = 3). The predominant withdrawal symptoms reported during this time were sweating, hot / cold flushes, yawning, lacrimation and muscle and bone aches. She felt somewhat better at three hours than at two, and subsequently left the clinic confident that she had been 'over the worst'. The following day on review she described a very difficult night - complaining of considerable anxiety, muscle and bone aches, sweating, disturbed sleep, and generally feeling 'wired'. She described taking 5 mg diazepam orally at around 3 am, and slept for approximately 5 to 6 hours. By the morning (day 9) she had improved considerably, and reported minimal discomfort (SOWS = 4, OOWS = 0). She took a 25 mg dose of naltrexone on day 2. On review the following day she described no withdrawal discomfort over the preceding 24 hour period, scoring 0 for both the SOWS and OOWS. Subject AA remained on naltrexone for the 4 week post withdrawal period.

Subject BB. 31 year old man with a history of several episodes of successful completion of outpatient withdrawal followed by very rapid relapses to heroin use. BB described a mild degree of withdrawal at baseline (SOWS = 8, OOWS = 3), scoring predominantly on symptoms of anxiety and cravings. BB complained of only a minor increase in withdrawal features over the subsequent 3 hour review period, peaking on the SOWS (11) one hour after the naltrexone dose; and peaking on the OOWS (6) at 2 -3 hours. Main withdrawal features during this observation period were: perspiration, yawning, rhinorrhoea, lacrimation, flushes, aches and nausea. By the evening, BB described that many of the early symptoms had diminished, but was experiencing anxiety, restlessness, muscle and bone aches, and abdominal cramps. The subject stated that 150 mcgm clonidine and 10 mg diazepam eased these symptoms for several hours. By the following day, most of the withdrawal discomfort had eased, reporting SOWS = 6, and OOWS = 2. No significant increase in withdrawal discomfort was reported after the second naltrexone dose. Subject BB discontinued naltrexone treatment after day 12 (4 days of naltrexone treatment), and relapsed into heroin use 2 days later. He re-presented to the clinic after several weeks and attempted withdrawal using symptomatic medication (buprenorphine was not available as per study protocol - see methods).

Subject CC. This 43 year old woman had previously experienced naltrexone treatment several years earlier, and entered withdrawal with the aim of re-commencing naltrexone. She

had described herself as being very fearful of withdrawal discomfort, and had been pleasantly surprised at the ease of her recent withdrawal using buprenorphine. At baseline she had some mild withdrawal discomfort (SOWS = 5, OOWS = 5). Approximately 2 hours after her initial naltrexone dose she described considerable withdrawal discomfort (SOWS = 26, OOWS = 5), complaining predominantly of anxiety, muscle and abdominal cramps, sweating, and restlessness. On returning home, she took the prescribed symptomatic medication (150 mcgm of clonidine and 10 mg diazepam) and went to bed. She awoke in the early hours of the morning still complaining of general withdrawal discomfort, took another 10 mg diazepam, but could not sleep again. The following morning she was experiencing mild withdrawal discomfort (SOWS = 12, OOWS = 3), but was reticent to take naltrexone on days 9 or 10. CC recommenced naltrexone on day 11, and remained in treatment for several months.

Subject DD. 46 year old woman had completed withdrawal with very minor discomfort, and commenced naltrexone on day 8. She reported minimal withdrawal at baseline (SOWS = 2, OOWS = 1), but within 2 hours experienced the onset of anxiety and a cluster of autonomic withdrawal features (SOWS = 7; OOWS = 5). On review the following day, DD described a very uncomfortable evening, complaining of worsening anxiety, restlessness, body aches, muscle and abdominal cramps, and several episodes of vomiting. Symptoms had peaked approximately six to ten hours after the naltrexone dose, and the withdrawal features had predominantly resolved by the following morning (SOWS = 9, OOWS = 0). She consented to taking only 12.5 mg naltrexone on day 9, but increased this to 25 mg on day 10. DD did not stabilise on naltrexone, complaining of persistent lethargy and dysphoria (recognised side effects to naltrexone), and ceased it after two weeks. She described not using heroin during the follow up period.

Subject EE: This 25 year old man commenced naltrexone on day 10. He reported no withdrawal discomfort either immediately prior or after his initial 12.5 mg dose of naltrexone. EE increased his dose on successive days, remaining in naltrexone treatment for the duration of the follow up period.

Subject FF. A 23 year old man who completed withdrawal on day 8 without heroin use, but had a busy work schedule for several days, and deferred naltrexone induction until day 11. FF described no withdrawal discomfort immediately before or following his initial naltrexone dose (SOWS at baseline = 5; at 2 hours = 4). He described no noticeable increase in withdrawal discomfort that evening, and continued in naltrexone treatment as per protocol for three weeks, prior to discontinuing naltrexone treatment.

In summary, five of the six subjects (83%) and three of the four 'day 8' subjects were inducted onto naltrexone (as evidenced by remaining in naltrexone treatment for at least one week), although only 3 subjects (50%) remained in naltrexone treatment for the 4 week follow up. All four subjects inducted on day 8 described a similar withdrawal response to naltrexone. They reported mild withdrawal features commencing one to two hours after the initial 12.5 mg dose, describing initially autonomic features of sweating, piloerection, runny nose and eyes. The severity of the withdrawal features progressed rapidly over subsequent hours, with patients principally complaining of anxiety, restlessness, skeletal muscle cramps, sweating, and backache. These peaked in severity within a period approximately 6 to 12 hours after the initial naltrexone dose, and were generally subsiding by the following day (12 to 18 hours later). Three of the 6 subjects described symptoms, most notably lethargy and fatigue, during the subsequent few days on naltrexone. These may have been persistent withdrawal features following naltrexone induction or side effects of naltrexone (Resnick 1977; San, Pomarol et al. 1991; Judson and Goldstein 1982).

The two subjects who commenced naltrexone on days 10 and 11 reported no withdrawal discomfort, nor any other difficulties during their naltrexone induction.

These findings suggest that induction onto naltrexone is possible at day 8, and generally tolerated by patients on an outpatient basis with minimal additional medication. However, delaying the naltrexone induction by a further two days may be preferable if the patient does not wish to experience withdrawal discomfort and is confident of not using heroin in the interval.

4.3.3.6 Comparison of outcomes in post withdrawal period by study site

Similar proportions of subjects at each site entered treatment in the post withdrawal period, and similar proportions were in treatment at day 35. There were no significant differences between the two sites regarding rates of participation in the different treatment modalities.

The various measures of heroin and other drug use, and psychosocial functioning were similar for subjects at the two sites. The only significant difference between the two sites was that the Sydney (Langton) subjects reported higher rates of benzodiazepine use in the post-withdrawal period compared to Melbourne (Turning Point) subjects ($t(67) = 2.59$, $p < 0.05$, 95% CI = 0.07 to 0.57), although the small difference in means between the two groups (approximately a quarter of a benzodiazepine tablet per day) is likely to not be clinically significant.

4.3.3.7 Summary of findings in post withdrawal period

The key findings from the post-withdrawal period were examined by randomised group and by post-withdrawal treatment status. There were high levels of ongoing participation in drug treatment by subjects in both randomised groups, although significantly more Experimental subjects entered and were retained in post-withdrawal treatment. Substitution treatment (methadone and buprenorphine) was the most widely used of the treatment modalities, accounting for over three quarters of subjects in treatment at day 35.

Overall, the general improvements that had occurred during the withdrawal episode on most measures of heroin use and psychosocial functioning were maintained over the post-withdrawal period. Subjects from the Experimental group reported significantly lower levels of heroin use as measured by the OTI and number of days used, and higher levels of psychosocial functioning over the month as measured by the SF-36. However, the Control group made substantial improvements in measures of psychosocial functioning by the end of the follow-up period, and there were no significant differences between groups on psychosocial functioning in the final week of follow up on the BASIS-32.

Importantly, subjects who were retained in treatment over the post-withdrawal period were performing better on almost all outcome measures compared to those subjects who had not entered, or had dropped out of post withdrawal treatment. Indeed, those in treatment continued to show improvements on most measures over the follow-up period, whereas as those not in treatment at day 35 were generally deteriorating in most measures. Interestingly, there were similar proportions of subjects who had remained abstinent from heroin over this time, however, most subjects in treatment had been able to sustain irregular heroin use, whereas most subjects who were not in treatment at day 35 had returned to daily heroin use by the end of the follow up period. Nevertheless, even those subjects not in treatment were still performing considerably better than they had been at baseline.

Multiple regression analysis indicated that the main predictors of levels of heroin use in the post withdrawal period were measures of heroin use at baseline and frequency of heroin use during the withdrawal episode. Predictors of participation in treatment during the post-withdrawal period were measures of heroin use at baseline (in particular average daily cost) for both Experimental and Control groups, retention in withdrawal treatment for the Experimental group, and the importance of reduced heroin use in the post-withdrawal period as a treatment goal for the Control group. Levels of heroin use during the withdrawal episode were not predictive of ongoing participation in drug treatment.

4.4. Discussion

This is the first randomised controlled study to demonstrate that buprenorphine has greater efficacy than clonidine and other symptomatic withdrawal medications for the outcomes most relevant to outpatient withdrawal services: reduction in heroin use during withdrawal, and enhanced treatment retention during the withdrawal and post-withdrawal periods. Subjects receiving buprenorphine also reported greater improvements with regard to severity of dependence and psychosocial functioning. Consistent with previous studies (Nigam, Ray et al. 1993; Cheskin, Fudala et al. 1994; O'Connor, Carroll et al. 1997), subjects randomised to buprenorphine also reported significantly less severe withdrawal symptoms. Importantly, the effect sizes on key outcome measures between the two groups were considerable, with Numbers Needed to Treat of generally less than 5 to 10 patients for most outcomes, demonstrating a considerable advantage in using buprenorphine over combination symptomatic medication. There were also considerable benefits with regard to incremental cost effectiveness over symptomatic medication in achieving heroin-free days during the withdrawal episode (ratio of 1.7 to 1), and in achieving heroin-free withdrawal episodes (ratio of 5.5 to 1). Given the large number of outpatient heroin withdrawal episodes attempted each year within Australia, the widespread use of buprenorphine should result in considerable improvements in the efficiency of withdrawal services.

4.4.1 Limitations of the study

Prior to considering the broader implications of the research, a number of limitations of the study need to be addressed. The most significant limitation of the study was that participants were not blinded to the medication regimes. The open label design may have biased the outcomes for the study, given the tendency for some subjects to assume that 'new' or 'investigational' medications are likely to be 'better' medications. This may have resulted in a number of subjects randomised to the Control Group becoming disillusioned with their treatment allocation, resulting in poorer treatment outcomes. Alternatively, it may have biased reporting on subjective outcome measures, such as levels of satisfaction with medication or global ratings of withdrawal discomfort. Attempts were made to limit the impact of expectancy, such as the recruitment of subjects from patients presenting for routine withdrawal services, with no advertising or promotion of the study; and the provision of information regarding the different withdrawal medications to subjects in a neutral manner so as to not favour either medication regime. Nevertheless, an element of bias is inevitable in open label studies.

Other limitations of the study were possibly less important. There was good follow up of subjects, with approximately 89% of all randomised subjects being followed up at day 8, and 80% being followed up at day 35. Drug use measures in the post withdrawal period were limited to self-report, without corroboration of objective urine drug screens. However, self-report data is usually considered reliable under the conditions in which the data was collected (Darke 1998): by research assistants not involved in clinical service delivery, and with no punitive consequences for subjects reporting continued heroin use during the post-withdrawal period. Self-reported heroin use during the withdrawal episode was consistent with the findings of urine drug tests during this period.

Attempts to generalise from these findings to broader populations of heroin users and treatment settings must take into consideration that heroin users with significant medical or psychiatric conditions, recent methadone treatment, or concomitant alcohol or benzodiazepine dependence were excluded from the study; and that the study was conducted in specialist treatment settings. Nevertheless, the almost identical findings for all the principal outcomes at two clinical sites in different cities enhances the degree of confidence that the results can be generalised to similar populations of heroin users attending specialist treatment settings. Finally, a longer period of post-withdrawal follow up would have been preferred in order to examine the broader impact of withdrawal and post-withdrawal services, but was not possible within the available resources.

The treatment protocol for the Control group appeared (at face value) to have been adequate with regard to the medication regime and intensity of ancillary services. Doses for clonidine in this study were comparable to previously reported outpatient regimes, there was general patient satisfaction with the adequacy of dosing levels, and the addition of ancillary medication particularly suited to the withdrawal symptoms least relieved by clonidine (benzodiazepines, anti-emetics, anti-spasmodic, and anti-inflammatory medications) should have intuitively resulted in enhanced outcomes compared to clonidine-only regimes. There was a relatively high level of contact between service providers and subjects, with an average of approximately 10 staff - patient contacts over the 8-day withdrawal episode. Yet despite what appeared to be 'adequate' treatment, the rate of abstinence from heroin during the withdrawal episode among the Control group in this study was quite low (4%), whereas most earlier studies of outpatient heroin withdrawal using clonidine report 'successful completion' rates in the range of 20 to 30% (Gowing, Ali et al. 2000; Lipton and Maranda 1983). However, as identified in Chapter 1, there are numerous difficulties in directly comparing findings across studies that employ different recruitment methods, subject populations, treatment protocols and outcome measures.

There are a number of factors that relate to this study that may explain the low 'abstinence' rate during the withdrawal episode seen in the Control group:

- Many subjects in the study were chronic and heavy heroin users, had multiple prior treatment attempts, few 'positive' social supports, and most (90%) were injecting heroin. In contrast, several previous withdrawal studies have recruited heroin users with less severe dependence, shorter duration of heroin use and better psychosocial functioning, for whom better outcomes may be expected (Blaine, Ling et al. 1994).

- Many previous outpatient withdrawal studies of clonidine have examined patients withdrawing from methadone maintenance treatment, not active heroin users. Patients attempting outpatient withdrawal from dependent heroin use may be more likely to continue heroin use during a withdrawal episode than patients withdrawing from methadone maintenance treatment with no recent history of heroin use (Gowing, Ali et al. 2000).

- This was a study of subjects presenting for withdrawal services, with the option of entering post-withdrawal treatment afterwards. Several prior studies (for example, Gerra, Marcato et al. 1995) have reported outcomes relating to the withdrawal episode for subjects enrolling in longer term, abstinence based treatment modalities (such as naltrexone maintenance treatment or therapeutic communities). It is likely that subjects enrolling in such long-term treatment programs will have higher rates of heroin cessation compared to a more general population of heroin users seeking withdrawal.

- The study generally inducted subjects and commenced treatment on the day of initial presentation to the clinics. This is in contrast to studies in which withdrawal treatment is commenced several days after the initial assessment of patients (potentially allowing less motivated patients to drop out prior to the withdrawal episode commencing); or alternatively, studies in which the withdrawal regime commences following a period of stabilisation on prescribed morphine or methadone (for example, Washton and Resnick 1981). Stabilisation for several days on methadone (or morphine) potentially allows for the interruption of daily behavioural patterns of heroin use in a manner that is not routinely seen in clinical withdrawal programs using symptomatic medication.

- As identified earlier, subjects were not blinded to their medication regime, and it is likely that a number of subjects were disappointed following randomisation to the Control group, with poor treatment outcomes as a consequence. Indeed, a quarter of Control subjects did not continue treatment beyond the first day, although treatment drop out soon after enrolment is not an uncommon event (for example, 9% of Experimental subjects did not

attend beyond the second day), and the majority of Control subjects were retained in withdrawal treatment.

- The availability and accessibility of heroin in the environment is likely to impact upon outcomes for individuals enrolled in outpatient treatment. At the time in which the study was conducted, heroin was widely available, inexpensive, and of high concentration in both Sydney and Melbourne (McKetin, Darke et al. 2000). The environmental context (availability and accessibility of heroin) in which earlier outpatient withdrawal studies have been conducted may have been different, thereby complicating comparisons with earlier research.

- Differences in how withdrawal outcomes are operationalised in studies have a considerable impact upon the reporting of findings. This study defined abstinence during withdrawal as negative urine tests for opiates on both days 5 and 8. Self-report data was available for 86% of Control subjects, and missing urine test results were assigned 'positive', according to protocol. In contrast, many previously reported studies have had considerably different end points and ways of reporting findings. For example, some studies (e.g. Nigam, Ray et al. 1993) disregard treatment drop-outs, and only report a survival analysis rather than an intention-to-treat analysis, thereby generally inflating 'success rates'. Other studies have not reported heroin use during outpatient withdrawal (e.g. O'Connor, Carroll et al. 1997), and use treatment protocol completion or antagonist challenges as their end points. However, a 'negative' naloxone challenge can be achieved after only several days without opiate use, and is therefore not necessarily a comparable outcome measure to urine results throughout an 8-day withdrawal episode. To highlight these points, had this study discounted treatment drop-outs from the final analysis, and had it used a negative opiate urine drug screen at day 8 as an operational measure of withdrawal success (as many, if not most, patients with a negative opiate urine at day 8 following minimal heroin use early in a withdrawal episode, can tolerate a dose of an opioid antagonist on day 8), then 13% of Control subjects (4 out of 32), and 34% of Experimental subjects (17 out of 50) 'successfully completed withdrawal'. This places the outcomes for the Control group in this study more broadly within the range reported in earlier outpatient clonidine studies of heroin withdrawal.

Although the abstinence rate of 4% seen in this trial appears low in comparison to earlier reported studies, this did not appear uncharacteristically low to experienced clinicians working at the study sites. Prior to commencing the study, clinicians at both sites estimated that between 5 and 10% of patients would not use heroin for at least one week during their initial attempt at symptomatic withdrawal (see Section 4.2.2.2).

4.4.2 The impact of outpatient withdrawal services for heroin users

In addition to comparisons between the two medication regimes, this study also provides an opportunity to consider the broader impact of outpatient withdrawal services for dependent heroin users. The general outcome for most subjects in the study was that they reduced (but did not cease) their heroin use, reduced their dependence on heroin, and improved their level of psychosocial functioning during the withdrawal episode. These improvements were generally maintained in the post-withdrawal period, with most subjects performing considerably better one month after withdrawal than prior to treatment entry. Whilst outcomes were enhanced for those subjects who were retained in some form of post withdrawal treatment, even those subjects who did not participate in further treatment beyond the withdrawal episode reported less heroin use and better levels of functioning four weeks later than at treatment entry.

4.2.2.1 Heroin use during withdrawal episode

The reduction in heroin use during the withdrawal episode was considerable - the average frequency of heroin use fell from three to four times a day in the week prior to treatment, to less than daily during the withdrawal episode. The majority of subjects in the Experimental Group and almost a quarter of Control subjects reported no heroin use or minimal heroin use (on 1 or 2 days) during the 8-day withdrawal episode. Most patients and clinicians would generally consider such a marked reduction in heroin use as a relatively successful attempt at outpatient heroin withdrawal. Most subjects (particularly those randomised to the Experimental condition) reported minimal discomfort during the withdrawal episode in association with these reductions in heroin use.

Despite the initial high degree of patient interest in ceasing heroin use during the withdrawal episode, only a minority of subjects (12% in the Experiment and 4% in the Control group) achieved this goal. Complete cessation of heroin use (as measured by urine testing) is a clearly defined, objective measure well-suited to research trials. However, abstinence during withdrawal is not the only clinically relevant outcome, and indeed, the broader benefits that were experienced by most subjects during and after the withdrawal episode occurred in a context of a reduction, not necessarily a cessation, in heroin use during the withdrawal episode. Furthermore, abstinence during withdrawal was not found to be predictive of performance in the post-withdrawal period. Multiple regression analysis indicated that the continuous measure of frequency of heroin use during the withdrawal episode was more predictive of post-withdrawal heroin use than the categorical measure of abstinence during withdrawal. Whilst not discounting abstinence as an important outcome measure, it should be seen as one end of a continuum. In this regard, parallels can be drawn with maintenance substitution treatment, in

which the accepted framework for evaluating treatment efficacy involves the primary outcomes of reduction in heroin use, retention in treatment, and reduction in drug-related morbidity and mortality.

4.4.2.2 Impact upon post-withdrawal outcomes

Importantly, the improvements in heroin use, severity of dependence and psychosocial functioning were generally maintained during the four-week follow up period. Most subjects reported using considerably less heroin in the month after withdrawal, than in the month prior to withdrawal treatment. Although only a small proportion reported complete abstinence during the 4-week post-withdrawal period (10% of the Experimental and 2% of the Control group), a considerable proportion used heroin infrequently during this time (for example, 21 / 49 or 43% of Experimental group and 10 / 44 or 23% of Control group reported using heroin on average less than once a week). Furthermore, subjects reported using less heroin on the occasions that they did use: the average daily cost of heroin at intake was $98 ± 73, whereas the average daily cost during the post-withdrawal period was $52 ± 55.

Approximately half of all subjects (62% of the Experimental Group and 39% of the Control group) were retained in drug treatment at day 35. Over three quarters of these subjects were enrolled in maintenance substitution treatment, reflecting its broad appeal to heroin users and its high rate of treatment retention (76% of those commencing substitution treatment were still in treatment at day 35). Considerably smaller numbers were retained in naltrexone treatment (14% of all subjects in treatment at day 35, with 50% of subjects commencing naltrexone being retained at day 35) or counselling only at day 35 (9% of all subjects). The high uptake and retention rate for substitution maintenance treatment and the lower rates for naltrexone treatment seen in this study are consistent with previous reports for these treatment modalities.

Subjects who were retained in post-withdrawal treatment had significantly better outcomes than those who did not enter, or those who dropped out of post-withdrawal treatment. This difference is most clearly highlighted by comparing measures of heroin use. On average, subjects retained in treatment reported using on half as many days in the preceding 4 weeks (8 compared to 16), and reported spending half as much money on those days compared to subjects not retained in post-withdrawal treatment. It is tempting to (intuitively) attribute the better outcomes as being a result of treatment in the post-withdrawal period. However, caution is needed in interpreting these findings and causality can not be assumed: an alternative case can be made that those subjects who were more likely to perform better (for whatever reason) were also more likely to remain in treatment. Nevertheless, the findings suggest that patients should be strongly encouraged to continue in longer-term drug treatment following withdrawal.

The high level of retention in post-withdrawal treatment and the improved outcomes for those retained in post withdrawal treatment in the study highlight the importance of having a range of post-withdrawal treatment choices available (to account for individual patient preferences and circumstances), and the importance of withdrawal services actively facilitating linkages to ongoing treatment. The high uptake of maintenance substitution treatment is particularly noteworthy, emphasising the need for flexible treatment pathways within withdrawal services that can accommodate those patients whose initial attempts at withdrawal prove 'unsuccessful'. It should be remembered that maintenance substitution treatment was available, but initially rejected, by all subjects at the time of enrolment in study. However, approximately 40% of all subjects (and over half of the Experimental group) were engaged in maintenance treatment at the end of the follow up period.

The longer-term impact of withdrawal upon heroin use and related outcomes is not addressed in this study. The subjects who were retained in post-withdrawal treatment (maintenance substitution, counselling or naltrexone treatment) could be expected to have longer term outcomes routinely associated with each of these treatment modalities, as the outcomes observed at day 35 would suggest. However, the longer-term outcomes for subjects who were not retained in post-withdrawal treatment are unknown. Most of these subjects continued to be better placed at day 35 compared to baseline on a range of measures for heroin use and psychosocial functioning. What remains unclear is how long such improvements last. At four weeks after the withdrawal episode, the outcomes for subjects no longer in treatment were deteriorating compared to day 8 measures for frequency of heroin use and severity of dependence on heroin. Two thirds of subjects not in treatment had resumed regular heroin use (OTI Q scores greater than 1.0), and a very real concern is that heroin use and related psychosocial parameters would further deteriorate with time. Longer term follow up of such subjects is required to ascertain the extent to which an isolated episode of withdrawal treatment can substantially alleviate heavy heroin use and related harms over time.

4.4.3 Using buprenorphine for managing heroin withdrawal

This section will examine particular issues specific to the use of buprenorphine for heroin withdrawal arising from this research. The study findings confirm earlier research which identified that buprenorphine has many of the properties required of a withdrawal medication (see Section 1.4.1 for review). Buprenorphine was easy to administer on a once-a-day supervised dosing regime without substantially disrupting work or other daily activities for most patients, and dispensing was linked to regular clinical reviews in the clinic settings. There were high levels of satisfaction among subjects with buprenorphine as a withdrawal

medication; and approximately three quarters of subjects identified the adequacy of buprenorphine regime as satisfactory, 19% indicated the doses were 'too low', and 8% indicated the doses had been 'much too low'.

This study compared short-term withdrawal using buprenorphine to a conventional symptomatic medication regime. As identified in Chapter 1, short withdrawal episodes predominate within the Australian treatment context, and gradual withdrawal services spanning weeks to months using substitution medications such as methadone have hitherto been uncommon. Nevertheless, longer withdrawal treatment episodes may have certain advantages for some patients, and further consideration should be given to comparing the efficacy of short versus gradual reduction regimes of buprenorphine. This has not been systematically examined in previous buprenorphine research for heroin withdrawal, and indeed, even the evidence regarding the optimal duration of methadone regimes for heroin withdrawal remains unclear despite over two decades of methadone-assisted withdrawal studies (see Chapter 1 for reviews). Related to this issue, further research is required which directly compares buprenorphine and methadone in gradual reduction regimes over several weeks, as the only previous comparative study was inconclusive (see Section 1.4.2 for review). Issues regarding the selection of different treatment approaches for withdrawal management are explored in the final Chapter.

4.4.3.1 Adverse events

Most side effects experienced with buprenorphine were generally mild, well tolerated and transient, typically occurring during the first few days of treatment. Most side effects to buprenorphine are characteristic of opioids and have been previously reported in similar proportions in the earlier Outpatient Dose Titration Study (Section 3.3.5), and in maintenance buprenorphine treatment (Ling, Charuvastra et al. 1998; Lange, Fudala et al. 1990). Headache, nausea and vomiting, drowsiness, sweating, and lethargy were reported by more than 5% of subjects.

An adverse event not characteristically seen with other opioid medications is that of precipitated withdrawal, reported by 13% of subjects receiving buprenorphine in this study. In most cases the features of precipitated withdrawal were mild, lasted for several hours, and occurred only after the first buprenorphine dose. However, there were two cases (3%) in which symptoms persisted beyond the first day (both in the context of continued regular heroin use during withdrawal), with patients complaining of moderate to severe features of precipitated withdrawal. Although this side effect can theoretically be avoided by delaying the first buprenorphine dose until the patient is experiencing withdrawal, in practice this is not always feasible - doses can not always be delayed in outpatient treatment due to closing times of

clinics or pharmacies, not all dispensing pharmacists are adequately trained to identify opiate withdrawal, and indeed many of the early features of opiate withdrawal are subjective rather than objective, relying on self-report of patients (which can be unreliable in a clinical context). Considerable emphasis needs to be given to training clinical staff and educating patients in the underlying mechanisms and potential risks of precipitated withdrawal (see discussion regarding the implementation of buprenorphine treatment in Chapter 5).

Mild and transient rebound withdrawal symptoms after the cessation of buprenorphine was experienced by approximately 9% of subjects; and a further 8% experienced rebound symptoms that were of moderate severity and/or had not subsided by day 8. This emphasises the need for continued monitoring and support of patients attempting withdrawal beyond the cessation of medication.

The emergence of withdrawal features following naltrexone induction suggests that complete reversal of tolerance had not occurred in these subjects by day 8, even though the last dose of buprenorphine had been 3 days earlier. Although rebound withdrawal symptoms were typically most pronounced in the 24 to 48 hours after the last dose of buprenorphine, the response to naltrexone on day 8 would suggest that the physiological withdrawal process (neuroadaptation reversal) had not been completed by this time, and that some withdrawal symptoms would persist, although it should be emphasised that subjective withdrawal symptoms persisting into the second week, particularly cravings, sleep and mood disturbances, following all forms of heroin withdrawal are common. All patients undergoing a brief buprenorphine withdrawal regime who do not commence naltrexone or substitution treatment should be warned of the potential persistence of low level withdrawal symptoms for some time after the discontinuation of buprenorphine, and should be encouraged to continue to participate in withdrawal services for several days beyond the cessation of buprenorphine.

4.4.3.2 Levels of functioning and participation in counselling during withdrawal

One of the benefits described by many subjects in this study was the ability of buprenorphine to relieve physical and psychological withdrawal symptoms (cravings, agitation, dysphoria and other mood disturbances), without causing the degree of sedation or drowsiness commonly associated with the use of clonidine and benzodiazepines (and as described by the majority of Control subjects in the study). This potentially reduces the risk of sedative overdose during buprenorphine-assisted heroin withdrawal. Furthermore, this allowed subjects using buprenorphine a better degree of day-to-day functioning during the withdrawal episode, and indeed many subjects continued their routine daily activities (e.g. work, study), a relatively uncommon event when using symptomatic medications. The capacity for buprenorphine to

adequately relieve withdrawal discomfort and mood disturbances without significant sedation, also enabled subjects to more effectively engage in counselling during the withdrawal period. As discussed in the introduction, counselling interventions during withdrawal are usually limited to maintaining motivation, providing support and assistance in coping with withdrawal symptoms and high-risk situations, and examining post-withdrawal treatment options. Although staff - patient contact time between the two study groups was comparable, a common impression among treatment staff was that subjects using buprenorphine generally required less time during appointments addressing issues such as day to day symptom relief, allowing more time to examine broader issues such as goal setting and post-withdrawal linkages.

4.4.3.3 Post-withdrawal treatment options

There are a wide variety of post-withdrawal treatment options available following buprenorphine assisted heroin withdrawal. The potential advantage of buprenorphine over other withdrawal medications in facilitating links to a broader range of post-withdrawal treatment modalities will be explored in greater detail in the final chapter.

Most subjects chose to continue buprenorphine, or commenced methadone treatment during the post-withdrawal period. The uptake of substitution treatment highlights the broad appeal of this treatment modality, being equally applicable to patients who wish to cease heroin use, and to those who are aiming to merely bring their heroin use under control.

As identified in Chapter 1.4.3, clinical procedures for induction onto naltrexone following buprenorphine treatment remain poorly understood, and as such, the experience from this study warrants closer examination. Induction onto naltrexone following buprenorphine treatment was attempted in 6 subjects during days 8 to 11 as per study protocol. Five of the six subjects remained on naltrexone for more than one week, with only one subject discontinuing naltrexone treatment after 4 days. The four subjects who commenced naltrexone on day 8 all experienced moderate to severe withdrawal discomfort within 2 to 4 hours after the first naltrexone dose and persisting for up to 12 to 18 hours. The early withdrawal features were predominately 'autonomic' in nature (sweating, piloerection, lacrimation and rhinorrhoea). These were subsequently replaced by: agitation, sleeplessness, sweating, hot and cold flushes, and abdominal cramps. Symptoms were somewhat relieved by symptomatic medication (clonidine and diazepam), and all cases were successfully managed at home under supervision of a friend or relative. The second dose of naltrexone resulted in less pronounced withdrawal discomfort, although most subjects continued to report side effects to naltrexone (particularly dysphoria and mild withdrawal) for several days. Interestingly, the 2 subjects who initiated naltrexone on days 10 and 11 (5 and 6 days after the last buprenorphine dose respectively)

described no withdrawal discomfort following naltrexone induction. Although these are small numbers, the findings suggest that wherever possible, the initiation of naltrexone should be delayed until more than 3 days after the last buprenorphine dose; however, in circumstances where the patient is concerned about relapse to heroin use, earlier induction onto naltrexone can be achieved as an outpatient, albeit with temporary features of moderate withdrawal severity requiring supervision and ancillary medications.

The commencement of naltrexone before day 8 was restricted by the study protocol. Umbricht and colleagues described a similar approach of initiating naltrexone on day 8 (after a 4 day buprenorphine regime) (Umbricht, Montoya et al. 1999), and these authors also noted an increase in withdrawal features following the initial (50mg) dose of naltrexone. Alternative strategies have been described in the research literature for earlier induction onto naltrexone (Umbricht, Montoya et al. 1999; O'Connor, Carroll et al. 1997). Low naltrexone doses can be administered during the period of buprenorphine dosing, with a gradual increase in naltrexone doses as buprenorphine doses taper off over several days (Umbricht, Montoya et al. 1999). There are potential advantages and disadvantages with each approach. The early naltrexone induction regime requires a shorter period of abstinence from heroin (e.g. less than 48 hours) prior to commencing naltrexone, which is likely to result in a greater proportion of heroin users being able to commence naltrexone treatment. However, this may not always be an advantage, as naltrexone treatment is not well suited to many heroin users (as evidenced by poor retention rates), and better longer term outcomes may be achieved by directing some patients towards maintenance substitution treatment. The early naltrexone induction regime has the advantage of an earlier resolution of withdrawal discomfort, whereas the late induction regime will result in peak withdrawal discomfort late in the withdrawal episode, often when patient motivation is waning. These are somewhat theoretical suppositions, and further research in this area is required.

4.4.4 Summary and conclusion

This open label randomised controlled trial compared the efficacy and cost effectiveness of a short term buprenorphine regime compared to clonidine, benzodiazepines and other symptomatic medications in the management of outpatient heroin withdrawal in specialist treatment settings. The outcomes seen in both groups suggest that withdrawal services are associated with a range of benefits for heroin users during, and in the immediate post-withdrawal period, such as reduced heroin use, reduced severity of dependence, and improved psychosocial functioning, although cessation of heroin use and continued abstinence was an uncommon outcome. There were high rates of retention in treatment 4 weeks after the

withdrawal episode, with substitution treatment as the main post-withdrawal treatment modality selected. In general, subjects who remained in treatment reported considerably better outcomes than those who had discontinued treatment by day 35.

The study demonstrated the enhanced efficacy and cost effectiveness of buprenorphine compared to the symptomatic medication regime. In general, buprenorphine-assisted heroin withdrawal achieved higher treatment retention rates, lower levels of heroin use and better symptom relief. Specifically, subjects randomised to the buprenorphine assisted withdrawal group:

- had significantly lower levels of heroin use and significantly lower severity of dependence on heroin during the outpatient withdrawal episode
- had significantly greater rates of treatment retention in the withdrawal episode
- reported significantly less severe opiate withdrawal symptoms
- reported significantly better levels of psychosocial functioning during the withdrawal episode
- reported higher levels of satisfaction with their medication and withdrawal treatment

Incremental cost effectiveness ratios indicate considerable advantages in using buprenorphine over symptomatic medications in achieving heroin-free days during the withdrawal episode (ratio of 1.7 to 1), and in achieving abstinence from heroin during the withdrawal episode (ratio of 5.5 to 1). There was a similar proportion of subjects reporting adverse events, and the profile of side effects reported in the study were anticipated for each of the medication regimes. There were no severe adverse events reported during the withdrawal episode. The use of other drugs was not significantly impacted upon during withdrawal in either group. The similar findings at each of the two study sites enhance the confidence with which the findings of this study can be generalised to other specialist treatment settings.

Principal findings during the four-week post withdrawal period included: (a) significantly more subjects in the Experimental group entered and remained in drug treatment; (b) subjects in the Experimental group reported significantly less heroin use than Control subjects; and (c) subjects in the Experimental group reported significantly higher levels of psychosocial functioning over the 4 week follow up period (SF-36 scores), although these differences were not significant on comparing levels of functioning by the final week of follow up (using the BASIS - 32).

Importantly, the effect sizes for differences between the two groups on the key outcome and process measures were considerable. Together with the enhanced cost-effectiveness of

buprenorphine, its widespread use for heroin withdrawal should lead to substantial improvements in the delivery and efficiency of withdrawal services for heroin users. The following (and final) chapter will examine issues regarding the uptake of buprenorphine within the drug treatment system, including the development of clinical guidelines for the use of buprenorphine in managing heroin withdrawal.

CHAPTER 5: THE ROLE OF BUPRENORPHINE IN THE MANAGEMENT OF HEROIN WITHDRAWAL

This final chapter examines some key issues in the implementation and uptake of buprenrophine in the management of heroin withdrawal, including the application of principles of evidence-based medicine in clinical-decision making for individual patients undergoing heroin withdrawal; and an examination of broader systemic issues likely to impact upon the uptake of this new approach to withdrawal management within the drug treatment system in Australia. To this end, the chapter concludes with a brief description of the process for the development of national clinical guidelines for the use of buprenorphine for heroin withdrawal in Australia.

5.1 Overview of research studies

5.1.1 Evidence based practice in the management of heroin withdrawal: identifying gaps in the evidence regarding buprenorphine

There is an increasing recognition of the importance of evidence-based practice in clinical medicine, integrating individual clinical expertise with the best available external evidence from systematic research (Sackett, Richardson et al. 1997). The application of the principles of evidence-based medicine to the management of heroin withdrawal is long overdue. As identified in the review of the literature in Chapter 1, there continue to be many unanswered (and in some cases, even unaddressed) questions regarding the safety, efficacy and cost-effectiveness of different withdrawal approaches. Two examples highlight this point. Firstly, although clonidine and methadone are among the two most widely used (and researched) medications for heroin withdrawal of the past two decades, there has been no randomised controlled trial directly comparing these two medications in the management of *outpatient heroin* withdrawal, the setting in which many (if not most) heroin users undergo withdrawal. Secondly, in the area of methadone-assisted heroin withdrawal, the 'optimal' duration of methadone reductions (that is, should we encourage 10 day, 10 week or six month reduction regimes) has not been systematically addressed in the research literature, and the evidence remains equivocal.

Whilst research has failed to address a number of important outstanding questions confronting clinicians and patients in this field, many historical and contemporary practices in the clinical management of heroin withdrawal are not based upon external evidence regarding safety,

efficacy or cost effectiveness. Exponents of evidence-based medicine have identified that, until recently, much of clinical medicine has considered it sufficient to understand the pathophysiological process of a disorder, and to prescribe treatments that had been shown to interrupt or otherwise modify this process (Sackett, Richardson et al. 1997). Hence in recent times, the dissemination and promotion of ultra-rapid opiate withdrawal has occurred despite a lack of evidence about the efficacy of such procedures. A significant task for the alcohol and drug field is to bridge this gap between research evidence and clinical practice in the area of withdrawal management.

This thesis has attempted to address some of the outstanding questions regarding the use of buprenorphine for the management of heroin withdrawal. A review of the research (Section 1.4) identified that: (i) buprenorphine has many of the desired pharmacological properties to treat heroin withdrawal - its use was consistent with the 'pathophysiological processes of the disorder'; and (ii) buprenorphine has been shown in three (of three) randomised trials to be more effective than clonidine in suppressing the severity of withdrawal symptoms. However, there were still considerable gaps identified in the available evidence. Most importantly:

(a) There remained uncertainty regarding the efficacy of buprenorphine in achieving clinical outcomes for heroin withdrawal other than the reduction of withdrawal symptoms. On using the evaluation framework for withdrawal services developed in Section 1.1.3, it was apparent that no previous study had demonstrated significantly greater rates of withdrawal completion for buprenorphine-assisted withdrawal compared to conventional approaches, no studies had demonstrated a greater reduction in heroin use during outpatient withdrawal compared to conventional approaches, and no study had examined post-withdrawal outcomes beyond induction onto one or two doses of naltrexone. This lack of demonstrated efficacy of buprenorphine across a broad range of withdrawal outcomes was due to the limited number of studies in this area (and in particular randomised trials), limited numbers of subjects in (most) studies, and due to evaluation frameworks which have focussed upon symptom relief in inpatient settings and/or studies with naltrexone induction as their end points. Whilst not discounting these as important outcomes, an understanding of broader withdrawal outcomes is critical in order to better understand the role of buprenorphine in the management of heroin withdrawal.

(b) There is considerable uncertainty as to how buprenorphine should be used for heroin withdrawal, due to the limited research examining many of the key issues confronting clinical decision-making (such as how much and for how long buprenorphine should be prescribed). This has been compounded by the fact that most earlier withdrawal studies have used different buprenorphine preparations (often with different bioequivalencies) to the commercially

available product (Subutex®). For example, there have been only two previous descriptions in the published literature of short outpatient buprenorphine withdrawal regimes (Diamant, Fischer et al. 1998; O'Connor, Carroll et al. 1997), neither of which used the sublingual Subutex® tablets commercially available in Australia.

5.1.2 Addressing the gaps in the evidence

The research studies in this thesis have attempted to address some of these gaps in the available evidence. The main study has been the randomised controlled trial of outpatient heroin withdrawal comparing buprenorphine and symptomatic medication regimes in 114 heroin dependent subjects. The framework for this evaluation was established in the Chapter One, identifying a number of key objectives for withdrawal services, with corresponding outcomes and process measures, from which to assess withdrawal services. The study demonstrated the significantly enhanced efficacy of buprenorphine over symptomatic medications in achieving key withdrawal outcomes for outpatient withdrawal, particularly

- the reduction in heroin use during and after withdrawal episode,
- higher rates of retention in withdrawal and post-withdrawal treatment,
- better relief of withdrawal symptoms during the withdrawal episode,
- better general psychosocial functioning and lower severity of dependence on heroin,
- higher levels of patient satisfaction with buprenorphine,
- greater cost-effectiveness

The findings of the randomised trial are the first demonstration of the enhanced efficacy of buprenorphine for most withdrawal outcomes, and will contribute to the evidence base upon which clinical practice draws from.

Questions concerning how buprenorphine should be used were examined in the first two studies of the thesis - Chapter Two examining dosing regimes in inpatient settings, and Chapter Three addressing dosing regimes for outpatient settings. These studies aimed to establish the range of doses of Subutex® required by Australian heroin users, important questions due to the considerable variation of buprenorphine doses and preparations reported in the published literature (ranging from regimes using maximum doses of less than 1 mg per day (Nigam, Ray et al. 1993), to regimes using doses of 12 mg per day (Umbricht, Montoya et al. 1999)). The investigations undertaken were dose titration studies, not randomised trials comparing the efficacy of different dosing regimes, and as such these studies do not claim to have identified the 'optimal' dosing regimes for withdrawal. Nevertheless, these studies provide a sense of the types of doses required by heroin users undergoing withdrawal in different settings, and provide a basis upon which clinicians can tailor doses according to individual circumstances.

Furthermore, the inpatient dose titration study examined, for the first time in the published literature, which patient factors impact upon dosing requirements of individual patients. This knowledge should further assist clinicians in determining dosing regimes for individual patients.

The studies have also provided some insight into, although not necessarily 'resolved', other outstanding questions regarding the use buprenorphine. The randomised trial has provided further evidence regarding the experience of outpatient induction onto naltrexone following short buprenorphine regimes, indicating that induction onto naltrexone can be accomplished soon after the cessation of buprenorphine dosing in an outpatient setting. The research has also provided a better understanding of the adverse events experienced during short buprenorphine withdrawal regimes, which had not previously been addressed in the published literature (see Gowing, Ali et al. 2000).

5.2. Tailoring withdrawal approaches for individual patients

As emphasised by exponents of evidence based medicine (Sackett, Richardson et al. 1997), the application of evidence based medicine is not about identifying from systematic reviews or meta-analyses which is the 'best' medication approach for treating all patients with a particular condition, nor is it about the development of 'cook book' recipes of medication regimes. Rather, the application of the principles of evidence-based practice in clinical decision-making regarding the management of heroin withdrawal must take into consideration a number of factors routinely confronted in clinical scenarios by service providers and individual patients. These include:

1. The evidence regarding the safety and efficacy of different withdrawal regimes.
2. The resources available for withdrawal, including treatment settings, the level of staff expertise, the extent of supervision, monitoring and support available during withdrawal, and the time frame in which withdrawal is to be conducted.
3. The preferences and consent of *informed* patients.
4. The post-withdrawal treatment options being considered by each patient.

This section profiles the different withdrawal approaches reviewed in Chapter 1 against each of these four factors, with particular attention to buprenorphine. A number of clinical scenarios highlight the importance of each of these factors:

- a heroin user who must continue to function in their daily routine (e.g. work) without having the capacity to take 'time out' may have difficulties attempting antagonist-

accelerated or symptomatic withdrawal due to the severity of withdrawal and the sedating effects of the medication regimes; and should perhaps consider a gradual reduction regime using methadone or buprenorphine, thereby postponing severe withdrawal features until respite from work or child care is organised.

- a patient who is very keen to commence long term naltrexone treatment should generally avoid methadone-assisted withdrawal, as the use of a long-acting opiate agonist will delay and complicate induction onto naltrexone.
- alternatively, the heroin user who is not interested in long term naltrexone treatment for relapse prevention should probably not be subjected to the expense and risks associated with antagonist-accelerated withdrawal.
- a heroin user who does not wish to use any opiate medication during withdrawal should avoid the use of methadone or buprenorphine.

5.2.1 Research evidence regarding safety and efficacy

Issues regarding the safety and efficacy of the four main medication approaches to heroin withdrawal were reviewed in detail in Sections 1.3 and 1.4. To this body of work can be added the findings from the research conducted as part of this thesis. The general trends of the comparative randomised trials of the different withdrawal medications are summarised in Table 5.1. The research evidence regarding the safety and efficacy of the different medications, and buprenorphine in particular, is accumulating, yet it appears that buprenorphine generally has better outcomes than adrenergic agonists. Further work comparing buprenorphine and methadone withdrawal is a high research priority, given the widespread use of methadone reductions in withdrawal programs internationally.

The available research evidence is however not limited to the findings of comparative randomised controlled trials. Chapter 1 reviewed the evidence regarding the relative merits and disadvantages of buprenorphine, methadone, adrenergic agonists, and naltrexone for the management of heroin withdrawal. Table 5.2 attempts to summarise the evidence regarding key issues in the use of each of the four different medication approaches against the main objectives and process measures for withdrawal services, incorporating the findings from the studies conducted in this body of research.

Table 5.1. General findings of randomised trials comparing medications for heroin withdrawal

	Methadone	Adrenergic agonists	Antagonist accelerated withdrawal
Adrenergic agonists	Broadly similar outcomes in inpatient settings (Chapter 1.3.1 & 1.3.2 for review) No direct comparison for outpatient heroin withdrawal		
Antagonist accelerated withdrawal	No direct comparison available in published research literature	Comparable regarding rates of withdrawal completion; and induction onto naltrexone (O'Connor et al 1997; Guerra et al 1995).	
Buprenorphine	Limited evidence (Bickel et al 1988) suggests buprenorphine and methadone comparable outcomes in gradual outpatient regimes. No direct comparison of short term withdrawal regimes.	Buprenorphine more effective in • reducing withdrawal severity (Nigam et al 1993; Cheskin et al 1994; O'Connor et al 1997; *Chapter 4*) • reducing heroin use in outpatient settings (*Chapter 4*) • increasing post-withdrawal treatment retention (*Chapter 4*). Comparable completion rates for inpatient withdrawal (Nigam 1993; Cheskin 1994)	Buprenorphine more effective in reducing withdrawal severity (O'Connor et al 1997). Comparable efficacy reported for completion rates and rates of induction onto naltrexone (O'Connor 1997).

Table 5.2 Comparison of four medication approaches against objectives of withdrawal services.

Treatment objectives	Methadone assisted	Adrenergic agonists (clonidine, lofexidine)	Buprenorphine assisted	Antagonist accelerated (naltrexone, naloxone)
To alleviate the severity of withdrawal discomfort	Delays onset of peak withdrawal symptoms until approximately time of last dose. Symptoms persist for ~ 10 - 14 days following last methadone dose (depending upon the duration of methadone treatment)	Relief of symptoms without delaying or prolonging withdrawal syndrome. Particularly effective in reducing 'autonomic' withdrawal features, but less impact upon cravings, muscle cramps, sleep or mood disturbances. Ancillary medications (e.g. benzodiazepines) are often used for refractory withdrawal symptoms.	Good relief of withdrawal symptoms. Using short courses (<1 week), symptoms peak in severity usually prior to second dose, with minimal or mild withdrawal following cessation of dosing in most patients. Prolonged courses (weeks) appear to have more severe and prolonged rebound withdrawal, often lasting for several (5 - 10) days.	Peak symptoms increased in severity and occur after initial antagonist dose. Peak withdrawal features of short duration (24-48 hrs), and require sedation (typically benzodiazepines) and other medications (typically adrenergic agonists). Residual low level symptoms often persist for several days.
To prevent the development of severe withdrawal sequelae and complications, including adverse events, overdoses or abuse of medication	Greater control over timing of peak withdrawal symptoms allows time to stabilise concomitant medical or psychiatric conditions. Risk of overdose in combination with other sedative drugs, or if initial methadone doses are too high (due to inadequate assessment and supervision). Methadone toxicity is potentially fatal. Extent of abuse of methadone is related to system of dispensing. Supervised dispensing limits abuse (e.g. injection) and diversion of methadone, however increases costs and inconvenience of service delivery.	Side effects (particularly hypotension with clonidine and sedation) are poorly tolerated in some individuals, and can limit use of effective doses. Risk of toxicity with high doses, and / or overdose in combination with other sedatives. Clonidine abuse has been reported and overdose is potentially fatal. Risk for abuse and/or diversion of ancillary withdrawal medications (benzodiazepines) Short duration of action requires multiple doses per day, and hence take-home medication in outpatient settings. This increases the potential for abuse and/or diversion.	Greater control over timing of peak withdrawal symptoms allows time to stabilise concomitant medical or psychiatric conditions. Risk of overdose in combination with other sedative drugs. Risk of precipitated withdrawal on commencing buprenorphine. Extent of abuse of buprenorphine is related to system of dispensing. Supervised dispensing limits abuse (e.g. injection) and diversion, however increases costs and inconvenience of service delivery.	The increase in withdrawal severity may complicate concomitant medical or psychiatric conditions. High incidence of (anticipated) adverse events requiring management (e.g. severe agitation, vomiting, diarrhoea, dehydration, delirium). Uncommon, but severe risks associated with heavy sedation or anaesthesia (e.g. death, respiratory infections) Risk of heroin overdose following the cessation of naltrexone treatment. Overdose risk may be due to markedly reduced tolerance to opioids, and from ancillary sedating medications (e.g. benzodiazepines, clonidine).

Table 5.2 - continued

	Methadone assisted	Adrenergic agonists	Buprenorphine assisted	Antagonist accelerated
To interrupt a pattern of regular and heavy heroin use	Methadone substitutes for heroin. It reduces heroin use by relieving withdrawal symptoms and cravings. Types of doses used in withdrawal do not generally block the effects of additional heroin use. Moderate and prolonged rebound withdrawal often associated with high rates of relapse upon the cessation of methadone.	Adrenergic agonists can indirectly reduce heroin use by alleviating withdrawal symptoms, but minimal impact upon cravings and no 'blockade' of the effects of additional heroin use. Adrenergic agonists do not prolong withdrawal, thereby reducing the period of time required for the reversal of tolerance.	Buprenorphine substitutes for heroin. It reduces heroin use by relieving withdrawal symptoms and cravings and doses > 4 mg block the effects of additional heroin use. Mild rebound withdrawal and short prolongation of withdrawal (in short courses) reduces opportunity for relapse to heroin use.	Naltrexone is very effective in reducing heroin use by blocking the effects of additional heroin use and reducing cravings. Few patients on naltrexone continue to use heroin regularly. Acceleration of withdrawal reduces the opportunity for relapse to heroin use.
To facilitate linkages to post withdrawal services	Methadone-assisted withdrawal is ideally suited to facilitating links to longer-term methadone maintenance programs. Patients who do not cease their heroin use during the withdrawal should generally not discontinue methadone. The use of methadone often delays the commencement of opiate-free post-withdrawal treatment. Naltrexone should be delayed for at least 7 to 10 days after methadone. Similarly, drug-free residential rehabilitation programs generally do not admit patients until the resolution of withdrawal symptoms (eg 5 to 10 days after the last dose). Many patients will relapse to heroin use in the intervening period.	Adrenergic agonists are particularly well suited to subjects considering drug free post withdrawal treatment modalities, such as residential services or naltrexone treatment. The sedating properties of clonidine and other common ancillary symptomatic medications (eg benzodiazepines), and the reduction of opioid tolerance associated with symptomatic withdrawal requires that additional caution be exercised in commencing substitution maintenance treatment, in order to prevent methadone related toxicity.	Buprenorphine is ideally suited to a range of post withdrawal treatment options. Buprenorphine can be continued as a maintenance program for those individuals unable or unwilling to consider complete abstinence from all opioids. Naltrexone can be commenced without significant delays, either during a short course of buprenorphine, or soon after its discontinuation. The limited prolongation of withdrawal should not delay entry into drug-free residential rehabilitation programs or other counselling programs.	Naltrexone accelerated withdrawal is ideally suited to those heroin users who wish to continue in long term naltrexone treatment. A limitation of this approach is that a considerable proportion of patients will discontinue naltrexone within days or weeks, and relapse to heroin use. Induction into substitution maintenance treatment is potentially complicated following naltrexone treatment due to the reversal of opioid tolerance, and the sedating properties of common ancillary medications (clonidine, benzodiazepines). Additional caution must be exercised in commencing maintenance substitution treatment.

Table 5.2 - continued

Process Issues	Methadone assisted	Adrenergic agonists (clonidine, lofexidine)	Buprenorphine assisted	Antagonist accelerated (naltrexone - clonidine)
Setting	Can easily be accommodated in an outpatient setting. Restricted use in inpatient settings due to the prolongation of withdrawal, and the increasingly shorter admission times available in withdrawal units.	Ideally suited to short-term residential withdrawal programs, where greater monitoring of side effects, response and dose titration is possible. Risks of side effects, abuse and / or diversion of medication require some degree of supervision in outpatient settings, and staff with some expertise in their use.	Suited to either short or longer gradual reduction regimes in outpatient settings. Supervised dispensing limits abuse or diversion potential. Short courses of buprenorphine (3 to 5 days) are well suited to residential withdrawal programs.	Ideally suited to residential settings due to the severity of withdrawal symptoms, levels of monitoring required, and the need for large amounts of ancillary medications. Rapid opiate withdrawal can be performed in outpatient settings, although this requires intensive resources and supervision by staff, family or friends in a stable environment
Cost and accessibility	Methadone is an opioid drug, often with restrictions regarding which service providers can prescribe and dispense the medication. This limits the availability and access to treatment. Furthermore, the regulatory controls regarding the use of methadone in many jurisdictions (e.g. permits), increases the paperwork and delays in commencing services.	Few restrictions in the use of these medications, and are widely available. Widespread prescribing of ancillary symptomatic medications for withdrawal (in particular benzodiapezines) may contribute to abuse, diversion and the expensive phenomenon of 'doctor shopping'.	Buprenorphine is an opioid medication, often with restrictions regarding which service providers can prescribe and dispense the medication. This limits the availability and access to treatment. Furthermore, the regulatory controls regarding the use of methadone in many jurisdictions (e.g. permits), increases the paperwork and delays in commencing services.	Ultra-rapid withdrawal procedures require intensive hospital settings and anaesthesia, thereby increasing the cost of treatment, and restricting accessibility. Supportive home environments and suitable support people are not available for many heroin users. This limits the accessibility of this treatment approach Service providers need considerable resources and expertise, and it is generally recommended that should only be attempted by specialists, thereby limiting its accessibility.

5.2.2 Resource availability and accessibility

An important feature of withdrawal services is that they should be readily accessible to patients, and withdrawal approaches which are simple to deliver and relatively inexpensive will offer advantages over resource intensive and expensive services (such as antagonist-accelerated withdrawal approaches). The experience of using buprenorphine in these research studies was that it is a relatively easy medication to use (in specialist agencies), amenable to both short inpatient and outpatient withdrawal settings, without requiring intensive resources from the patient or service. The incremental cost of delivering outpatient withdrawal services with buprenorphine was comparable to using symptomatic medications, and buprenorphine was found to be considerably more cost-effective than conventional symptomatic medication in an outpatient setting. The once-a-day outpatient dosing regimes did not significantly interfere with patient lifestyle, although this may be difficult to co-ordinate in rural or remote treatment settings. Issues regarding the uptake of buprenorphine treatment by service providers and its accessibility as a treatment option will be considered further in Section 5.3.

5.2.3 Patient preference

The vast majority of subjects in the three studies expressed high rates of satisfaction with buprenorphine, and it is likely that buprenorphine will become a popular medication for withdrawal among heroin users. However, these findings were among a group of heroin users who were prepared to participate in these studies, and may not reflect the preferences of all heroin users. There will be a proportion of heroin users who are reticent to use an opioid medication for withdrawal; there will be others who prefer the use of a full opioid agonist such as methadone; and a proportion of heroin users will be attracted to the idea of an 'anaesthetised' withdrawal using ultra-rapid accelerated withdrawal procedures.

5.2.4 Post-withdrawal treatment options

In order to optimise retention in post-withdrawal treatment, withdrawal regimes should be initiated which are matched to the post-withdrawal treatment options best suited to each patient. As described earlier, the use of methadone for withdrawal complicates induction into abstinence oriented post-withdrawal treatment (such as naltrexone or residential rehabilitation programs), however facilitates entry into methadone maintenance treatment; whereas the use of naltrexone for withdrawal is not appropriate for the large numbers of heroin users who are not prepared or suited to continue in long term naltrexone treatment. Ideally, these issues should be identified at the commencement of treatment.

Unfortunately, the optimal post-withdrawal treatment modality can often be difficult to identify at initial presentation and clinical assessment, for a number of reasons. One important issue is that most heroin users identify long term abstinence as a treatment goal, yet only a (small) proportion achieve this outcome even in the short term[5], so that linking patients into abstinence-based post-withdrawal treatment modalities (such as naltrexone) at the outset of withdrawal attempts may not always be appropriate, despite the initial wishes of patients (and their families). Another difficulty in matching patients to post-withdrawal treatment at the commencement of a withdrawal episode is that many heroin users presenting for withdrawal services may have unrealistic expectations of the need for longer term treatment, and/or may be unfamiliar with, or ambivalent about, longer term treatment options. In some circumstances, the capacity for long-term treatment planning at the initial assessment is limited due to inadequate assessment time, staff expertise, or due to the patient presenting in crisis, with crisis management becoming the focus of the initial interventions.

A potential advantage of using buprenorphine for withdrawal is the greater variety of post-withdrawal treatment options available compared to the other withdrawal medication approaches. Rather than attempting to identify appropriate post-withdrawal treatment options at the initial presentation, the patient can be stabilised on buprenorphine for several days, with minimal withdrawal discomfort, sedation or inconvenience. During this time, the patient and clinicians have the opportunity to examine longer-term treatment needs and explore available options. Patients who are keen to commence naltrexone treatment can be inducted onto naltrexone either while the patient is taking buprenorphine, or after a brief interlude of several days. For the majority of patients, continued use of buprenorphine for a longer period of time may be preferable, either as a gradual reduction withdrawal regime, or as a long-term maintenance medication. Transfer to methadone can also be an option, particularly for those individuals who have difficulties stabilising on buprenorphine (for example, those continuing to use heroin). Alternatively, patients wishing to discontinue all medication can do so, with minimal rebound withdrawal. The use of buprenorphine for heroin withdrawal can be considered as a 'gateway' for heroin users entering treatment, linking withdrawal with post-withdrawal services. The gateway model of treatment is schematised below. A similar model has been developed for the use of buprenorphine as a maintenance medication (Ling 1998), emphasising the versatility of buprenorphine in treatment planning.

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[5] Note, that this is not necessarily a reflection of poor withdrawal treatment, nor of unmotivated patients - patients usually desire the best possible treatment outcomes in most areas of clinical medicine - for example, if patients undergoing surgery for cancer were asked "how important is a complete cure of your cancer", the vast majority could be expected to respond: "very important".

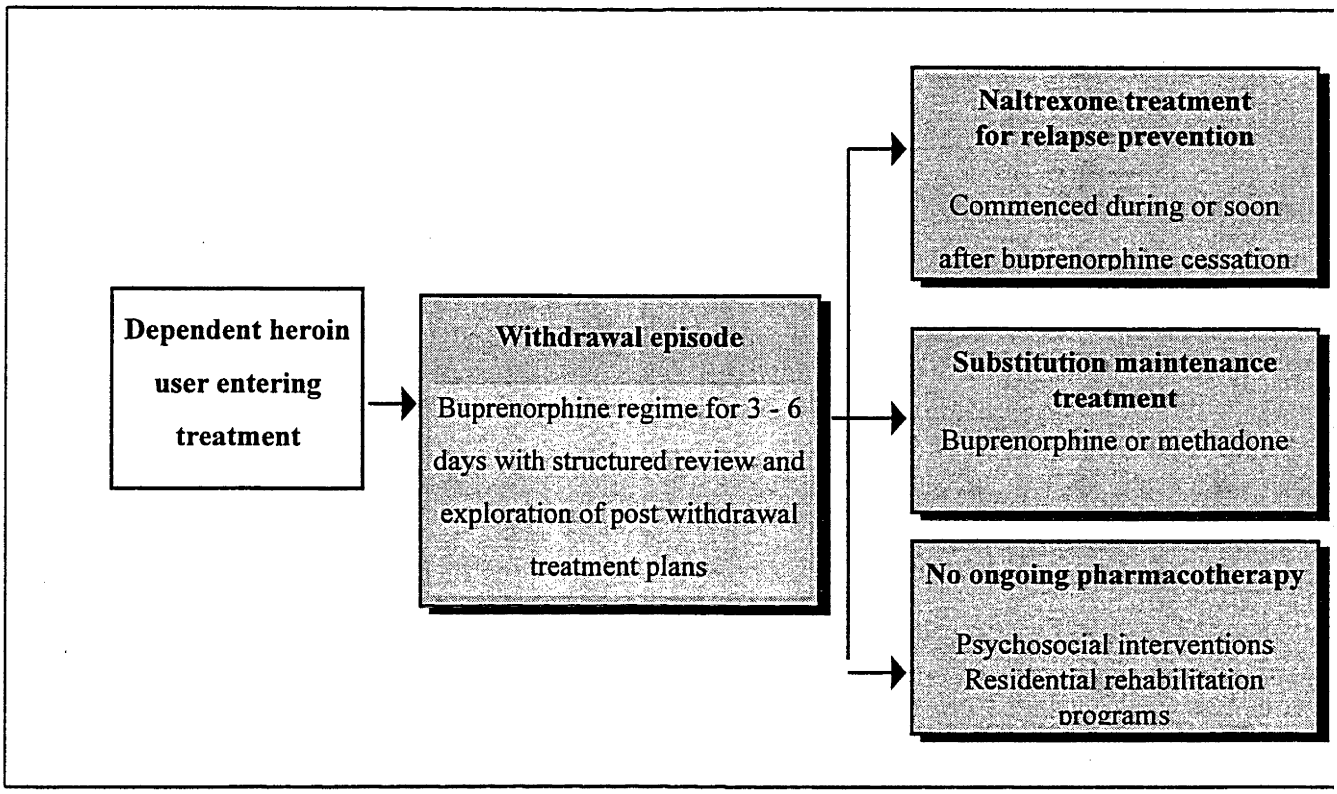

Figure 5.1. Gateway model of withdrawal management with buprenorphine

The combination of these four factors – safety, efficacy and cost effectiveness, ease of service delivery and accessibility, high levels of patient satisfaction, and greater flexibility with regards to post withdrawal treatment options - all suggest that buprenorphine provide a significant development in the management of heroin withdrawal for individual patients. The next section will explore issues regarding the dissemination of buprenorphine for this purpose.

5.3 The uptake of buprenorphine for withdrawal in treatment systems

5.3.1 Factors impacting upon the uptake of treatment innovations

The previous section examined issues regarding the choice of medication regimes for individual patients, assuming these options are readily available in the treatment system. However, it would be incorrect to assume that drug treatment systems will automatically embrace buprenorphine as a maintenance or withdrawal medication. There are historical examples of treatment systems not widely incorporating pharmacotherapies that have been shown to be safe, effective and cost efficient treatment approaches. Most notably has been the

limited uptake of LAAM, which despite the favourable available evidence regarding its safety and efficacy, it remained under-utilised throughout the 1990's in most countries in which it had been registered (Rawson, Hasson et al. 1998).

This process can be understood by recognising that the uptake of a new treatment innovation in the health sector is influenced by a number of factors. Barriers to improving clinical effectiveness may include inadequate dissemination of information on effective interventions, failure of clinicians to act on information received, disincentives to change (such as financial considerations), or public perceptions of the appropriateness of new interventions which conflict with the best available evidence. In considering how clinical interventions can be made more effective, (Haines, Freemantle et al. 1996) identified five characteristics of treatment innovations that influence their uptake by the health sector. The characteristics of buprenorphine-assisted heroin withdrawal are considered for each:

1. Relative advantage: how much better is the new intervention than available interventions Previous research, and the findings of the randomised trial suggest that buprenorphine-assisted withdrawal is associated with considerably better outcomes than combined symptomatic medications. Most importantly, the effect sizes for key outcomes in this study were considerable, indicating that few patients need to undergo buprenorphine-assisted withdrawal in order for clinicians and patients to see advantages on a range of outcomes (NNT on most key withdrawal outcomes were less than 10).

2. *Compatibility: the extent to which the intervention is compatible with existing understandings, values and systems.* The principle of using substitution medication for managing withdrawal is well established (nicotine replacement therapy, benzodiazepine reductions, methadone-assisted heroin withdrawal). Although buprenorphine has a number of pharmacological properties than differ from methadone, the fundamental principles of its use are not dissimilar. Buprenorphine can be successfully used in short courses, in order to be compatible with the model of brief withdrawal episodes (particularly inpatient services), which predominate in Australia (or can be used in more protracted reduction regimes, as is more common in Europe and the USA).

3. Complexity: is the new intervention too difficult to learn or do. The general experience from these studies was that buprenorphine-assisted heroin withdrawal is not difficult to deliver within specialist treatment settings. The extent to which these findings can be replicated in general practice settings is currently being examined in a randomised trial in Sydney comparing buprenorphine withdrawal (and a three month post-withdrawal treatment phase) in a specialist outpatient drug clinic and general practitioner settings (personal

communication, James Bell, Nov 2000). The uptake of buprenorphine by service providers will be facilitated by the development and dissemination of clinical guidelines, training programs, and relevant patient literature. These resources have been prepared for use in Australia, and are discussed in the following section.

4. Trialability: the capacity for service providers and patients to 'give it a go' without too much long-term commitment or investment. In addition to having access to clinical guidelines and training programs, service providers must be able to trial buprenorphine without too much commitment or investment. On this point, buprenorphine has certain advantages over antagonist-accelerated withdrawal procedures (particularly ultra-rapid opiate withdrawal), which require considerable initial resource allocation and investment in training. However, the main issue regarding the 'trialability' of buprenorphine relates to its regulatory controls. Buprenorphine is an opioid medication, and will therefore be subject to certain regulatory restrictions in most countries. For example in Australia, restrictions regarding its use are being introduced which are generally similar to those in place for methadone treatment: in which only medical practitioners who have undergone approved training will be authorised to prescribe buprenorphine, with authorised pharmacies dispensing buprenorphine under supervision. The rationale for these restrictions is to enhance the quality (safety and effectiveness) of service provision (Allsop, Bell et al. 1997), and to limit the extent of diversion and abuse of medication. However, this approach is likely to result in a restriction of the accessibility of treatment with buprenorphine, as only a small proportion of Australia's medical practitioners are authorised to prescribe medications such as methadone. For example, a review of the Victorian community based methadone program indicated that less than 5% of registered general practitioners are authorised to prescribe methadone (Lintzeris, Koutroulis et al. 1996). It is unclear as to how the small number of authorised prescribers will meet the additional demand for heroin withdrawal services using buprenorphine. Patient demand may result in an substantial increase in the number of doctors prepared to become an authorised prescriber of substitution pharmacotherapies; or the small number of authorised service providers may result in the limited availability of buprenorphine as a withdrawal medication.

Several countries have proceeded with a more liberal approach to the availability of buprenorphine treatment than the system proposed for Australia. In particular, France has allowed buprenorphine to be widely prescribed by any medical practitioner, without conditions of supervised dispensing. Whilst this has resulted in widespread availability of buprenorphine treatment, with approximately 50,000 heroin users being prescribed buprenorphine (Auriacombe, Franques et al. 2001), this has not been without certain

problems. Individual patient outcomes may be compromised by unsupervised dispensing and by inadequately skilled service providers, and there must be some concerns regarding the safety of buprenorphine when diverted to non-treatment populations (Reynaud, Petit et al. 1998; Obadia, Perrin et al. 2001; Tracqui, Kintz et al. 1998). Interestingly, despite the absence of restrictions for medical practitioners to prescribe buprenorphine in France, a similar trend has been observed where only a minority of medical practitioners become involved in treating heroin users, and indeed the majority of heroin users are treated by a very small proportion of doctors (Moatti, Souville et al. 1998).

5. *Observability: do the clinician & patient get positive outcomes.* There were highly favourable responses to buprenorphine from patients and clinicians.

Based on the factors identified by Haines and colleagues, the uptake of buprenorphine within the Australian treatment system appears promising, although not without potential barriers. Clearly, many of the decisions made by governments and the pharmaceutical industry will substantially impact upon the uptake of buprenorphine in Australia (and elsewhere). These include: which doctors and pharmacists are allowed to prescribe and dispense buprenorphine; the availability of clinical guidelines and training programs for service providers; the regulations regarding supervised versus unsupervised dispensing; and mechanisms for funding buprenorphine treatment. Buprenorphine is a relatively expensive medication in comparison to methadone or clonidine, and although the cost of buprenorphine for short withdrawal regimes is not prohibitive, many patients will not be able to afford gradual reductions regimes (over weeks or months), or the benefits of post-withdrawal buprenorphine maintenance treatment without some form of subsidisation.

5.3.2 Clinical guidelines for the use of buprenorphine in managing heroin withdrawal

The previous discussion identified several key issues in the uptake of buprenorphine by the Australian treatment system, such as having sufficient numbers of service providers authorised to deliver buprenorphine treatment, the dissemination of knowledge and expertise regarding its use (particularly clinical guidelines and training programs), and the extent of government subsidisation of the cost of the medication. This section examines the development of clinical guidelines and procedures regarding the use of buprenorphine for the management of heroin withdrawal.

Developing clinical guidelines

Clinical guidelines have been defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical conditions" (Institute of Medicine 1992). Clinical procedures refer to the processes involved in the delivery of treatment. Guidelines and procedures are aimed at ensuring efficiency, effectiveness and appropriateness of healthcare intervention (Miles and Lugon 1996).

There is considerable literature regarding the development of guidelines for clinical practice, which is beyond the scope of this thesis. Contemporary approaches (Grimshaw and Russell 1993; Grimshaw, Freemantle et al. 1995; Eccles, Clapp et al. 1996; National Health and Medical Research Council 1998) emphasise that central factors in the validity and integrity of clinical guidelines are:

- A systematic review of available evidence. A systematic review requires the application of definitive search strategies and inclusion criteria for studies. This is in preference to methods utilising consensus of expert opinion (which may perpetuate the biases or traditions of practice of those involved), or unsystematic review of the literature.
- Linking guidelines to available evidence. Guidelines should link the recommendations with the quality of the supporting evidence.
- Inclusion of all relevant disciplines in the process of guideline development.

The evidence considered by most systematic reviews of an area of clinical practice is often limited to findings from randomised controlled trials (Sacket 1986)). However, there is also recognition by many commentators that there are considerable 'grey zones' of clinical practice where the evidence in relation to competing clinical options is incomplete or contradictory (Naylor 1995; Polychronis, Miles et al. 1996; Lomas, Anderson et al. 1988). In such circumstances consensus approaches for developing guidelines are required, in order to avert was has been termed by one author as "paralytic indecision" on the behalf of clinicians. In practice, most clinical guidelines utilise a combination of evidence based and consensus based recommendations, preferably with an indication as to the quality of the evidence supporting each recommendation.

Another factor to be taken into consideration in the development of guidelines is the extent to which recommended practices are realistic and practical for the given clinical situation (Fowkes 1982). Clinicians are less likely to adhere to guidelines or take up recommendations if they are not compatible with existing understandings, values or systems of service delivery (Haines, Freemantle et al. 1996).

The development of national clinical guidelines for buprenorphine-assisted heroin withdrawal

The need for the development of clinical guidelines for the use of buprenorphine for managing heroin withdrawal and for maintenance treatment was identified by the National Expert Advisory Committee for Illicit Drugs (NEACID), pending the registration and introduction of buprenorphine into Australia for the management of heroin dependence. A similar process has led to the development of guidelines for the use of naltrexone for the management of opioid dependence (Bell, Kimber et al. 1999). A national consensus panel of senior clinicians, researchers and consumer representatives were brought together under the auspices of NEACID to develop national clinical guidelines, with the final report becoming the National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence (Lintzeris, Clark et al. 2001), of which a chapter is dedicated to the use if buprenorphine in managing heroin withdrawal. A copy of the published guidelines is included as Appendix 3.

Whilst these guidelines are the product of a consensus panel, I was the principle author of these guidelines, and in particular, the section on heroin withdrawal draws heavily from research undertaken as part of this thesis. The systematic review of buprenorphine in heroin withdrawal has been conducted as part of this thesis (Section 1.4) and a separate systematic Cochrane review process was completed contemporaneously (Gowing, Ali et al. 2000). The findings of the inpatient and outpatient dose titration studies, and experiences with naltrexone induction have informed the development of the recommendations regarding dosing regimes contained in the national guidelines, although it is recognised that further research is required on these topics. These guidelines will need to be updated as more experience with buprenorphine-assisted withdrawal accumulates, and as better evidence becomes available.

It should also be noted that the recommended dosing regimes for inpatient and outpatient heroin withdrawal using buprenorphine developed in this research have also been adopted by the pharmaceutical company Reckitt Benckiser in Australian (and international) product labels for Subutex® (see Appendix 4).

In addition to the development of clinical guidelines, a Subutex® National Training Package for Health Professionals (Lintzeris, Connolly et al. 2001) has been published by the pharmaceutical company Reckitt Benckiser, to assist in the dissemination of clinical expertise among service providers. Again, the module on heroin withdrawal in this training package is based upon the work of this thesis, and is consistent with the national clinical guidelines. This

training package has formed the basis for training of medical practitioners and pharmacists across Australia since the registration of Subutex®.

5.4 Conclusion

This research has examined a number of issues relating to the use of buprenorphine in managing heroin withdrawal. Having established a framework for evaluating withdrawal services, a review of the literature identified several areas requiring further investigation, which were then investigated in three separate research trials. The first trial identified suitable dosing regimes for inpatient heroin withdrawal using the commercially available preparation (Subutex®), including an examination of the impact of patient characteristics upon dosing requirements. The second study developed a suitable brief, outpatient dosing regime for heroin withdrawal, which was subsequently examined in the third and largest study - a randomised controlled trial of buprenorphine compared to symptomatic medication (including clonidine and benzodiazepine). This study demonstrated buprenorphine to be superior to conventional symptomatic withdrawal mediations on most outcomes. This study was the first trial to demonstrate enhanced outcomes of retention in withdrawal and post-withdrawal treatment, reduction in heroin use during withdrawal episode, enhanced psychosocial outcomes, and greater cost-effectiveness for buprenorphine compared to symptomatic medication. From this research, the 'gateway model' of using buprenorphine as the primary medication option for heroin users entering withdrawal services has been developed, allowing greater flexibility in post-withdrawal treatment matching. The findings of this research have subsequently been incorporated into national clinical guidelines and training programs for health professionals in the management of heroin withdrawal with buprenorphine.

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APPENDICES

BUPRENORPHINE IN THE MANAGEMENT OF HEROIN WITHDRAWAL

DR N LINTZERIS

List of Appendices

APPENDIX 1

Outpatient Heroin Withdrawal Using Buprenorphine Randomised Control Trial

Turning Point Alcohol & Drug Centre, Victoria
The Langton Centre, Sydney

Case Record Forms

Case Record Forms (CRF'S)

Telephone / Triage Assessment

- T.A.W.Checklist (F144TAW.DOC)

Day 1 (Intake) Clinician Assessment

- Turning Point Assessment Module
- Patient Information Sheets (F146INFO.DOC)
- Brief Screening Form (F145BRSN.DOC)
- Study Rejection Form (F151RJCN.DOC)

Day 1 (Intake) Medical Officer Assessment

- Medical History Summary (F04MED2.DOC)
- Client Physical Examination (F05aPHYS.DOC)
- Medication History (F155MDHX.DOC)
- Birth Control Assessment (F05bBRTH.DOC)
- DSM-IV Criteria For Opiate Dependence (F33DSMOP.DOC)
- Consent for DPU Information (F116DPUC.DOC)
- H&CS Permit Application for Treatment with Schedule 8 Drugs.
- Client Eligibility Validation (F156VALD.DOC)

Day 1 (Intake) Research Assessment

- Resesrach Consent Form (F154CONS.DOC)
- Follow -up Locator Form & Consent (F51FUP.DOC)
- Previous Drug Treatments & Additional Demographics (F148TMNT.DOC)
- Opiae Treatment Index (OTI) - Section 2 (F19OTI2.DOC)
- Basis - 32 (F17BASIS.DOC)
- LEEDS Dependence Questionnaire (F18LEEDS.DOC)
- Health Status Profile (SF-36) (F55SF36.DOC)
- The Assessment of Quality of Life Index (AQOL)
- Goals of Treatment (F149Goal.DOC)
- Withdrawal Expectance V.A.S. (F150EXPC.DOC)

Clinical Data Collection During Withdrawal Episode

- Contact Record Form (F152CNTC.DOC)
- Clinician report Form (F08bOOWS.DOC)
- Client Report Form (F08cSOWS.DOC)
- Review Form (F153REV.DOC)

Day 8 - Post-Withdrawal Treatment Medical Assessment

- Post-withdrawal Eligibility Checklist (F163DAY8.DOC)
- Patient Information Sheets for Post-withdrawal Treatment Options (F160INF2.DOC)
- Patient Consent Form (F154CONS.DOC)
- Opiate Antagonist Challenge Withdrawal Rating Form (F164CHAL.DOC)
- Summary of Adverse Events (F165ADEV.DOC)

Day 8 - Research Assessment

- Weekly Drug Use Diary (F157DIRY.DOC)
- Medication History (F155MDHX.DOC)
- Utilisation of Other Health Services (F162SERV.DOC)
- LEEDS Dependence Questionnaire (F18LEEDS.DOC)
- BASIS-32 (F17BASIS.DOC)
- Client Ratings of Withdrawal (F158RATG.DOC)
- Attainment of Client Goals - day 8 (F159GA.DOC)
- Client Satisfaction with Medication (F161SATS.DOC)

Day 1 -35 - Termination from the Study: Medical Assessment

- Summary of Adverse Events (F165ADEV.DOC)
- Termination From the Study (F168TERM.DOC)

Day 35 - Research Assessment (Follow-up)

- Opiate Treatment Index (OTI) - Section 2 (F19OTI2.DOC)
- Basis - 32 (F17BASIS.DOC)
- LEEDS Dependence Questionnaire (F18LEEDS.DOC)
- Health Status Profile (SF-36) (F55SF36.DOC)
- Attainment of Client Goals - day 35 (F166GA2.DOC)
- Previous Drug Treatments - day 35 (F167TMT2.DOC)
- AQOL

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

T.A.W. CHECKLIST

Office Use only

Client Name _____

Study Code |_|_|_|_| Staff Initials |_|_| Date |_|_| / |_|_| / |_|_|_|_|
day month year

A. POTENTIAL ELIGIBILITY CRITERIA

Is the client aged between 18 - 65 years?	1[ ]	Yes	0[ ]	No**
Is the client is heroin dependant?	1[ ]	Yes	0[ ]	No**
Is the client dependant on alcohol, benzodiazepines or other psychostimulants?	1[ ]	Yes**	0[ ]	No
Is the client seeking outpatient treatment at Turning Point and is geographically appropriate?	1[ ]	Yes	0[ ]	No**
Does the client have any major medical or psychiatric problems?	1[ ]	Yes**	0[ ]	No
Has the client been in any form of methadone treatment in the last 2 months?	1[ ]	Yes**	0[ ]	No
Is the client pregnant or breastfeeding?	1[ ]	Yes**	0[ ]	No

ANY TICK IN SECTION MARKED WITH A '**' RESULTS IN INELIGIBILITY FOR HWBR

B. DOES THE CLIENT HAVE A CURRENT PARTNER WHO IS ALSO CONSIDERING OUTPATIENT HEROIN WITHDRAWAL AT TURNING POINT?

1[ ] Yes 0[ ] No

C. OUTCOME OF TELEPHONE ASSESSMENT / TRIAGE OR OTHER COMMENTS

Randomised Trial of Outpatient Heroin Withdrawal
Background Information for Clients

Overview of the research

Turning Point is conducting a study looking at different medications for treating heroin withdrawal. The aim of the study is to see how a new medication, buprenorphine, compares to current medications used for treating heroin withdrawal. It is a randomised trial, which means that the withdrawal medication that a client gets is determined by chance (randomly). This is the only way to really know which medication works better for most people in withdrawal. There are two stages to the research:

Withdrawal treatment.

This is an 8 day outpatient withdrawal program at Turning Point. Services include counselling and support during withdrawal, and the use of one of two medication regimes.

- Symptomatic medication for heroin withdrawal: this includes doses of clonidine (Catapress®), diazepam (Valium®), ibuprofen (Brufen®), metoclopramide (Maxolon®), Lomotil ®, quinine and Buscopan® tablets. Medications are available for the first 6 days, with higher doses during the first 3 days when symptoms are usually more severe. All medication is dispensed daily from the Turning Point pharmacy.
- Buprenorphine: this is an opiate type medication that is only available for treating heroin use in Australia as part of research. Buprenorphine is available for 5 days as part of the withdrawal, with tablets being dispensed daily from the Turning Point pharmacy.

Clients who volunteer for the study do not choose which type of medication they get: that is done randomly by a computer, with every client having a 50% chance of getting either the symptomatic withdrawal or buprenorphine medication for their withdrawal . Counselling and support will be the same for clients in both groups.

Post withdrawal treatment

Following the withdrawal period (8 days), all clients have the option of continuing in some form of treatment at Turning Point (although continued treatment is not mandatory). The choice of post withdrawal treatment must be made during the first 3 days after the withdrawal episode has finished (days 8, 9 or 10). There are 3 types of treatment to choose from:

- Counselling only: individual counselling with a counsellor is available, with up to 2 counselling sessions per week. Counselling usually focuses on reducing the risk of relapse to heroin use
- Naltrexone treatment: clients who have not used heroin during their withdrawal (with 'clean' urines on days 5 and 8 of the detox) may choose to start naltrexone treatment. Naltrexone is a medication that 'blocks' the effects of heroin use, and many people find it useful in preventing relapse to heroin. However, before commencing naltrexone, clients must have a Narcan challenge test done, to make sure that they do not go into major withdrawal after starting naltrexone. Naltrexone tablets should be taken once every day. Naltrexone is dispensed daily at Turning Point for the first three days, then weekly.
- Maintenance treatment: clients may choose to enter maintenance treatment with an opiate medication. Clients in the buprenorphine group may choose to enter buprenorphine or methadone treatment, while clients from the symptomatic medication group may choose to enter methadone treatment. This requires daily dosing at Turning Point for both groups.

Clients do not have to make a decision about post withdrawal treatment until day 8, 9 or 10. However, it is important that if clients are interested in naltrexone treatment, then they should not use heroin during the withdrawal episode.

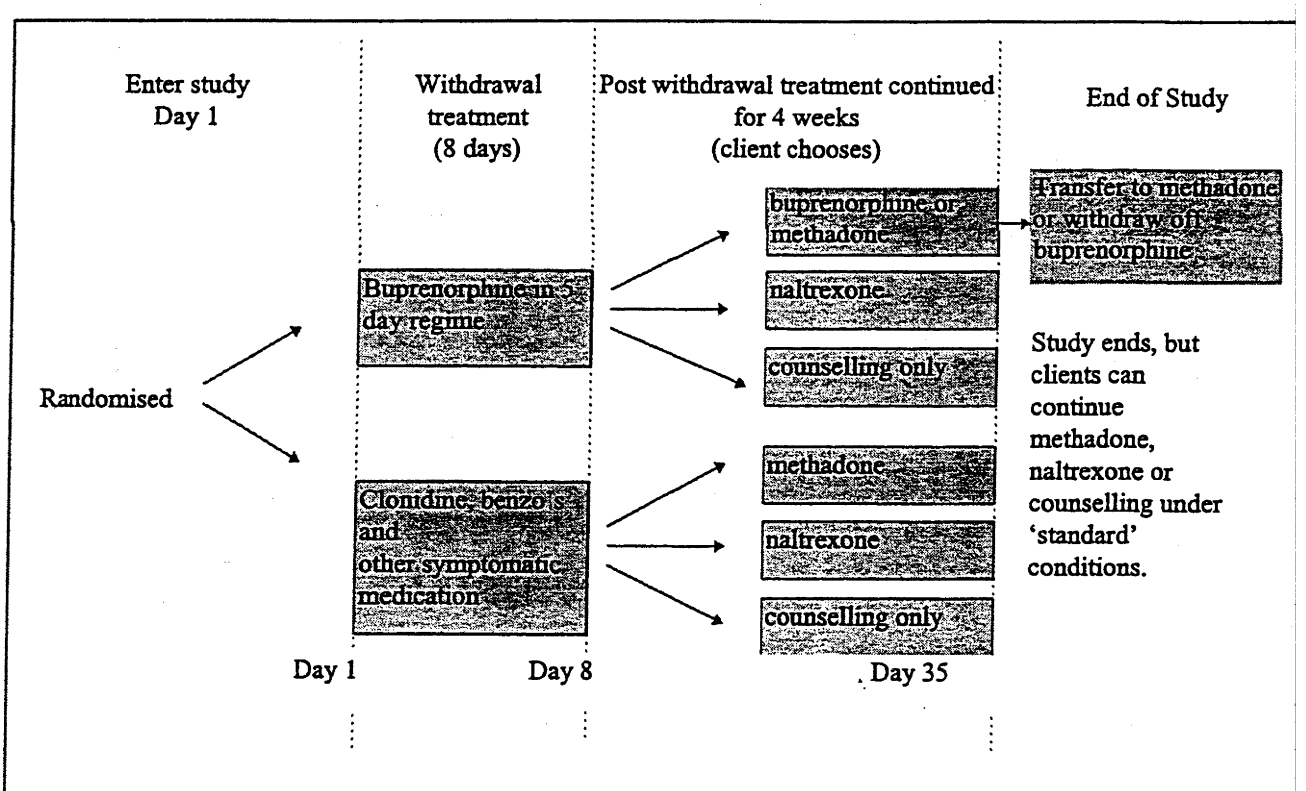
The post withdrawal treatments are available as part of the study for four weeks. If clients wish to continue counselling, methadone or naltrexone treatment after this time, they can do this as part of standard treatment. Unfortunately, long term treatment with buprenorphine is not available. As such, clients still on buprenorphine at the end of the four week period will have the option of withdrawing off their buprenorphine over a two week period, or transferring to methadone maintenance treatment.

- Maintenance treatment: clients may choose to enter maintenance treatment with an op medication. Clients in the buprenorphine group may choose to enter buprenorphine methadone treatment, while clients from the standard medication group may choose to e methadone maintenance treatment. This requires daily dosing at Turning Point for both grou

You do not have to make a decision about your post withdrawal treatment until day 8, 9 or 10, more information will be given to you towards the end of the withdrawal episode about wha involved in each of the treatment options. However, it is important to remember that if you interested in naltrexone treatment, then you should not use heroin during the withdrawal episode.

The post withdrawal treatments are available as part of the study for four weeks, during wh clients do not have to pay for their treatment or for their medication. If clients wish to conti methadone or naltrexone treatment after this time, they can do this as part of standard treatment, clients must pay the usual fees for their treatment ($ 25 to 30 per week for methadone, approximately $35 per week for naltrexone treatment). Unfortunately, long term treatment v buprenorphine is not available. As such, clients still on buprenorphine at the end of the four w period will have the option of withdrawing off their buprenorphine over a two week period, transferring to methadone maintenance treatment. Ongoing counselling at Turning Point can organised with your case worker.

The research project is summarised in the following diagram



What's involved in participating in the research project?

The following is a summary of what is involved for people who choose to enter the research:

1. *Admission procedures*. This includes a clinical assessment and an interview with the researcher. This takes about 3 hours in total.

2. *An 8 day outpatient withdrawal program at Turning Point*. This involves daily attendance and contact with a worker at Turning Point for counselling, support and monitoring of how things are going in withdrawal. The types of medication used for each client is randomly chosen. Medication is dispensed daily.

3. *A research interview on day 8*. This takes about 45 minutes and clients are reimbursed $20 for their time.

4. *The option of entering a number of forms of ongoing treatment after withdrawal*. These include:

- ☑ naltrexone treatment
- ☑ maintenance treatment with methadone or buprenorphine
- ☑ counselling without any medication.
- ☑ Clients do not have to enter ongoing treatment if they do not want to.

Treatment is continued as part of the research for 4 weeks. Clients get to choose to enter one of these treatments within the first 3 days of finishing the withdrawal program (days 8, 9 or 10). Even if you continue to use heroin or do not every day during the withdrawal episode (the first week), you can still enter these forms of ongoing treatment. Clients who miss 2 or more *consecutive* days during the withdrawal episode can not be guaranteed post withdrawal treatment options.

5. *A research interview after 5 weeks* (day 35). This again takes about 45 minutes and clients get reimbursed $20 for their time. We want to talk to all clients who enter the research at this time, not just the ones who stay in treatment. The involvement in research finishes for clients at this time.

6. *Ongoing treatment*. Even though the research study for clients finishes after 5 weeks, ongoing treatment will be provided for clients. Clients can stay on naltrexone or on methadone, and clients can continue counselling. Clients on buprenorphine however can not continue long term buprenorphine treatment. At this point in time, clients can choose to swap over to methadone treatment, or else can withdraw off buprenorphine over a two week period. Clients must commence paying for their methadone or naltrexone at this point in time.

Participation in the study is voluntary, and clients can decide to cease their involvement in the study at any point in time. This also means stopping the study medications, although routine treatment services will be available for you at Turning Point.

Who can enter the study?

The research is looking at the treatment of people going through outpatient heroin withdrawal. However the treatment programs that have been designed may not suitable for everyone wanting to do heroin withdrawal, in particular, other forms of treatment or medication may be better for some people who:

- require other medications during withdrawal due to regular use of other drugs (such as alcohol, benzodiazepines, methadone);

- have particular medical (eg chronic pain) or psychiatric (eg anxiety, depression) treatment ne
- are homeless and would be better off with an inpatient detox
- have had side effects to the medications being used in the withdrawal
- are pregnant or breast feeding

In order to determine if you are eligible for the study, we need to do the following:

☑ a routine clinical assessment by an alcohol and drug worker and then by a medical office Turning Point. This takes about 60 to 90 minutes in total, and will include questions about treatment you are interested in, your recent and past drug use, previous treatment, medical psychiatric history, current social circumstances, and a medical examination.

☑ check proof of your identity (photo ID is preferable)

☑ urine test looking at recent drug use and to exclude pregnancy (where relevant)

☑ check with the Victorian Department of Human Services about any recent methadone treatme

☑ any investigations considered important by your medical officer

If all this is OK, then the client may volunteer to enter the research study. This involves a 30 to minute interview with a researcher who will:

☑ get written informed consent to enter the study

☑ collect some more information (eg about your drug use, previous experience of withdrav psychological well being)

☑ do the randomisation as to which type of withdrawal treatment you can get

☑ organise details about follow up research interviews in one week and five weeks time

People who do not meet the criteria to enter the research will have normal treatment service Turning Point available to them.

Entry into the research study is entirely voluntary. If you choose to not enter research study, t standard withdrawal treatment and other treatment services will be available for you.

Withdrawal treatment as part of the research

Most of the withdrawal services in the research are similar to normal services at Turning Point. T involves:

☑ *Counselling and support during withdrawal*: counselling is kept fairly low key, mainly look at things such as coping with withdrawal symptoms and cravings, drug use during withdraw side effects, and future treatment options.

☑ *Information*: knowing what is going on and having information about getting through her withdrawal is important. You will be given a booklet that outlines alot of this information.

☑ *Daily attendance for medication:* the research requires that you attend daily for medication Turning Point. We normally recommend this for most clients doing withdrawal at Turning Po

☑ *Urine drug screens*: this is not part of normal withdrawal treatment at Turning Point, but is p of the research. We want to get urine drug screens at days 5 and 8 of the withdrawal. This particularly important for people thinking about doing naltrexone treatment afterwards.

☑ *Medication*. The medication used during withdrawal is determined by chance (randomisation this is part of the research study and not part of usual practice at Turning Point. There are t types of medication being used: standard medications and buprenorphine. Each is describ below.

Withdrawal with symptomatic medication

The medications that are used for 'symptomatic' heroin withdrawal at Turning Point are:

Diazepam. This is a sedative that can help with anxiety during withdrawal and with sleep problems. The usual doses are up to 5 mg (one tablet) four times a day over the first 3 days then reducing doses (by one tablet per day) over the next 3 days. This medication is commonly known as Valium® or Ducene®.

Clonidine. This is a medication that is usually used for treating high blood pressure, but is also a very useful medication for treating the symptoms of opiate withdrawal and also has a sedating effect. International research suggests that it is the most effective medication routinely available for opiate withdrawal. However, it can cause problems of lowering blood pressure, which may make some people feel giddy, or light headed, particularly when standing up from a sitting or lying position. This should not be a problem at the doses we prescribe, but please tell the staff if you are having such symptoms, and we will usually take your blood pressure while you are taking it. The clonidine is prescribed for up to 6 days. This medication is commonly known as Catapress®.

Metoclopramide. This is a medication that can help reduce feelings of nausea and vomiting. It is commonly known as Maxolon®.

Ibuprofen. This is a medication related to aspirin, that is usually used for treating arthritis, and can be useful for helping relieve the joint aches common in heroin withdrawal. It should be taken with food, as it can sometimes cause stomach irritation on an empty stomach. The dose we usually prescribe is one tablet (400 mg) four times a day for three days then one tablet three times a day for 3 days. This medication is commonly known as Brufen®.

Lomotil ®. This is medication for relieving diarrhoea. Taken as one or two tablets up to twice a day as needed.

Quinine. This is a medication that is sometimes useful for relieving muscle cramps, particularly at night time.

Buscopan®. This medication can help relieve abdominal cramps. Taken as one tablet three or four times a day as needed.

All these medications are dispensed daily from the Turning Point pharmacy. Maximum doses of the medications are set as part of the research. Medications such as codeine (eg Panadeine forte®) propoxyphene (eg Doloxene®) or methadone are not available as part of the study.

Buprenorphine assisted withdrawal

Buprenorphine is an opioid drug that has similar properties and effects to other opiates. Buprenorphine is only available for treating heroin use in Australia as a research medication, although it is available for the treatment of heroin dependence in France.

Buprenorphine relieves symptoms of heroin withdrawal, reduces cravings for heroin use and reduces the effects of any additional heroin use. Unlike other opiates (such as methadone or morphine), buprenorphine does not appear to prolong the duration of opiate withdrawal symptoms when given for short periods of time (less than one week). These factors make it a promising medication in the treatment of heroin withdrawal.

Buprenorphine is manufactured as thin white oval tablets. These tablets are placed under the ton and take about 2 to 3 minutes to dissolve (on average). They should not be swallowed or chewe this will considerably lessen their effect. It is important that you take the medication as directed the clinic staff. No additional tablets will be given to you if they are taken incorrectly.

As with other opiates, buprenorphine may have a number of side effects. These are most commo constipation, tiredness, sleepiness, dizziness, nausea and headaches. Side effects are usually m short lasting and cease on stopping the medication.

The doses of buprenorphine used in the study are as follows:

Day of withdrawal	Dose of buprenorphine (sublingual tablets)
Day 1	6 mg
Day 2	10 mg +/- 2mg
Day 3	10 mg +/- 2mg
Day 4	8mg +/- 2mg
Day 5	4 mg
Total dose	38 mg +/- 6mg

These doses were found to be effective in an earlier study of heroin withdrawal conducted Turning Point in 1998. There is the capacity to alter doses on days 2,3 and 4 of the withdrawal 2mg (up or down) according to how severe the withdrawal is and any side effects experienc Buprenorphine is not available after day 5 as part of the withdrawal program. Other medication the management of heroin withdrawal (eg sleeping tablets) will not be routinely available for peo on the buprenorphine.

Caution about using other drugs during withdrawal

The use of other sedative drugs in combination with buprenorphine, diazepam or clonidine c be dangerous and may lead to overdose and death. This includes drugs such as alcohol, sleep tablets or tranquillisers (eg Valium, Serepax, Mogadon, temazepam, Rohypnol), antidepressa or other opiates. Furthermore, the effects of these medications can last for several days after last dose. This means that you should not use other sedative drugs for several days after your l dose of withdrawal medication without checking with your doctor.

Medications will not be dispensed if a client presents intoxicated. Clients can refuse a dose medication at any time.

Post withdrawal treatments

The option of entering ongoing treatment after withdrawal is open to all clients who enter t research. The three main types of treatment options are:

- Counselling: individual counselling with a counsellor is available, with up to 2 counselli sessions per week. Counselling usually focuses on reducing the risk of relapse to heroin use

- Naltrexone treatment: clients who have not used heroin during their withdrawal (with 'clea urines on days 5 and 8 of the detox) may choose to start naltrexone treatment. Naltrexone is medication that 'blocks' the effects of heroin use, and many people find it useful in preventi relapse to heroin. However, before commencing naltrexone, clients must have a challenge t done with either Narcan or naltrexone, to make sure that they do not go into severe withdraw

after starting full doses of naltrexone. Naltrexone tablets should be taken once every day. Naltrexone is dispensed daily at Turning Point for the first week, then weekly.

- Maintenance treatment: clients may choose to enter maintenance treatment with an opiate medication. Clients in the buprenorphine group may choose to enter buprenorphine or methadone treatment, while clients from the standard medication group may choose to enter methadone maintenance treatment. This requires daily dosing at Turning Point for both groups.

You do not have to make a decision about your post withdrawal treatment until day 8, 9 or 10, and more information will be given to you at the end of the withdrawal episode about what is involved in each of the treatment options. However, it is important to remember that if you are interested in naltrexone treatment, then you should not use heroin during the withdrawal episode.

If you are particularly interested in getting more information about these treatment options before the end of the withdrawal, then talk to you doctor or case worker.

Other business .....

- Participation in the study will require you to comply with the normal procedures and rules of Turning Point, and with any scheduled counselling sessions.

- If you join the study, we will also request that you consent to allowing the medical staff to access information from the Drugs of Dependence Unit of the Victorian Department of Human Services (who keep records of who is in methadone treatment in Victoria). This is only for the purpose of being certain that you have not been treated with methadone or other opiates in the preceding 2 months. This involves a separate consent form (Consent Form B).

- Information you provide to the research staff will be held as confidential and not made available to the clinical staff. The exception to this is where the research staff have grave concerns regarding your immediate safety or the safety of others. In such circumstances, the research staff will inform you of their concerns (if possible) prior to notifying the clinical staff. This can not be guaranteed however in the (unlikely) event of a court subpoena specifically requesting access to your research records.

- All medical records will be held as confidential, and not be made available to staff not directly involved in your care or in the research study. This can not be guaranteed however in the event of a court subpoena specifically requesting access to your medical records.

- The results of the study may be published or discussed, but no individual participating in the study will be identified in any way.

- We cannot guarantee that you will find buprenorphine to be a satisfactory medication in withdrawal, and we do not hold out that you will receive any benefits from participating in this study.

And finally .....

The study is being run by researchers from Turning Point, St.Vincent's Hospital, The National Centre for Epidemiology and Population Health at the Australian National University in Canberra, Melbourne University, and The Langton Centre in Sydney. The project is principally funded by the

Victorian government's Turning The Tide initiatives. The buprenorphine medication is bei provided by the pharmaceutical company Reckitt & Colman.

Compensation

The sponsor of this study, Turning Point, has undertaken to adhere to guidelines for compensation to patients whose health is affected by taking part in the study. A copy of these Australian Pharmaceutical Manufacturers Association guidelines is available for you to peruse. If an injury occurs to you as a result of participation in this study as a result of the study medication, clinical intervention or procedure provided for by the protocol, you have the right to seek compensation, either through the procedure outlined in the guidelines or by normal legal channels.

2. Advice on Avoiding Pregnancy

You should avoid becoming pregnant during the course of this trial if you are taking the investigational medications buprenorphine or naltrexone. If you become pregnant you will have to withdraw from the trial and you will be medically followed up carefully until delivery. These precautions are necessary because the information on the effects on the unborn or newborn baby o drugs like buprenorphine or naltrexone is still very limited.

3. Information and / or complaints

Turning Point and St Vincent's Hospital requires all investigators to carry out their investigations under guidelines issued by the World Health Organisation, The National Health and Medical Research Council and the Therapeutic Goods Administration of the Commonwealth Department o Health and Family Services. These guidelines have been drawn up to protect the interests of peopl who agree to take part in medical research.

If you require further information concerning the project in which you are involved, you should contact the principal investigator responsible for this project:

Dr Nicholas Lintzeris
Turning Point Alcohol and Drug Centre
54 Gertrude Street, Fitzroy, VIC 3065
Telephone (03) 9254 8061

If you have any complaints about any aspects of the study or the way in which it is being conducte then you should contact

Professor Margaret Hamilton
Director of Turning Point Alcohol and Drug Centre
54 Gertrude Street, Fitzroy, VIC 3065
Telephone (03) 9254 8061

You will be given a copy of this form to keep.

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)
BRIEF SCREENING FORM

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ]. [ ][ ]. [ ][ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

INSTRUCTIONS: This form is to be completed jointly by the withdrawal worker and medical officer, after during the clinical assessment.

A. INCLUSION CRITERIA

1. Between 18-65 years of age (inclusive)?	1[ ] Yes	0[ ] No
2. DSM-IV diagnosis of current heroin dependence?	1[ ] Yes	0[ ] No
3. Heroin use within the past 48 hours? (client self report)	1[ ] Yes	0[ ] No
4. Able to meet attendance requirements for study?	1[ ] Yes	0[ ] No
5. Able to give informed consent?	1[ ] Yes	0[ ] No

If NO to any (1 - 5) do not proceed with enrolment -- client is not eligible for the trial. Complete the Study Rejection Form.

B. EXCLUSION CRITERIA

6. In methadone or other opioid treatment in the last two months? (client self-report)	1[ ] Yes	0[ ] No
7. Dependent upon, intoxicated or withdrawing from alcohol, BZDs or other drugs?	1[ ] Yes	0[ ] No
8. Pregnant, or breastfeeding? (client self-report)	1[ ] Yes	0[ ] No
9. Active or unstable medical conditions?	1[ ] Yes	0[ ] No
10. Active or unstable psychiatric conditions?	1[ ] Yes	0[ ] No
11. Known hypersensitivity / side effects with buprenorphine?	1[ ] Yes	0[ ] No
12. Currently receiving buprenorphine from another source?	1[ ] Yes	0[ ] No
13. Currently enrolled in another clinical trial?	1[ ] Yes	0[ ] No

If YES to any (6 - 13) do not proceed with enrolment -- client is not eligible for the trial. Complete the Study Rejection Form.

C. OTHER

1. Does the client meet the initial screening criteria?	1[ ] Yes	0[ ] No
2. Has the client seen and read a copy of the Patient Information Sheets?	1[ ] Yes	0[ ] No
3. Is the client still interested in participating in this study?	1[ ] Yes	0[ ] No

If NO to any question (1-3) do not proceed with enrolment -- inform research assistant of unsuccessful screening. Make alternate arrangements for client withdrawal. Complete the Study Rejection Form.

[If the client meets the initial eligibility criteria please contact the research assistant to arrange client enrolment.]

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)
STUDY REJECTION FORM

Research Use Only

Research No. [| | | |] Date [| |] . [| |] . [| | | |]

Study Code [H | W | B | R] Site Code [T | P] Client Initials [| |] Staff Initials [| |]

INSTRUCTIONS: This form is to be completed by a member of clinical staff and forwarded to the Research Assistant once completed.

A. REASONS FOR REJECTION

1. THE CLIENT WAS NOT ELIGIBLE	**1[ ] Yes**	**0[ ] No**
• The client was between the ages 18 - 65 years	1[ ] Yes	0[ ] No
• The client met DSM-IV diagnosis of current heroin dependence.	1[ ] Yes	0[ ] No
• The client was dependant or withdrawing from alcohol, BZDs or other drugs. Please specify _____	1[ ] Yes	0[ ] No
• Had the client used heroin within the past 48 hours	1[ ] Yes	0[ ] No
* UDS [ ]		
* Self report [ ]		
• Was the client able to commit to attendance requirements of the study, (ie, daily attendance for first 8 days).	1[ ] Yes	0[ ] No
• Was the client to give informed consent?	1[ ] Yes	0[ ] No
• Has the client been in a methadone program in the last 2 months.	1[ ] Yes	0[ ] No
• Is the client pregnant or breastfeeding.	1[ ] Yes	0[ ] No
* UDS [ ]		
* Self report [ ]		
• Does the client have any active or unstable medical / psychiatric conditions. Please specify _____	1[ ] Yes	0[ ] No
• Other. Please specify _____	1[ ] Yes	0[ ] No
2. THE CLIENT WAS ELIGIBLE, BUT DECLINED PARTICIPATION	**1[ ] Yes**	**0[ ] No**

B. ALTERNATIVE MANAGEMENT

Please indicate the alternative treatment management in place for the client.

_____

_____

_____

_____

Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Medical Assessment
(intake)

- Medical History Summary
- Physical Examination
- Medication History
- Birth Control Assessment
- DSM-IV Assessment for Opiate Dependence
- Consent for DPU
- DPU Permit Application
- Client Eligibility Validation

1999

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT MEDICAL HISTORY SUMMARY

Research Use Only	Clinic & Research Use Only
Research No. |_|_|_|_|	Date |_|_|.|_|_|.|_|_|_|_|
Study Code |H|N|B|R| Site Code |T|P|	Client Initials |_|_| Staff Initials |_|_|

TO BE COMPLETED BY A MEDICAL OFFICER ONLY AFTER ASSESSMENT

A. MEDICAL HISTORY

1. Has the client had any significant abnormalities diseases or disorders of the following:

	1 = YES 0 = NO	IF YES, BRIEFLY DESCRIBE THE PROBLEM & ACTION TAKEN
Head, eyes, ears, nose, throat		
Cardiovascular		
Respiratory		
Gastrointestinal		
Genito-urinary		
Musculo-skeletal		
Neurological		
Endocrinological		
Allergies		
Skin		
Psychiatric		

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

CLIENT MEDICAL HISTORY SUMMARY CONTINUED...

A. MEDICAL HISTORY CONTINUED

1(Cont.). Has the client had any significant abnormalities diseases or disorders of the following:

	1 = YES 0 = NO	IF YES, BRIEFLY DESCRIBE THE PROBLEM
Hepatitis B		
Hepatitis C		
HIV		
Other *(please specify)* _____		

B. MEDICAL STATUS - MEDICAL ISSUES IN NEED OF ATTENTION

1. Does the client has any current or ongoing medical problems other than drug addiction? 1[ ] Yes
If YES, list these problems below 0[ ] No

Nature of the problem	Duration of problem (days, mths, yrs)	Current Severity (I)	Current Action Taken (II)	C O
A.				
B.				
C.				
D.				

(I) SEVERITY codes
1 = Mild
2 = Moderate
3 = Severe

(II) ACTION TAKEN codes
0 = None
1 = Outpatient treatment
2 = In-patient treatment

(III) OUTCOME codes
1 = Resolved, no sequelae
2 = Continuing, not yet resolved
3 = Resulted in chronic or prolonged condition, severe & permanent disability
4 = Unknown

This medical history was completed by
(please print name & date)

_____ _____

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT PHYSICAL EXAMINATION

Research Use Only

Research No. |_|_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Clinic & Research Use Only

Date |_|_|.|_|_|.|_|_|_|

Client Initials |_|_|_| Staff Initials |_|_|_|

A. VITAL SIGNS *(may be completed by MEDICAL OFFICER or NURSE - please fill in your name below)*

NAME : **DATE :**

1. Height (cm) - *(shoes off & to nearest cm)* |_|_|_| **cm**

2. Weight (kg) - *(outer clothing off & to nearest kg)* |_|_|_| **kg**

3. Temperature (°C) (please ✓) [ ] Afebrile [ ] Febrile |_|_|.|_| °C

4. Blood pressure - sitting (mmHg) |_|_|_| **SYSTOLIC** |_|_|_| **DIASTOLIC**
   - *use LEFT arm*
   - *Client must have rested for 5 min*
   - *Measure to nearest 5mmHg*

5. Pulse rate - resting (beats/min) |_|_|_|

6. Respiration - resting (breaths/min) |_|_|

7. Blood Alcohol Concentration (%) |_|.|_|_|_| %

8. Pupil Size (please circle) 1mm● 2mm● 3mm● 4mm● 5mm● 6mm● (or more)

9. Are the pupils reactive? (please circle) Yes / No Are both pupils equal? (please circle) Yes / No

10. Is there evidence of injecting drug use (ie, injection marks on arms)? (please circle) Yes / No

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT PHYSICAL EXAMINATION

B. PHYSICAL EXAMINATION *(to be completed by a MEDICAL OFFICER only - please fill in your name below)*		
NAME : **DATE:**	**0 = Not checked** **1 = N.A.D** **2 = Abnormal**	**Describe any abnormality**
10. Head, eyes, ears, nose, throat		
11. Nutrition / Hydration		
12. Heart		
13. Lungs		
14. Abdomen		
15. Extremities		
a. injection sites		
b. available veins		
16. Skin		
17. Lymph Nodes		
18. Other Physical Findings *(please specify)* _____ _____ _____		

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT PHYSICAL EXAMINATION

Research Use Only

Research No. |_|_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Clinic & Research Use Only

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_|_| Staff Initials |_|_|_|

C. MENTAL STATE EXAMINATION *(to be completed by a MEDICAL OFFICER only - please fill in your name below)*

NAME : DATE :	0 = Not checked 1 = N.A.D 2 = Abnormal	Describe any abnormality
19. Appearance		
20. Consciousness		
21. Speech		
22. Mood		
23. Affect		
24. Thought		
a. Stream		
b. Content		
25. Perception		
26. Orientation (T, P,P)		
27. Memory		
28. Insight		
29. Judgement		

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|

CLIENT PHYSICAL EXAMINATION

D. OTHER (To be completed by a MEDICAL OFFICER only - (please fill in your name below)

_____

27. Global Assessment of Functioning **GAF Score :** ☐☐☐

28. Is the client intoxicated? (please circle)

1 ——— 2 ——— 3 ——— 4 ——— 5

not intoxicated — moderately intoxicated — severely intoxicated

29. Is the client in withdrawal? (please circle)

1 ——— 2 ——— 3 ——— 4 ——— 5

not withdrawing — moderate withdrawal — severe withdrawal

30. Is the client able to give Informed Consent? (please ✓) 1[ ] Yes 0[ ] No

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT PHYSICAL EXAMINATION

Research Use Only

Research No. |_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Clinic & Research Use Only

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_| Staff Initials |_|_|

E. INVESTIGATIONS ORDERED *(to be completed by a MEDICAL OFFICER only - please fill in your name below)*

NAME : DATE :	Ordered 1 = Yes 0 = No	Date Ordered	Specimen Collected (Date & By whom)
Pregnancy Test			
Urine Drug Screen			
Full Blood Examination			
Liver Function Test			
Urea & Electrolytes			
Serology Screen			
Urinalysis			
Other _____			
Other _____			
Other _____			

MEDICATION HISTORY

Clinic & Research Use only

Research Use Only

Date	Client Initials	Staff Initials	Research No.	Study Code	Site Code
__/__/____	__ __	__ __	__ __ __	H W B R	T P

PAST PRESCRIPTION OF OTHER MEDICATION (IN LAST WEEK) - EXCLUDE STUDY MEDICATIONS

Medication (Generic Name only)	Drug Code (Research Purposes)	Prescribed Dose	Time Since Taken Last Dose & Date	Dose Last Taken	Date Began / Ceased Treatment	Reason for Prescription	Prescribing Doctor
1.		Dose : _____ Frequency : _____ Route : _____	Time __ : __ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
2.		Dose : _____ Frequency : _____ Route : _____	Time __ : __ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
3.		Dose : _____ Frequency : _____ Route : _____	Time __ : __ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
4.		Dose : _____ Frequency : _____ Route : _____	Time __ : __ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|__|

MEDICATION HISTORY cont

PAST PRESCRIPTION OF OTHER MEDICATION (IN LAST WEEK) *Continued ....*

Medication (Generic Name only)	Drug Code (Research Purposes)	Prescribed Dose	Time Since Taken Last Dose & Date	Dose Last Taken	Date Began / Ceased Treatment	Reason for Prescription	Prescribing Doctor
5.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
6.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
7.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
8.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
9.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		

CLIENT NAME _____ UR NUMBER [ ][ ][ ][ ][ ][ ]

BIRTH CONTROL ASSESSMENT

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Clinic & Research Use Only

Date [ ][ ] - [ ][ ] - [ ][ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

This form is to be completed by a MEDICAL OFFICER during the assessment of female participants.

1. Is the patient of child-bearing potential?
   1[ ] Yes
   0[ ] No *Go to question 1b*

1b. If NO, specify the reason
   1[ ] Hysterectomy *Go to question 1c*
   2[ ] Tubal ligation *Go to question 1c*
   3[ ] Post menopausal *Go to question 1c*
   4[ ] Other (Please specify _____) *Go to question 1c*

1c. If patient answered question 1b, give date of surgery or completion of menopause
(Signed Release of information Form Required)
[ ] - [ ] - [ ] Day Month Year
1[ ] **Surgery**
2[ ] **Menopau**

2. Is the patient nursing an infant?
   1[ ] Yes *NOT ELIGIBLE FOR NPP TRIAL*
   0[ ] No

3. What method of birth control is the patient using?
   0[ ] None
   1[ ] Oral Contraceptive
   2[ ] IUD
   3[ ] Barrier Methods (Condom / Diaphragm)
   4[ ] Rhythm Method
   5[ ] Abstinence from heterosexual sex
   6[ ] Deproprovera
   7[ ] Other *(please specify* _____)
   8[ ] Not applicable (*why* _____)

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

DSM-IV CRITERIA FOR OPIATE DEPENDENCE

Research Use Only

Research No. |__|__|__|__|

Study Code |H|W|B|R| Site Code |T|P|

Clinic Use

Date |__|__|.|__|__|.|__|__|__|

Client Initials |__|__| Staff Initials |__|__|

INSTRUCTIONS: This form is to be completed by jointly by the assessment worker and medical officer after assessment

A. SUBSTANCE DEPENDENCE - CRITERIA

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

1. Tolerance, as defined by either of the following: 1[ ] Yes 0[ ] No

   a. A need for markedly increased amounts of the substances to achieve intoxication or the 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: 1[ ] Yes 0[ ] No

   a. The characteristic withdrawal syndrome of the substance (see Withdrawal criteria)
   b. The same (or 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 1[ ] Yes 0[ ] No

4. There is a persistent desire or unsuccessful efforts to cut down or control substance use 1[ ] Yes 0[ ] No

5. A great deal of time is spent in activities necessary to obtain the substance (eg. visiting multiple doctors or driving long distances), using the substance (eg. chain smoking), or recover from its effects 1[ ] Yes 0[ ] No

6. Important social, occupational or recreational activities are given up or reduced because of substance use 1[ ] Yes 0[ ] No

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 (eg. current cocaine use despite recognition of cocaine induced depression, of continued drinking despite recognition that an ulcer was made worse by alcohol consumption) (DSM IV) 1[ ] Yes 0[ ] No

8. **Total number of DEPENDENCE criteria met (total no. of 'Yes' responses) =** |__| (max 7)

9. Does the participant satisfy the criteria of opiate dependence? =>3 met 1[ ] Yes 0[ ] No

CONSENT FOR DPU INFORMATION (CONSENT FORM B)

Research Use Only

Study Code |H|W|B|R| Site Code |T|P|

Date |__|__|.|__|__|.|__|__|__|__|

Client Initials |__|__| Staff Initials |__|__|

I, ..., born on the |__|__| / |__|__| / |__|__|__|__|
day month year

allow an officer from the Drugs and Poisons Unit of the Victorian Department of Human Services to provide information to Dr ..... regarding whether I have had a permit for methadone or other opiate medications in the preceding eight week period.

Dated: |__|__| / |__|__| / |__|__|__|__|

Signed: .....

Witness: .....

DPU USE ONLY

Active Permit within the Last Eight Weeks 1[ ]Yes 0[ ] No

Date of Last Dose |__|__| / |__|__| / |__|__|__|__|

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)
CLIENT ELIGIBILITY VALIDATION

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ].[ ][ ].[ ][ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

INSTRUCTIONS: This form is to be completed by the medical officer and withdrawal worker prior to cl enrolment in buprenorphine study. PLEASE TICK THE APPROPRIATE BOX FOR EACH QUESTION.

A. CRITERIA

1. Between 18-65 years of age (inclusive). 1[ ] Yes 0[ ] No

* What evidence of proof of age and identity have been recorded on file?

1 [ ] Drivers licence
2 [ ] Passport
3 [ ] Health care card
4 [ ] Medicare card
5 [ ] Other (Please specify _____)
6 [ ] None***

2. DSM-IV diagnosis of current heroin dependence. 1[ ] Yes 0[ ] No

3. Confirmation that the client is not dependant or withdrawing from alcohol, BZDs or other drugs (from clinical assessment) 1[ ] Yes 0[ ] No

4. Confirmation of heroin use within the past 48 hours (UDS). 1[ ] Yes 0[ ] No

* Was an instant urine drug screen conducted?

1 [ ] Yes
2 [ ] No***

* Instant urine drug screen result:

1 [ ] Positive opiates
2 [ ] Negative***

5. Confirmation that the client is not pregnant or breastfeeding. 1[ ] Yes 0[ ] No

* Was a urine sample collected for pregnancy testing? (females only)

1 [ ] Yes
2 [ ] No***

* Has the client received pre-pregnancy test counselling?

1 [ ] Yes
2 [ ] No***

* Urine pregnancy test result:

1 [ ] Positive***
2 [ ] Negative

6. Confirmation that the client has no major medical or psychiatric conditions (from medical assessment) 1[ ] Yes 0[ ] No

CLIENT ELIGIBILITY VALIDATION

CONTINUED ...

7. Were other blood investigations ordered? 1[ ] Yes 0[ ]

(Please specify _____)

* Do the other blood test results warrants client exclusion?

1 [ ] Yes***
2 [ ] No

8. Confirmation from DPU. Has the client been in a methadone program in the last 2 months? **1[ ] Yes*** 0[ ]**

* Client consent for **DPU** release of information signed?

1 [ ] Yes
2 [ ] No***

9. The client has read the patient information sheets and been given the opportunity to ask questions and have them answered. **1[ ] Yes 0[ ]**

10. Attendance requirements have been explained and client able to meet the study's requirements? **1[ ] Yes 0[ ]**

11. Social circumstances suitable for an outpatient withdrawal program? (ie. client is not homeless) **1[ ] Yes 0[ ]**

12. The client is willing and able to give informed consent? **1[ ] Yes 0[ ]**

An answer of YES must be obtained to all the BOLD typefaced questions (excluding q.8) before the client can be enrolled in the study.

If a response has been recorded for responses marked *** the client is not eligible - do not proceed with enrolment. Complete Study Rejection Form.

B. CLIENT STUDY / TRIAL ENROLMENT STATUS

1. Individual's enrolment status?
   1[ ] Ineligible
   2[ ] Eligible & to be enrolled
   3[ ] Eligible but declines

IF ENROLLED IN THIS STUDY/TRIAL:

2. Date client was enrolled in the study/trial? Day [ ] Month [ ] Year [ ]

HEROIN WITHDRAWAL USING BUPRENORPHINE

PATIENT DECLARATION / CONSENT

Research Use Only

Study Code H W B R Site Code T P	Date __/__/__
	Client Initials ___ Staff Initials ___

ST VINCENT'S HOSPITAL

CONSENT OF PATIENT TO PARTICIPATE IN RESEARCH STUDY

PROTOCOL NO. (SVH) : ____/___ ____ (Office use only)

NAME OF PATIENT:

U.R. NO:

NAME OF INVESTIGATORS:

Dr Nicholas Lintzeris,
Dr Gabriele Bammer,
Professor Greg Whelan,
Dr James Bell,
Alison Ritter,
Damian Jolley

STUDY TITLE:

"Randomised Controlled Trial of Outpatient Heroin Withdrawal using Buprenorphine"

I _____ have had the purpose and nature of this research study explained to me by a member of Clinical Staff at Turning Point Alcohol & Drug Centre. The methods and procedures of this study, and the risks and discomfort that may be associated with my participation have also been explained to me. I have been given a copy of the Patient Information Sheets and have read and understood them.

I am willing to take part in this study and I consent to all of the procedures with their associated risks as has been explained to me. I understand that I am free to withdraw from this study at any time without cost to myself and without jeopardising the management of my condition and the future care and attention that I will receive. I have read/had translated to me the above explanation and understand it.

Signed: _____
(Patient / Guardian / Next Friend)

Witness _____

Date __/__/____
day month year

TREATMENT WITH DRUGS OF ADDICTION

H&C
HEALTH A
COMMUNI
SERVICE

DRUGS, POISONS AND CONTROLLED SUBSTANCES ACT 1981

(Notice of and application for permit to administer, prescribe or supply.)

PART A: (THIS SECTION SHOULD BE COMPLETED IN ALL CASES)

Sex: M/F

Name of Patient: Date of Birth:

(Block Letters) (Family Name) (Given Name)

Private Address of Patient:

Postcode:

Name and Address of Medical Practitioner:

Postcode:

Telephone No. of Medical Practitioner:

Name and Address of Hospital Where the Patient Is Undergoing Treatment: (If Applicable)

Clinical Diagnosis:

PART B: (THIS SECTION SHOULD BE COMPLETED IF THE PATIENT REQUIRES CONTINUING TREATMENT)

Drug(s) of Addiction for Which Permit Is Requested:

(Name and Form of Drug)

Dose:

Frequency of Administration:

Duration for Which Such Drug/Drugs Have Been Used:

Details of Other Treatment: (if applicable)

I have/have not previously applied for a permit to administer, prescribe or supply a drug of addiction for this patient.

If yes, please indicate name of drug and approximate date of application.

PART C: (THIS SECTION IS A NOTICE TO THE EFFECT THAT DRUGS OF ADDICTION HAVE BEEN MADE AVAILABLE TO THE PATIENT NAMED IN PART A HEREOF, BUT ARE NO LONGER BEING PRESCRIBED)

Drug/Drugs Used:

Duration of Treatment:

Signature of Medical Practitioner:

Date:

OFFICE USE ONLY

(Please see over)

EXPLANATORY NOTES

TREATMENT WITH DRUGS OF ADDICTION

Under the terms of the Drugs, Poisons and Controlled Substances Regulations 1985, a medical practitioner sho not administer, prescribe or supply the following drugs of addiction—amphetamines, dextromoramide, methac or methylphenidate, unless he first holds a permit from the Department of Health and Community Services to For all other drugs of addiction, an initial period of four weeks of treatment is allowed, after which a permit is required.

A medical practitioner should not administer, prescribe or supply a drug of addiction for a patient believed to drug dependent unless he first holds a permit to do so.

Also, please note that this form should not be used for application for a permit to treat an opiate dependent pa with methadone syrup for which purpose Form DP 41 is available.

Any further information required may be obtained from:

Drugs and Poisons Unit
Health and Community Services
Phone: 412 7928/7958 or 7969

All correspondence should addressed to:

Chief Drugs and Poisons Officer
Drugs and Poisons Unit
P.O. Box 4057
Melbourne 3001

Outpatient Heroin Withdrawal Using Buprenorphine Randomised Control Trial

Research Assessment
Intake Data Collection

- Research Consent Form (St. V's ethics)
- Follow-up Locator Form
- Previous Drug Treatment & Additional Demographics Form
- Opiate Treatment Index - section 2
- LEEDS Dependence Questionnaire
- BASIS - 32
- Health Status Profile (SF - 36)
- AQOL
- Goals Of Treatment (V.A.S.)
- Withdrawal Expectancy (V.A.S.)

1999

FOLLOW-UP LOCATER INFORMATION

Research Use Only

Study Code H W B R Site Code T P

Date . .

Client Initials Staff Initials

Participant's full name: _____

Participant's aliases or nicknames: _____

MAILING ADDRESS IF DIFFERENT FROM RESIDENTIAL ADDRESS (AS SPECIFIED ON CLIENT REGISTRATION FORM)

MAILING ADDRESS

SUBURB/TOWN POSTCODE STATE

TELEPHONE BUSINESS HOURS MOBILE PHONE

TELEPHONE AFTER HOURS

SECOND CONTACT PERSON (eg. parent, close relative)

CONTACT NAME RELATIONSHIP TO YOU

ADDRESS

SUBURB/TOWN POSTCODE STATE

TELEPHONE BUSINESS HOURS MOBILE PHONE

TELEPHONE AFTER HOURS

NAMES AND PHONE NUMBERS OF TWO PEOPLE WHO WOULD KNOW YOUR ADDRESS OR PHONE NUMBER IF YOU MOVED DURING THE COURSE OF THE STUDY

PERSON 1

TELEPHONE BUSINESS HOURS MOBILE PHONE

TELEPHONE AFTER HOURS

PERSON 2

TELEPHONE BUSINESS HOURS MOBILE PHONE

TELEPHONE AFTER HOURS

FOLLOW-UP LOCATER INFORMATION- CONSENT

Research Use Only

Study Code H W B R Site Code T P	Date __/__/__ Client Initials ___ Staff Initials ___

I, ..., (full name of trial participant)
agree to providing additional details about my addresses and contacts on page two of this form.

I understand that this information will be used only if the researcher is unable to contact me for appointments
follow-up interviews.

I understand that when the researcher makes contact with the people nominated on page 2, that he/she will n
mention my drug or alcohol use history or status, or that I am participating in a project about drug treatment, o
the researcher is calling from Turning Point Alcohol & Drug Centre, and that the researcher will not in any othe
way disclose that the research project is related to drug use.

Signed: ..... Date: _____/_____/____
(participant)

Researcher: ..... Date: _____/_____/____

OUTPATIENT HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

PREVIOUS DRUG TREATMENTS & ADDITIONAL DEMOGRAPHICS

Research Use Only

Research No. ____	Date ____ . ____ . ____
Study Code H W B R Site Code T P	Client Initials ____ Staff Initials ____

INSTRUCTIONS - Ask the client to self-report the number of times they have participated (a) ever AND (b) in the past 12 months, in the following forms of treatment.

A. Previous Drug Treatment

HOW MANY TIMES HAVE YOU PARTICIPATED IN :	Ever	In past 12 months
1. **Outpatient withdrawal with or without medication** (including attempts with GP, A&D Agency, Home Based Withdrawal etc.)	____	____
2. **Inpatient withdrawal** with or without medication	____	____
3. **Rapid Opiate withdrawal using Naltrexone**	____	____
4. **Cold Turkey** (unassisted withdrawal) with or without medication	____	____
5. **Methadone Maintenance**	____	____
6. **Naltrexone Maintenance treatment**	____	____
7. **Maintenance Treatment with other substitution pharmacotherapy** (eg. Buprenorphine, LAAM)	____	____
8. **Outpatient counselling** not as part of other listed treatment	____	____
9. **Residential Rehabilitation** (eg. Therapeutic Community)	____	____
10. **Other** (Please specify _____)	____	____

B. Drug use status of your current partner

11. What is the current drug use status of your partner (please tick ✓ one box only)

(a)	Don't have a current partner	[ ]
(b)	Current partner is a non-heroin user	[ ]
(c)	Current partner is a dependant heroin user	[ ]
(d)	Current partner is a non-dependant heroin user	[ ]

C. Drug use status of your current place of accommodation.

12. How many adults live in your current place of accommodation? |___|___|___|

13. What is the current drug use status of your place of accommodation (please tick ✓ one box only)

(a)	Don't have a current accommodation	[ ]
(b)	I live alone	[ ]
(c)	Majority of adults are non-heroin users	[ ]
(d)	Majority of adults are dependant heroin users	[ ]
(e)	Majority of adults are non-dependant heroin users	[ ]

OPIATE TREATMENT INDEX

Research Use Only

Research No. |_|_|_|_|_|

Study Code |H|N|B|R| Site Code |T|P|

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_|_| Staff Initials |_|_|_|

SECTION II

NB: *For all categories, if the subject responds that their last use of the drug was more than a month ago, score zero for that category. Do not include use on the day of interview.*

Day this form was completed (circle)

MON TUE WED THUR FRI SAT SUN

HEROIN

Now I'm going to ask you some questions about heroin (smack, hammer, horse, scag).

1. On what day did you last use heroin? _____
2. How many hits/smokes/snorts did you have on that day? _____
3. On which day before that did you use heroin? _____
4. And how many hits/smokes/snorts did you have on that day? _____
5. And when was the day before that? _____

5a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $_____

5b. On how many days in the past **four weeks** have you used any heroin? _____days

q1 = , q2 = , t1 = , t2 = Q ☐

POLY-DRUG USE

Other Opiates

These questions are about your use of opiates other than heroin (eg. street methadone/done, morphine, pethidine codeine).

6. On what day did you last use opiates other than heroin? (do not include legally obtained methadone) _____
7. How many pills, doses etc. did you have on that day? _____
8. On which day before that did you use opiates other than heroin? _____
9. And how many pills, doses etc. did you have on that day? _____
10. And when was the day before that? _____

10a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

NOTE: Include only cost of other opiods obtained illicitly - not on prescription.

q1 = , q2 = , t1 = , t2 = Q

Alcohol

These questions are about your use of alcohol.

11. On what day did you last drink alcohol? _____

12. How much alcohol did you drink on that day? _____

	Wine	Spirits	Beer	Fortified Wine
	Wine Gl. (120 ml)	Nips (30 ml)	Glasses (200 ml)	Port Gl. (60 ml)
	Bottles (750 ml)	Doubles (60 ml)	Pots (285 ml)	Bottles (750 ml)
	Flagons (1.5 lt)	Bottles (750 ml)	Cans/Stubbies (375 ml)	Flagons (1.5 lt)
	Casks (___lit.)			
No. Standard Drinks				

Total Standard Drinks _____

13. On which day before that did you drink alcohol? _____

14. And how much did you drink on that day? _____

	Wine	Spirits	Beer	Fortified Wine
	Wine Gl. (120 ml)	Nips (30 ml)	Glasses (200 ml)	Port Gl. (60 ml)
	Bottles (750 ml)	Doubles (60 ml)	Pots (285 ml)	Bottles (750 ml)
	Flagons (1.5 lt)	Bottles (750 ml)	Cans/Stubbies (375 ml)	Flagons (1.5 lt)
	Casks (___lit.)			
No. Standard Drinks				

Total Standard Drinks _____

15. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q

Cannabis

These questions ask you about your use of marijuana (dope, grass. hash. pot).

16. On what day did you last use marijuana? _____

17. How many joints, bongs, etc. did you have on that day? _____

18. On which day before that did you use marijuana? _____

19. And how many joints, bongs etc. did you have on that day? _____

20. And when was the day before that? _____

20a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $_____

q1 = , q2 = , t1 = , t2 = Q ☐

Amphetamines

These questions ask you about your use of amphetamines (speed).

21. On what day did you last use amphetamines? _____

22. How many tablets/snorts/hits did you have on that day? _____

23. On which day before that did you use amphetamines? _____

24. And how many tablets/snorts/hits did you have on that day? _____

25. And when was the day before that? _____

25a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $_____

q1 = , q2 = , t1 = , t2 = Q ☐

Cocaine

These questions ask you about your use of cocaine (coke, snow, crack)

26. On what day did you last use cocaine? _____

27. How many snorts/hits/smokes etc. did you have on that day? _____

28. On which day before that did you use cocaine? _____

29. And how many snorts/hits/smokes etc. did you have on that day? _____

30. And when was the day before that? _____

30a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Tranquillisers (Benzodiazepines)

These questions ask you about your use of tranquillisers (eg. Serepax, Valium, Rohypnol, Mogadon)

31. On what day did you last use tranquillisers? _____
32. How many pills did you have on that day? _____
33. On which day before that did you use tranquillisers? _____
34. And how many pills did you have on that day? _____
35. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q

Hallucinogens

These questions ask you about your use of hallucinogens (eg. LSD/acid, ecstasy, magic mushrooms)

36. On what day did you last use hallucinogens? _____
37. How many tabs/pills etc. did you have on that day? _____
38. On which day before that did you use hallucinogens? _____
39. And how many tabs/pills etc. did you have on that day? _____
40. And when was the day before that? _____

40a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Inhalants

These questions ask you about your use of inhalants (eg. amyl nitrate/rush, glue, laughing gas, aerosols petrol)

41. On what day did you last use inhalants? _____

42. How many sniffs did you have on that day? _____

43. On which day before that did you use inhalants? _____

44. And how many sniffs did you have on that day? _____

45. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q [ ]

Tobacco

46. **Finally, if you smoke cigarettes, how many do you usually smoke each day?** _____

DRUG USE SUMMARY

Heroin Use Total [ ] Poly-drug use total [ ]

POLY- DRUG USE

Heroin	[ ]	Cocaine	[ ]
Other Opiates	[ ]	Tranquillisers	[ ]
Alcohol	[ ]	Hallucinogens	[ ]
Cannabis	[ ]	Inhalants	[ ]
Amphetamines	[ ]	Tobacco	[ ]

General Comments on Drug Use

LEEDS DEPENDENCE QUESTIONNAIRE

Research Use Only

Research No. | | | | | | | | | | |

Study Code | H | W | B | R | Site Code | T | P |

Date | | | . | | | . | | | | |

Client Initials | | | Staff Initials | | |

In answering this questionnaire:

* think about the last week
* think specifically about your heroin use
* tick the answer most appropriate to you

B. LEEDS DEPENDENCE QUESTIONNAIRE

(✓Appropriate Box)

No.	Question	0= Never	1= Some-times	2= Often	3 Nea Alw
1	Do you find yourself thinking about when you will next be able to take Heroin?				
2	Is taking heroin more important than anything else you might do during the day?				
3	Do you feel that your need for heroin is too strong to control?				
4	Do you plan your day around taking heroin?				
5	Do you take heroin in a particular way in order to increase the effect it gives you?				
6	Do you take heroin morning, afternoon & evening?				
7	Do you feel that you have to carry on taking heroin once you have started?				
8	Is getting the effect you want more important than the heroin you use?				
9	Do you want to take more heroin when the effect starts to wear off?				
10	Do you find it difficult to cope with life without heroin?				
(Office use only)	SCORE FOR EACH COLUMN				
	TOTAL SCORE				

BASIS - 32

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ].[ ][ ].[ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

A. BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32) INSTRUCTIONS

Below is a list of problems and areas of life functioning in which some people experience difficulties. Using the scale below, WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY Y HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0	no difficulty
1	a little difficulty
2	moderate difficulty
3	quite a bit of difficulty
4	extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, indicat that there is NO DIFFICULTY (IE. '0')

Example

To what extent are you experiencing difficulty in the area of FRIENDSHIPS [2]

B. THE BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32)

TO WHAT EXTENT ARE YOU EXPERIENCING DIFFICULTY IN THE AREA OF :

1. MANAGING DAY-TO-DAY LIFE (Eg. getting to places on time, handling money, making everyday decisions) [ ]
2. HOUSEHOLD RESPONSIBILITIES (Eg. shopping, cooking, keeping room clean, other chores) [ ]
3. WORK (Eg. completing tasks, performance level, finding/ keeping a job) [ ]
4. SCHOOL (Eg. academic performance, completing assignments, attendance) [ ]
5. LEISURE TIME OR RECREATIONAL ACTIVITIES [ ]
6. ADJUSTING TO MAJOR LIFE STRESSES (Eg. separation, divorce, moving. new job / school, a death) [ ]
7. RELATIONSHIPS WITH FAMILY MEMBERS [ ]
8. GETTING ALONG WITH PEOPLE OUTSIDE OF THE FAMILY [ ]
9. ISOLATION OR FEELINGS OF LONELINESS [ ]
10. BEING ABLE TO FEEL CLOSE TO OTHERS [ ]
11. BEING REALISTIC ABOUT YOURSELF OR OTHERS [ ]
12. RECOGNISING AND EXPRESSING EMOTIONS APPROPRIATELY [ ]

... continued next page ...

BASIS - 32

WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY YOU HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0	no difficulty
1	a little difficulty
2	moderate difficulty
3	quite a bit of difficulty
4	extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, indi that there is NO DIFFICULTY (IE. '0')

A. BASIS - 32 CONTINUED ...

13. DEVELOPING INDEPENDENCE, AUTONOMY	[ ]
14. GOALS OR DIRECTIONS IN LIFE	[ ]
15. LACK OF SELF-CONFIDENCE, FEELING BAD ABOUT YOURSELF	[ ]
16. APATHY, LACK OF INTEREST IN THINGS	[ ]
17. DEPRESSION, HOPELESSNESS	[ ]
18. SUICIDAL FEELINGS OR BEHAVIOUR	[ ]
19. PHYSICAL SYMPTOMS (Eg. headaches, aches & pains, sleep disturbances, stomach aches, dizziness)	[ ]
20. CONFUSION, CONCENTRATION & MEMORY	[ ]
21. FEAR, ANXIETY OR PANIC	[ ]
22. DISTURBING OR UNREAL THOUGHTS OR BELIEFS	[ ]
23. HEARING VOICES, SEEING THINGS	[ ]
24. MANIC, BIZARRE BEHAVIOUR	[ ]
25. MOOD SWINGS, UNSTABLE MOODS	[ ]
26. UNCONTROLLABLE, COMPULSIVE BEHAVIOUR (Eg. eating disorder, hand washing, hurting yourself) Please specify _____	[ ]
27. SEXUAL ACTIVITY OR PREOCCUPATION	[ ]
28. DRINKING ALCOHOLIC BEVERAGES	[ ]
29. TAKING ILLEGAL DRUGS, MISUSING DRUGS	[ ]
30. CONTROLLING TEMPER (Eg. outbursts of anger or violence)	[ ]
31. IMPULSIVE, ILLEGAL OR RECKLESS BEHAVIOUR	[ ]
32. FEELING SATISFACTION WITH YOUR LIFE	[ ]

Office use only

TOTAL SCORE |_|_|_|

HEALTH STATUS PROFILE (SF - 36)

Research Use Only

Research No. ⎣ ⎣ ⎣ ⎣ ⎦	Date ⎣ ⎣ ⎦.⎣ ⎣ ⎦.⎣ ⎣ ⎣ ⎦
Study Code ⎣H⎣W⎣B⎣R⎦ Site Code ⎣T⎣P⎦	Client Initials ⎣ ⎣ ⎦ Staff Initials ⎣ ⎣ ⎦

Instructions: *This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.*

Answer every question by selecting the appropriate answer. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent..1
Very good..2
Good..3
Fair..4
Poor..5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better than 1 year ago..1
Somewhat better now than 1 year ago..2
About the same as 1 year ago..3
Somewhat worse now than 1 year ago..4
Much worse now than 1 year ago..5

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

circle one number in each row

	Yes Limited Alot	Yes Limited a little	No, not Limited at
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a kilometre**	1	2	3

HEALTH STATUS PROFILE (SF - 36)

continued from page 1

h.	Walking **several blocks**	1	2	3
i.	Walking **one block**	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the **past four weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

		YES	NO
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Were limited in the **kind** of work or other activities	1	2
d.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past four weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

		YES	NO
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

HEALTH STATUS PROFILE (SF - 36)

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Nor of th tim
a.	Did you feel full of pep? (energy)	1	2	3	4	5	6
b.	Have you been a very nervous person?	1	2	3	4	5	6
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d.	Have you felt calm and peaceful?	1	2	3	4	5	6
e.	Did you have a lot of energy?	1	2	3	4	5	6
f.	Have you felt downhearted and blue?	1	2	3	4	5	6
g.	Did you feel worn out?	1	2	3	4	5	6
h.	Have you been a happy person?	1	2	3	4	5	6
i.	Did you feel tired?	1	2	3	4	5	6

HEALTH STATUS PROFILE (SF - 36)

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered wit social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

11. How TRUE or FALSE is each of the following statements for you?

		Definitely True	Mostly True	Don't Know	Mostly False	Defini Fal
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

THE ASSESSMENT OF QUALITY OF LIFE (AQOL) INDEX

Research Use Only

Research No. |__|__|__|__|__|__|__|

Study Code |__|__|__|__|__| **Site Code** |__|__|__|

Date |__|__|.|__|__|.|__|__|__|__|

Client Initials |__|__|__| **Staff Initials** |__|__|__|

ADVICE FOR RESPONDENT PROVIDED BY AN INTERVIEWER RELATION TO ADMINISTERING THE ASSESSMENT OF QUAL OF LIFE (AQOL) INSTRUMENT

Q1 refers to prescribed medicines. These are medici prescribed for the client by a doctor. This DOES NOT incl the study medications: METHADONE, LA BUPRENORPHINE or NALTREXONE.

It should include any other regular medication prescribed b doctor (for example, benzodiazepines, pain kill antidepressants, asthma drugs, contraceptives etc).

Q2 If the client uses a medication obtained from sources oth than a doctor's prescription (for example over the coun drugs or benzodiazepines bought from the streets) that shou be recorded here.

Q3 Covers the need for regular medical treatment. The treatme provided within the current study (i.e. an initial assessme provision of the study medication or attending group sessio as a part of Naltrexone trial) SHOULD NOT BE RECORDE HERE. However if the same (methadone/LAAM/Buprenorphine prescriber) also provides REGULAR treatment for a medical condition, that should recorded here.

The Assessment of Quality of Life (AQOL) Index

INSTRUCTIONS: Please circle the alternative that best describes you during the last week.

1 ***Concerning the use of prescribed medicines:***

A. I do not or rarely use any medicines at all
B. I use one or two medicinal drugs regularly
C. I need to use three or four medicinal drugs regularly
D. I use five or more medicinal drugs regularly

2 ***To what extent do I rely on medicines or a medical aid? (NOT glasses or a hearing a (For example: walking frame, wheelchair, prosthesis etc.)***

A. I do not use any medicines and/or medical aids
B. I occasionally use medicines and/or medical aids
C. I regularly use medicines and/or medical aids
D. I have to constantly take medicines or use a medical aid

3 ***Do I need regular medical treatment from a doctor or other health professional?***

A. I do not need regular medical treatment
B. Although, I have some regular medical treatment, I am not dependent on this
C. I am dependent on having regular medical treatment
D. My life is dependant upon regular medical treatment

4 ***Do I need any help looking after myself?***

A. I need no help at all
B. Occasionally I need some help with personal care tasks.
C. I need help with the more difficult personal care tasks
D. I need daily help with most or all personal care tasks

5 ***When doing household tasks: (For example, preparing food, gardening, using the vid recorder, radio, telephone or washing the car)***

A. I need no help at all
B. Occasionally I need help with household tasks
C. I need help with the more difficult household tasks
D. I need daily help with most or all household tasks

6 ***Thinking about how easily I can get around my home and community:***

A. I get around my home and community by myself without any difficulty
B. I find it difficult to get around my home and community by myself
C. I cannot get around the community by myself, but I can get around my home with some difficulty
D. I cannot get around either the community or my home by myself

7 ***Because of my health, my relationships (for example: with my friends, partner or pare generally:***

A. Are very close and warm
B. Are sometimes close and warm
C. Are seldom close and warm
D. I have no close and warm relationships

8 ***Thinking about my relationships with other people:***

A. I have plenty of friends, and am never lonely
B. Although I have friends, I am occasionally lonely
C. I have some friends, but am often lonely for company
D. I am socially isolated and feel lonely

9 ***Thinking about my health and my relationship with my family:***

A. My role in the family is unaffected by my health
B. There are some parts of my family role I cannot carry out
C. There are many parts of my family role I cannot carry out
D. I cannot carry out any part of my family role

10 ***Thinking about my vision, including when using my glasses or contact lenses if ne***

A. I see normally
B. I have some difficulty focusing on things, or I do not see them sharply. For example: sm print, a newspaper, or seeing objects in the distance
C. I have a lot of difficulty seeing things. My vision is blurred. For example I can see just e to get by with
D. I only see general shapes or I am blind. For example: I need a guide to move around

11 ***Thinking about my hearing, including using my hearing aid, if needed:***

A. I hear normally
B. I have some difficulty hearing or I do not hear clearly. For example: I ask people to spea or turn up the TV or radio volume
C. I have difficulty hearing things clearly. For example I do not understand what is said. I us do not take part in conversations because I cannot hear what is said
D. I hear very little indeed. For example: I cannot fully understand loud voices speaking dir me

12 ***When I communicate with others; (for example: by talking, listening, writing or sign***

A. I have no trouble speaking to them or understanding what they are saying
B. I have some difficulty being understood by people who know me well. I have great troub understanding what others are saying to me
C. I am only understood by people who know me well. I have great trouble understanding w others are saying to me
D. I cannot adequately communicate with others

13 ***If I think about how I sleep:***

A. I am able to sleep without difficulty most of the time
B. My sleep is interrupted some of the time, but I am usually able to go back to sleep withou difficulty
C. My sleep is interrupted most nights, but I am usually able to go back to sleep without diffi
D. I sleep in short bursts only. I am awake most of the night.

14 ***Thinking about how I generally feel:***

A. I do not feel anxious, worried or depressed
B. I am slightly anxious, worried or depressed
C. I feel moderately anxious, worried or depressed
D. I am extremely anxious, worried or depressed

15 ***How much pain or discomfort do I experience?***

A. None at all
B. I have moderate pain
C. I suffer from severe pain
D. I suffer unbearable pain

Now that you have finished, please go back and check you have answered all the questions.
THANK YOU

OUTPATIENT HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

GOALS OF TREATMENT

Research Use Only

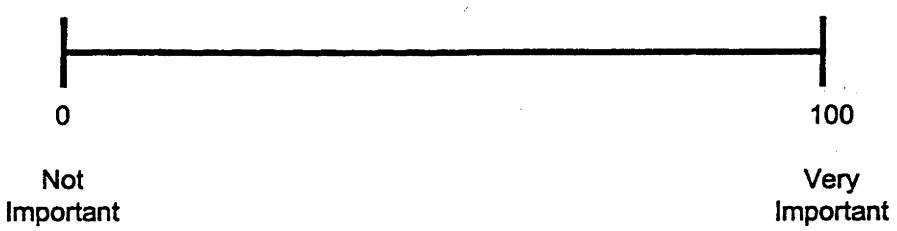
Research No. ____	Date ____ . ____ . ____
Study Code H W B R Site Code T P	Client Initials ____ Staff Initials ____

INSTRUCTIONS - Identify your (the client) current treatment goals by indicating on the following visua analogue scales where feel best represents your view. Please mark a VERTICAL SLASH through the lin (for ALL of the presented treatment goals) to indicate the level of importance to you, for this treatment episode.

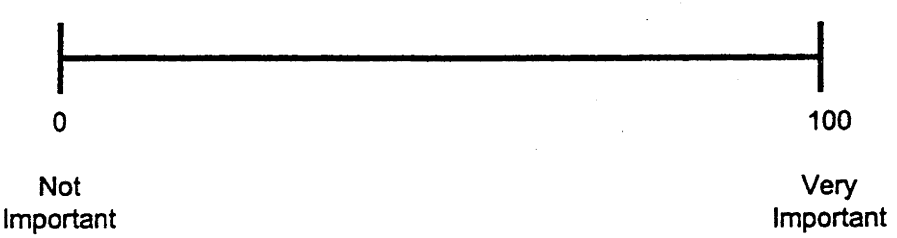
0 = Achieving this goal is of no importance

100 = Achieving this goal is of great importance

"GOAL 1 - To cease heroin use throughout the withdrawal episode (8 days)'

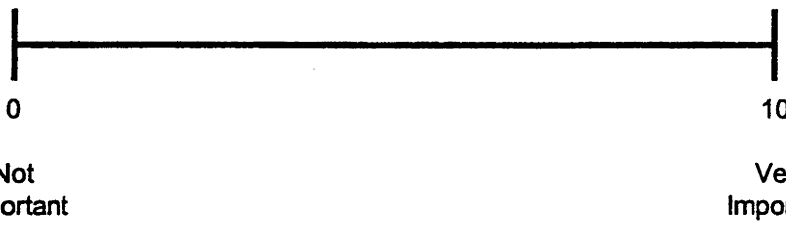


"GOAL 2 - To reduce heroin use during the 8 day withdrawal episode"

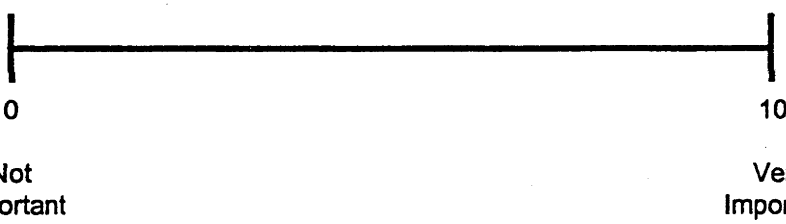


GOALS OF TREATMENT

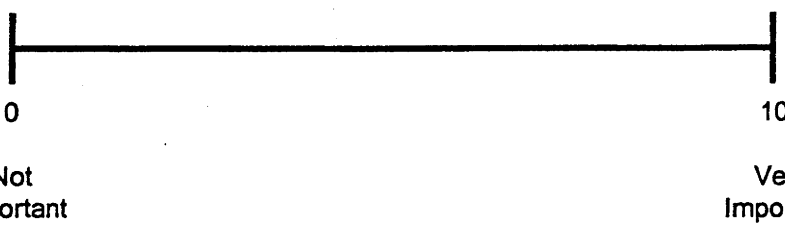
"GOAL 3 - To get heroin use 'under control' by the end of the 8 day withdrawal period"



"GOAL 4 - To participate in ongoing treatment after the 8 day withdrawal"



"GOAL 5 - To cease heroin use for at least one month after completing the 8 day withdraw period"



OUTPATIENT HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

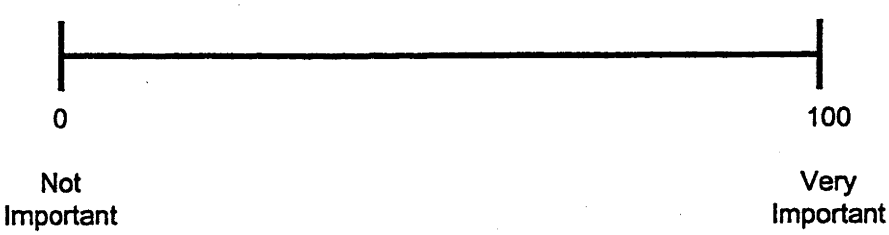
GOALS OF TREATMENT

Research Use Only

Research No.	Date
Study Code H W B R Site Code T P	Client Initials Staff Initials

"GOAL 6 - To reduce heroin use for at least one month after completing the 8 day withdrawa period"

"GOAL 7 - To get heroin use under control for at least one month after completing the 8 day withdrawal period"



Research Use Only

GOAL #	Total mm	GOAL #	Total mm
Goal 1		Goal 5	
Goal 2		Goal 6	
Goal 3		Goal 7	
Goal 4			

OUTPATIENT HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

WITHDRAWAL EXPECTANCY V.A.S

Research Use Only

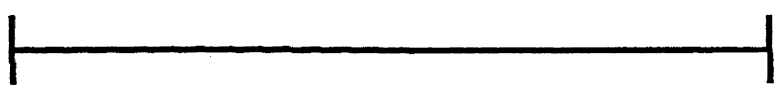
Research No. ____	Date ____ . ____ . ____
Study Code ____ Site Code ____	Client Initials ____ Staff Initials ____

A. EXPECTANCY REGARDING THIS WITHDRAWAL

"How severe do you think this withdrawal episode will be?"

Please indicate on the following scale by marking a slash through the line as to where you think best represent how much discomfort you expect to experience during this withdrawal episode.

0 = predict no discomfort will be experienced this heroin withdrawal and,
100 = predict the most severe withdrawal symptoms ever experienced.



0 — No Discomfort Will Be Experienced

100 — Most Severe Discomfort Will Be Experienced

Research Use Only

Total mm ____

NHMRC Clinical Trials Centre
Randomisation Service: Instruction Sheet
NEPOD06: A randomised controlled trial of outpatient heroin withdrawal using Buprenorphine

The NHMRC Clinical Trials Centre (CTC) randomisation service is staffed on a roster basis by about 30 individuals. The service is currently provided to over 40 trials from 6.00 am to 8.00 pm. When you telephone the randomisation line the first questions you will be asked will focus on identifying the specific trial to which you want to randomise.

1. Make sure you have all the information required for randomisation in front of you **BEFORE** you telephone the randomisation service.
   a) It is recommended that the Randomisation Form provided (or similar) be used.
2. Telephone the randomisation line on 1800 027 928
3. State specifically that you want to randomise to the NEPOD06 trial.
4. You will then be asked for the following information (in this order).
   a) Surname: if you do not want to provide the patient's Surname, you may record the subject number or the initial
   b) First name: if you do not want to provide the patient's First name, you may record the subject number or the initial
   c) ID/MRN: the subject number
   d) Date of birth: in dd/mm/yy form. If you do not want to provide a data of birth you may give the dummy date of birth 01/01/99.
   e) Hospital code / site code. This is a 3 digit code. The first digit indicates the city the site is based in. The remaining 2 digits identify the specific site.
      i) There are the following choices:
         101, Langton Clinic, Sydney
         201, Turning Point, Melbourne
         301, Peel St Clinic, Brisbane
         601, Palm Beach Clinic, Gold Coast
      ii) You must provide this number.
   f) Strata: the choices are: Methadone (1) or Heroin (2). All subjects on this trial should be in the Heroin strata.
5. When data collection is complete the computer will then perform the randomisation. There may be a short delay.
6. The data manager will then read out:
   - a randomisation number
   - the result of the randomisation (ie Sublingual Buprenorphine or Symptomatic withdrawal medication)

   a) **You should write this information down.**
   b) You will then be asked to repeat the information back to the data manager.
7. The randomisation is then complete.
8. A confirmation of randomisation form will then be faxed to you.

Randomisation Form: NEPOD 06

1. Surname (or initial): _____

2. First name (or initial): _____

3. ID/MRN (or subject code): _____

4. Date of birth: _____

5. Hospital code
   - ☐ 101 (Langton Clinic)
   - ☐ 201 (Turning Point)
   - ☐ 301 (Peel St Clinic)
   - ☐ 601 (Palm Beach Clinic)

6. Strata
   - ☐ 1 (Methadone)
   - ☐ 2 (Heroin)

Telephone the randomisation line on 1800 027 928

Randomisation result

Randomisation number: _____

Randomised to:

- ☐ Experimental Arm: 5 day withdrawal regime of Sublingual Buprenorphine
- ☐ Control Arm: Symptomatic withdrawal medication

Date: _____

Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Data collection during episode of withdrawal treatment

- Contact Record Form
- Client Report Form
- Clinician Report Form
- Review Form

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CONTACT RECORD FORM

Clinic Use — **Research Use Only**

Date |__|__|/|__|__|/|__|__|__|__| Client Initials |__|__| Staff Initials |__|__| Research No. |__|__|__|__| Study Code H W B R Site Code T P

INSTRUCTIONS : Commence completion of this form once the client has been randomised. Do not include time spent on admission assessments. This form is to be completed by the Clinician following each client consultation.

DATE CLIENT ENROLLED IN TRIAL : |__|__| . |__|__| . |__|__|__|__|
day month year

Date	Duration of Consultation (minutes)	Clinician Name	Clinician Designation (eg. M.O., nurse, pharmacist)	Tasks Completed (please tick ✓)				Reason for Consultation please use code 0 = Review as per normal protocol 1 = Additional Review
				Client Review Form	Clinician Review Form	Review Form	Urine Drug Screen	
	|__|__|__|							
	|__|__|__|							
	|__|__|__|							
	|__|__|__|							
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CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

CLIENT REPORT FORM

Research Use Only	Clinic & Research Use Only
Research No. |_|_|_|_|_|	Date |_|_|.|_|_|.|_|_|_|
Study Code |_|_|_|_| Site Code |_|_|_|	Client Initials |_|_| Staff Initials |_|_|

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.

A. TIME OF FORM COMPLETION |_|_| : |_|_| **AM / PM**

B. 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					

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

CLIENT REPORT FORM

B. WHICH TREATMENT MEDICATION ARE YOU CURRENTLY RECEIVING? (Please circle)

Buprenorphine Naltrexone Clonidine Methadone LAAM

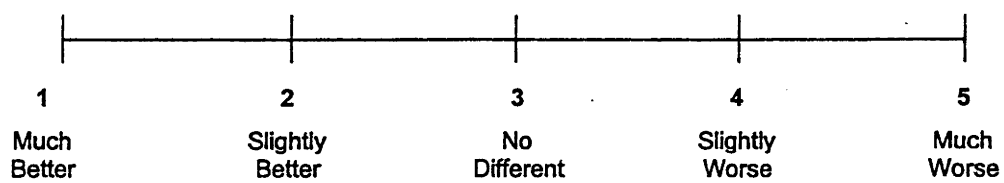
C. COMMENTS ON MEDICATION RECEIVED

Only complete this section below once per day (morning)

How would you rate yesterday's total dose? (please ✓ tick)

1 = much too low |__|
2 = too low |__|
3 = about right |__|
4 = too high |__|
5 = much too high |__|

Please rate how you slept last night **in comparison** to how you **normally** sleep. Place a circle around the cor response.



Please list any side effects to the treatment medication that you experienced.

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

CLINICIAN REPORT FORM

Research Use Only

Research No. |__|__|__|__|

Study Code |__|__|__|__| Site Code |__|__|

Clinic & Research Use Only

Date |__|__|.|__|__|.|__|__|__|

Client Initials |__|__| Staff Initials |__|__|

Staff Name & Signature : _____

Time : |__|__| : |__|__|

A. PHYSICAL OBSERVATIONS

Pupil size (mm) (please circle) 1mm● 2mm● 3mm● 4mm● 5mm● 6mm● (or mo

BP(mmHg) |__|__|__| / |__|__|__| **Pulse rate** (b/min) |__|__|__|

Respiratory rate (b/min) |__|__| **BAL reading (%)** |__|.|__|__|__|

Level of Consciousness
(please ✓tick)

0 = drowsy, no response to verbal stimuli [ ]
1 = drowsy but responds (alert) to stimuli [ ]
2 = alert (normal) [ ]
3 = agitated [ ]

Speech
(please ✓tick)

0 = slurred [ ]
1 = normal [ ]
2 = pressured [ ]

Gait
(please ✓tick)

1 = normal [ ]
0 = impaired [ ]

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

CLINICIAN REPORT FORM

B. OBJECTIVE OPIATE WITHDRAWAL SCALE

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 PEROID. Add up the total score for all of the observations to get the overall withdrawal score.

Observations	Scoring	Score
1. Yawning	0 = no yawns 1 = ≥ 1 yawns	
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		

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

REVIEW FORM

Research Use Only	Clinic Use
Research No. |__|__|__|__|	Date |__|__|.|__|__|.|__|__|__|
Study Code |H|W|B|R| Site Code |T|P|	Client Initials |__|__| Staff Initials |__|__|

INSTRUCTIONS : This form is to be completed by the Clinician following each client consultation.

Staff Name & Signature : _____

Staff Designation : _____ Time : |__|__| : |__|__|

A. SELF REPORT DRUG USE BY CLIENT SINCE LAST REVIEW

Drug used	Amount used	r.o.a	When used	Reason for drug use

[1] [*Reasons for use* may be: to avoid withdrawal discomfort (severe symptoms / cravings); for intoxication; situational factors, other]

.....

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.....

B. SELF REPORT USE OF STUDY MEDICATIONS - Please include the number of tablets (administered from T/P Pharmacy) taken since the last review. Answer for each of the listed medications.

• Valium |__|__|	• Clonidine |__|__|
• Brufen |__|__|	• Buscopan |__|__|
• Maxalon |__|__|	• Quinine |__|__|
• Lomotil |__|__|	

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

REVIEW FORM

B. WHAT TREATMENT MEDICATION IS THE CLIENT RECEIVING? _____

C. STAFF ASSESSMENT OF DOSE ADEQUACY.

Please rate the adequacy of preceding day's total dose:

1 = much too low
2 = too low
3 = about right
4 = too high
5 = much too high
N/A = did not present, dose withheld

SCORE |___|

D. CLINICIAN ASSESSMENT OF ADVERSE EVENTS.

Description of adverse event reported by client / observed by clinician. Include description, onset, other potent causes, examination findings, management, outcome, likely relationship to the study medication (highly unlike unlikely / possible / probable/ likely / highly likely)

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D. OTHER ISSUES DISCUSSED IN CONSULTATION / PLAN FOR NEXT CONSULTATION

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Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Medical Assessment
(day 8)

- Post-withdrawal Eligibility Checklist
- Patient Information Sheets (Post-withdrawal Treatment Options)
- Consent Form for post-withdrawal treatment
- Opioid Antagonist Challenge Withdrawal Rating Form
- Summary of Adverse Events

1999

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

POST-WITHDRAWAL ELIGIBILITY CHECKLIST

Research Use Only

Research No. [| | | |]

Study Code [H|W|B|R] Site Code [T|P]

Date [| |] . [| |] . [| | | |]

Client Initials [| |] Staff Initials [| |]

A. WHAT TREATMENT MEDICATION DID THE CLIENT RECEIVE?

(please tick ✓)

BUPRENORPHINE [ ]

CLONIDINE [ ]

B. POST-WITHDRAWAL ELIGIBILITY CRITERIA

Attendence Issues :

- Did the client meet the attendence requirements for the 8 day withdrawal period? (ie, did not miss 2 or more consecutive days) [ ] yes* [ ] no

Opiate Use during 8 day withdrawal episode :

- Self - report of opiate use [ ] yes* [ ] no
- Urine Drug Screen

Day 5 [ ] positive * [ ] negative [ ] results not confirmed ** [ ] specimen not provided*
Day 8 [ ] positive * [ ] negative [ ] results not confirmed ** [ ] specimen not provided*

- Instant Urine Drug Screen (Accusign) - day 8 [ ] positive * [ ] negative

Liver Function Test

- Is the ALT > 3 times normal range [ ] yes* [ ] no

Information & Consent :

- Has the client been given a copy of the Patient Information Sheets [ ] yes [ ] no*
- Has the client given informed consent [ ] yes [ ] no*

If response is marked with a * or ** do NOT commence post-withdrawal treatment with Naltrexone. Client is ineligible.

C. POST - WITHDRAWAL TREATMENT

Post - Withdrawal Options	*Eligible for Treatment*	*Treatment Entered*
• Counselling Only	[ ] yes [ ] no	[ ] yes [ ] r
• Naltrexone Treatment	[ ] yes [ ] no	[ ] yes [ ] r
• Buprenorphine Treatment	[ ] yes [ ] no	[ ] yes [ ] r
• Methadone Treatment	[ ] yes [ ] no	[ ] yes [ ] r
• Complete Symptomatic Withdrawal	[ ] yes [ ] no	[ ] yes [ ] r
• Undecided	n/a	[ ] yes [ ] r

D. DAY 10 OUTCOME

What post-withdrawal treatment did the client enter? _____

Comments _____

Randomised Trial of Outpatient Heroin Withdrawal using Buprenorphine

Information for Clients

POST WITHDRAWAL TREATMENT OPTIONS

After withdrawal, the study offers a range of treatment options. These services are available as part of the study for 4 weeks. After this time, you may continue the treatment independent of the study, as part of 'routine' treatment (with the exception of buprenorphine). Each treatment is described below.

Treatment as part of the research is free of charge during the first 4 weeks. A fee for medication applies after this time.

You do not have to enter any ongoing treatment. However, you must make a decision about entering these treatment options during the first three days after the withdrawal has finished - on days 8, 9 or 10. Naltrexone, methadone or buprenorphine treatment are not routinely available at Turning Point, so you can only enter these treatments during this three day period.

You can not change the type of treatment you are in during the four week period (eg, you can not start on naltrexone and then change to methadone after 2 weeks).

You can cease treatment at any time. However, if you cease treatment, you will not be able to enter treatment again as part of the study. Other treatment plans can be considered with your doctor and case worker.

If you miss more than 3 consecutive days of treatment with naltrexone, methadone or buprenorphine then your treatment program as part of the research will be ceased. Alternative treatment plans can be considered.

If you are interested in other forms of treatment (eg residential rehabilitation), this may be organised with your doctor and case worker

Counselling

Individual counselling is available with one of the workers at Turning Point (generally your withdrawal worker). In general, 2 counselling sessions per week are available for four weeks, although this can be negotiated with your counsellor. The general aim of counselling will be to assist you to meet your goals around drug use or other issues. Counselling can assist you with strategies aimed at preventing relapse into regular heroin, or dealing with problems related to your drug use.

Naltrexone Treatment

Naltrexone is a medication that is used to reduce relapse to regular heroin use in people who have already gone through withdrawal. Naltrexone has been used in the treatment of heroin use in the USA and other countries for over 10 years, but it is not registered for use in Australia yet. It is therefore not widely available in Australia.

Previous studies have shown that naltrexone reduces relapse to regular heroin use and reduces cravings for heroin. Studies also indicate that naltrexone works best for those people who are

motivated to remain abstinent from heroin use, and where ongoing counselling and support are pa of treatment.

Naltrexone is an opioid antagonist - it works to block the effects of opiates by binding to opiate receptors in the brain and preventing other opiates from working. This means that the 'high' from any heroin use is greatly reduced. Most people finding that heroin use is not worthwhile while taking naltrexone. Naltrexone has this effect for up to 3 days, so it takes up to 3 days before peopl can feel stoned from heroin.

Getting started on naltrexone

Taking naltrexone after recent opiate use will send you into severe opiate withdrawal. Therefore, before you start naltrexone, you must not have used heroin or other opiates for at least 7 days. Naltrexone is only available for people who have not used heroin during the withdrawal episode, and this must be confirmed by urine tests on days 5 and 8 of the withdrawal. Also, a naloxone challenge test is conducted for those people who used symptomatic medication for withdrawal. Th is to make sure that you do not get severe withdrawal discomfort when starting naltrexone. This is done by giving you an injection of naloxone (Narcan) and observing if there is a withdrawal reaction within the next 15 minutes. If this is OK, then you can commence naltrexone immediately If you do have a severe reaction to the naloxone challenge test, then we recommend you wait another 24 hours before having another challenge test.

For those people who used buprenorphine for withdrawal, a test dose of naltrexone is used. This is low dose of naltrexone (12.5 mg), and clients are asked to stay at the clinic for 3 hours after the do to make sure they do not have any withdrawal reaction.

The routine with naltrexone

Naltrexone is dispensed daily for the first week at Turning Point, initially at 25 mg per day (half a tablet) for the first three days, increasing to 50 mg per day (a full tablet). After a week, naltrexone i dispensed weekly, but you should keep taking a tablet once a day.

Part of naltrexone treatment involves regular (weekly) contact with your doctor, and with your counsellor. Naltrexone is available for the first 4 weeks for free. After this time (after the research has finished), you will have to commence payments for naltrexone treatment - it usually costs abou $5 per dose per day (~$150 per month).

Side effects

Mild side effects have been reported with naltrexone in about 5 to 15% of people taking it. The most common symptoms reported by more than 10% of people are opiate withdrawal symptoms during the first week on naltrexone, such as sleep problems, anxiety, abdominal cramps, nausea, diarrhoea, joint and muscle aches, headache. These usually settle down within the first week of treatment with naltrexone.

Less common side effects include: feeling down or flat, irritability, skin rash and sexual difficulties Most of these symptoms are usually mild and short lasting. Overall, naltrexone is considered to be safe medication. Please tell your treatment team if you have any side effects. One concern however is the effects upon people with severe liver disease, and therefore all people thinking of starting naltrexone must have liver function tests first.

A possible, but rare side effect of the naloxone (Narcan®) challenge test is the onset of pulmonary oedema (fluid in the lungs). This can be severe and needs treatment in hospital.

Pregnancy and breast feeding
The safety of naltrexone in pregnancy has not been proven, therefore we recommend that pregnant or breast feeding women do not take naltrexone. Women taking naltrexone should avoid becoming pregnant during the course of this trial - this often means using a reliable form of contraception. If a woman taking naltrexone becomes pregnant, they must stop taking naltrexone immediately and consider other forms of treatment.

Overdose risk
It is important to remember that after a period of withdrawal, and particularly after being on naltrexone, your tolerance for opiates will be very much reduced. This means that if you stop taking naltrexone, even small amounts of heroin will get you very stoned, and may cause overdose.

Buprenorphine Treatment

Buprenorphine is an opioid drug that has similar properties and effects to other opiates. Buprenorphine is only available in Australia as a research medication, although it is available for the treatment of heroin dependence in France.

Buprenorphine relieves or prevents symptoms of heroin withdrawal, reduces cravings for heroin use and reduces the effects of any additional heroin use. Buprenorphine also is reported to have much milder withdrawal symptoms on stopping it compared to other opiates such as morphine, heroin or methadone.

Buprenorphine is manufactured as thin white oval tablets. These tablets are placed under the tongue and take about 2 to 3 minutes to dissolve (on average). They should not be swallowed or chewed as this will considerably lessen their effect. It is important that you take the medication as directed by the clinic staff. No additional tablets will be given to you if they are taken incorrectly.

Doses of buprenorphine are usually commenced around 4 to 8 mg per day and increased over the next few days until the client is comfortable. Most people find that daily doses of between 8 and 16 mg per day are adequate. Buprenorphine is dispensed once a day. No take aways are available as part of the study.

Side effects
As with other opiates, buprenorphine may have a number of side effects. These are most commonly: constipation, tiredness, sleepiness, dizziness, nausea and headaches. Side effects are usually mild, short lasting and cease on stopping the medication.

Pregnancy and breast feeding
The safety of buprenorphine in pregnancy or breastfeeding has not been proven and therefore we recommend that pregnant or breast feeding women do not take buprenorphine. It is recommended that women taking buprenorphine should use reliable contraception, which you can discuss with your doctor or other health care workers. If a woman taking buprenorphine becomes pregnant, they must stop taking buprenorphine immediately and consider other forms of treatment such as methadone.

Caution about using other drugs with buprenorphine
The use of other sedative drugs in combination with buprenorphine can be dangerous and may lead to overdose and death. This includes drugs such as alcohol, sleeping tablets or tranquillisers (eg Valium, Serepax, Mogadon, temazepam, Rohypnol), antidepressants or other opiates. Furthermore, the effects of buprenorphine can last for several days after the last dose. This

means that you should not use other sedative drugs for several days after your last dose buprenorphine without checking with your doctor.

Medications will not be dispensed if a client presents intoxicated. Clients can refuse a dose medication at any time.

Availability of buprenorphine after the research

Unfortunately, long term treatment with buprenorphine is not an option in this study. At the end c the research (after 4 weeks of buprenorphine treatment), clients on buprenorphine have one of tw options -

- to transfer to methadone maintenance treatment and continue long term treatment on methadone; or
- to withdraw off buprenorphine. This can take up to 2 weeks, so in total, the maximum duratio of buprenorphine treatment available after withdrawal is 6 weeks.

Methadone Treatment

Methadone is an opioid drug that is widely used around Australia for the treatment of heroin dependence. It is a substitution medication - that is, it reduces or prevents features of heroin withdrawal, cravings for heroin, and at high doses also reduces the effects of additional heroin use It has been shown to be a safe and effective treatment approach in numerous studies around the world. Detailed description of methadone treatment is available in the client handbook "*Methado treatment in Victoria*" which will be given to you.

As methadone is an opiate, it has side effects common with other opiates. These include sedation, drowsiness, constipation, sweating, nausea, vomiting, reduced libido, fluid retention, skin rashes. Many of these side effects are mild and short lasting, while others persist (eg constipation). Other less common side effects are described in the booklet on methadone. One of the concerns often described with methadone is difficulties in coming off methadone, with prolonged withdrawal discomfort.

Methadone is dispensed as a syrup which you drink. Doses are dispensed daily from the Turning Point pharmacy. Clients can receive take aways for methadone (one per week) after 3 months in treatment - but this does not apply for the 4 week study. Doses are adjusted according to any symptoms of heroin withdrawal, cravings, side effects or additional drug use that you may be experiencing.

Methadone treatment during the research study (first 4 weeks) will be provided free of charge at Turning Point pharmacy. If you wish to stay in methadone treatment after the study has finished, then you will have to commence paying usual methadone dispensing fees (~$25 to 30 per week). You can transfer to a community based pharmacy at this time.

Pregnancy and breast feeding

Methadone is relatively safe in pregnancy and for breast feeding, and is the recommended form of treatment for pregnant heroin users in Australia. Some babies are born with features of opiate withdrawal, but this is usually mild and short lasting, and does not appear to be related to the dose of methadone that the mother was taking.

Caution about using other drugs with methadone

The use of other sedative drugs in combination with methadone can be dangerous and may le to overdose and death. This includes drugs such as alcohol, sleeping tablets or tranquillisers (Valium, Serepax, Mogadon, temazepam, Rohypnol), antidepressants or other opiate

Furthermore, the effects of methadone can last for several days after the last dose. This means that you should not use other sedative drugs for several days after your last dose of methadone. Medications will not be dispensed if a client presents intoxicated. Clients can refuse a dose of medication at any time.

Other Business

1. Compensation

The sponsor of this study, Turning Point, has undertaken to adhere to guidelines for compensation to patients whose health is affected by taking part in the study. A copy of these Australian Pharmaceutical Manufacturers Association guidelines is available for you to peruse. If an injury occurs to you as a result of participation in this study as a result of the study medication, clinical intervention or procedure provided for by the protocol, you have the right to seek compensation, either through the procedure outlined in the guidelines or by normal legal channels.

2. Advice on Avoiding Pregnancy

You should avoid becoming pregnant during the course of this trial if you are taking the investigational medications buprenorphine or naltrexone. If you become pregnant you will have to withdraw from the trial and you will be medically followed up carefully until delivery. These precautions are necessary because the information on the effects on the unborn or newborn baby of drugs like buprenorphine or naltrexone is still very limited.

3. Information and / or complaints

Turning Point and St Vincent's Hospital requires all investigators to carry out their investigations under guidelines issued by the World Health Organisation, The National Health and Medical Research Council and the Therapeutic Goods Administration of the Commonwealth Department of Health and Family Services. These guidelines have been drawn up to protect the interests of people who agree to take part in medical research.

If you require further information concerning the project in which you are involved, you should contact the principal investigator responsible for this project:

Dr Nicholas Lintzeris
Turning Point Alcohol and Drug Centre
54 Gertrude Street, Fitzroy, VIC 3065
Telephone (03) 9254 8061

If you have any complaints about any aspects of the study or the way in which it is being conducted then you should contact

Professor Margaret Hamilton
Director of Turning Point Alcohol and Drug Centre
54 Gertrude Street, Fitzroy, VIC 3065
Telephone (03) 9254 8061

HEROIN WITHDRAWAL USING BUPRENORPHINE

PATIENT DECLARATION / CONSENT

Research Use Only

Study Code H W B R Site Code T P	Date __/__/____
	Client Initials ___ Staff Initials ___

ST VINCENT'S HOSPITAL

CONSENT OF PATIENT TO PARTICIPATE IN RESEARCH STUDY

PROTOCOL NO. (SVH) : ____ / ___ ____ (Office use only)

CONSENT FOR : (please tick ✓)

- WITHDRAWAL TREATMENT [ ]
- POST-WITHDRAWAL TREATMENT [ ]

NAME OF INVESTIGATORS:

Dr Nicholas Lintzeris,
Dr Gabriele Bammer,
Professor Greg Whelan,
Dr James Bell,
Alison Ritter,
Damian Jolley

STUDY TITLE:

"Randomised Controlled Trial of Outpatient Heroin Withdrawal using Buprenorphine"

I _____ have had the purpose and nature of this research study explained to me by a member of Clinical Staff at Turning Point Alcohol & Drug Centre. The methods and procedures of this study, and the risks and discomfort that may be associated with my participation have also been explained to me. I have been given a copy of the Patient Information Sheets and have read and understood them.

I am willing to take part in this study and I consent to all of the procedures with their associated risks as has been explained to me. I understand that I am free to withdraw from this study at any time without cost to myself and without jeopardising the management of my condition and the future care and attention that I will receive. I have read/had translated to me the above explanation and understand it.

Signed: _____
(Patient / Guardian / Next Friend)

Witness _____

Date __/__/____
day month year

CLIENT NAME _____ UR NUMBER |_|_|_|_|_|_|

OPIOID ANTAGONIST CHALLENGE
WITHDRAWAL RATING FORM

Research Use Only

Research No. |_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Clinic & Research Use Only

Date |_|_|.|_|_|.|_|_|_|

Client Initials |_|_| Staff Initials |_|_|

This form is to be completed by the medical officer during the Naloxone or Naltrexone Challenge Test.

SECTION A

This section is to be completed by the medical officer five minutes after the naloxone injection or 3 hours after naltrexone is administered, and involves making a global observation of the patient. Please rate the presence and severity of the patient's withdrawal symptoms by placing a tick next to your response.

1. Is the patient displaying signs of withdrawal from opioids?

1 [ ] Yes

0 [ ] No

2. If you answered 'yes' to Question 1, please indicate with a tick the severity of the signs the patient is displaying.

1 [ ] Mild

2 [ ] Moderate

3 [ ] Severe

SECTION B

The medical officer should tell the participant that any symptoms they are experiencing are likely to continue if they are inducted to naltrexone today. Please indicate the participant's response with a tick.

1. Are the symptoms you are experiencing tolerable?

1 [ ] Yes (without symptomatic medication)

2 [ ] Yes (with symptomatic medication)

0 [ ] No

2. Do you want to begin taking naltrexone today?

1 [ ] Yes

0 [ ] No

SECTION C

1. Individual's dosing status?

1 [ ] Ineligible

2 [ ] Eligible and prescription written

3 [ ] Eligible but declines

SUMMARY OF ADVERSE EVENTS

(BASED ON VA / NIDA FORM)

Research Use Only

Research No. |_|_|_|_|_|

Study Code H W B R Site Code T P

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_| Staff Initials |_|_|

A. PERIOD OF REVIEW :

From Date |_|_|.|_|_|.|_|_|_|_| To Date |_|_|.|_|_|.|_|_|_|_|

B. WHAT TREATMENT MEDICATION DID THE CLIENT RECEIVE?

(please tick ✓)

BUPRENORPHINE [ ]

CLONIDINE [ ]

C. ADVERSE EVENTS

Date of Onset	Nature of Illness, Event or Abnormal Lab Value	I. Type of Report	II. Relatedness	III. Level of severity	IV. Action Taken	V. Outcome	Date Resolv
	1.						
	2.						
	3.						
	4.						
	5.						
	6.						
	7.						
	8.						

I. Type of report	II. Relatedness	II. Severity	IV. Action Taken	V. Outcome
1 = Anticipated adverse event *2 = Unanticipated adverse event* *3 = Concomitant illness* *4 = Development of clinically significant abnormal lab value* *5 = Serious adverse event*	*1 = Definitely study drug related* *2 = Probably study drug related* *3 = Possibly study drug related* *4 = Unrelated to study drug*	*1 = Mild* *2 = Moderate* *3 = Severe***	*1 = None required* *2 = Prescription drug therapy* *3 = In-patient hospitalisation* *4 = Prescription drug therapy & hospitalisation* *6 = Medical specialty consultation required* *7 = Randomisation code broken* *8 = Other (please specify)*	*1 = Resolved* *2 = Unresolved* *3 = Resulted in chronic condition or severe / permanent disability*** *4 = Deceased*** *5 = Unknown*

*** Complete Serious Adverse Events Form (F10SAdv.Doc)*

Continued Next Page ....

SUMMARY OF ADVERSE EVENTS
(BASED ON VA / NIDA FORM)

C. Is a Serious Adverse Events form required? 1[ ] Yes 0[ ] No

Adverse Event Number (from table overleaf)	Date Serious Adverse Event form completed.
	__/__/____
	__/__/____
	__/__/____
	__/__/____

INFORM PRINCIPLE INVESTIGATOR WITHIN 12 HOURS OF SERIOUS ADVERSE EVENT

D. Comments : _____

_____

_____

_____

_____

✶ ***PLEASE FORWARD THIS FORM TO THE PRINCIPLE INVESTIGATOR AT TURNING POINT A.S.A.P.***

Principle Investigator's Signature and Date

_____ __/__/____

Principle Investigator's Comments : _____

_____

_____

_____

_____

_____

Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Research Assessment
Day 8 Data Collection

- Weekly Drug Use Diary
- Medication History
- Utilisation of Other Health Services
- Leeds Dependence Questionnaire
- BASIS - 32
- Client Ratings of Withdrawal
- Attainment of Client Goals - day 8
- Client Satisfaction with Medication

1999

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)
WEEKLY DRUG USE DIARY

Research Use Only

Research No. [| | | |]

Study Code [H | W | B | R] Site Code [T | P]

Date [| |] . [| |] . [| | | |]

Client Initials [| |] Staff Initials [| |]

DATES OF REVIEW

FROM [| |] . [| |] . [| | | |]
day month year

TO [| |] . [| |] . [| | | |]
day month year

Please answer every question honestly. Ask for help if you do not know what to do.

Drug Class	Have you used this drug since commencing this withdrawal program? (please tick ✓)	If YES, how many times have you used it since commencing this withdrawal program?	How many hits, snorts, drin did you have since commencing this withdraw program?
Heroin	1 [ ] YES 2 [ ] NO		
Street Methadone	1 [ ] YES 2 [ ] NO		
Other opiates (eg. pethidine, codeine, mersyndol)	1 [ ] YES 2 [ ] NO		
Stimulants (eg cocaine, amphetamines)	1 [ ] YES 2 [ ] NO		
Hallucinogens(eg. ecstasy, trips)	1 [ ] YES 2 [ ] NO		
Benzodiazepines (eg. rohypnol, valium) - ***excluding study medications***	1 [ ] YES 2 [ ] NO		
Alcohol	1 [ ] YES 2 [ ] NO		
Cannabis	1 [ ] YES 2 [ ] NO		
Other (please specify) _____	1 [ ] YES 2 [ ] NO		

MEDICATION HISTORY

Clinic & Research Use only

Research Use Only

Date	Client Initials	Staff Initials	Research No.	Study Code	Site Code
__/__/____	__	__	____	HWBR	TP

PRESCRIPTION OF OTHER MEDICATION (IN LAST WEEK) - EXCLUDE STUDY MEDICATIONS

Medication (Generic Name only)	Drug Code (Research Purposes)	Prescribed Dose	Time Since Taken Last Dose & Date	Dose Last Taken	Date Began / Ceased Treatment	Reason for Prescription	Prescribing Doctor
1.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
2.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
3.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
4.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		

CLIENT NAME _____ UR NUMBER |__|__|__|__|__|__|

MEDICATION HISTORY cont

PAST PRESCRIPTION OF OTHER MEDICATION (IN LAST WEEK) *Continued ....*

Medication (Generic Name only)	Drug Code (Research Purposes)	Prescribed Dose	Time Since Taken Last Dose & Date	Dose Last Taken	Date Began / Ceased Treatment	Reason for Prescription	Prescribing Doctor
5.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
6.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
7.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
8.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		
9.		Dose : _____ Frequency : _____ Route : _____	Time __:__ Date __/__/__	Dose : _____ Route : _____	Began __/__/__ Ceasesd __/__/__		

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

UTILISATION OF OTHER HEALTH SERVICES

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ].[ ][ ].[ ][ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

DATES OF REVIEW

FROM [ ][ ] day . [ ][ ] month . [ ][ ][ ][ ] year

TO [ ][ ] day . [ ][ ] month . [ ][ ][ ][ ] year

Service	Have you used this service since commencing this withdrawal program? (please tick ✓)	If YES, how many times have you used this service since commencing this withdrawal program?	Was your visit to this ser related to this withdraw episode? (please tick ✓)
Other Medical Practitioner (eg. GP) Please specify _____	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO
Other Health Professional (eg. dentist, counsellor) Please specify _____	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO
Hospital	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO
Natural Therapies (eg. herbal remedies, acupuncture, yoga) Please specify _____	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO
Masseuse	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO
Other Please specify _____	1 [ ] YES 2 [ ] NO		1 [ ] YES 2 [ ] NO

LEEDS DEPENDENCE QUESTIONNAIRE

Research Use Only

Research No. |_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_| Staff Initials |_|_|

In answering this questionnaire:

* think about the last week
* think specifically about your heroin use
* tick the answer most appropriate to you

B. LEEDS DEPENDENCE QUESTIONNAIRE (✓Appropriate Box)

No.	Question	0= Never	1= Some-times	2= Often	3= Near Alwa
1	Do you find yourself thinking about when you will next be able to take Heroin?				
2	Is taking heroin more important than anything else you might do during the day?				
3	Do you feel that your need for heroin is too strong to control?				
4	Do you plan your day around taking heroin?				
5	Do you take heroin in a particular way in order to increase the effect it gives you?				
6	Do you take heroin morning, afternoon & evening?				
7	Do you feel that you have to carry on taking heroin once you have started?				
8	Is getting the effect you want more important than the heroin you use?				
9	Do you want to take more heroin when the effect starts to wear off?				
10	Do you find it difficult to cope with life without heroin?				
(Office use only)	SCORE FOR EACH COLUMN				
	TOTAL SCORE				

BASIS - 32

Research Use Only

Research No. [ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ].[ ][ ].[ ][ ][ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

A. BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32) INSTRUCTIONS

Below is a list of problems and areas of life functioning in which some people experience difficulties. Using the scale below, WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY YO HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0	no difficulty
1	a little difficulty
2	moderate difficulty
3	quite a bit of difficulty
4	extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, indicat that there is NO DIFFICULTY (IE. '0')

Example

To what extent are you experiencing difficulty in the area of FRIENDSHIPS [2]

B. THE BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32)

TO WHAT EXTENT ARE YOU EXPERIENCING DIFFICULTY IN THE AREA OF :

1. MANAGING DAY-TO-DAY LIFE (Eg. getting to places on time, handling money, making everyday decisions) [ ]
2. HOUSEHOLD RESPONSIBILITIES (Eg. shopping, cooking, keeping room clean, other chores) [ ]
3. WORK (Eg. completing tasks, performance level, finding/ keeping a job) [ ]
4. SCHOOL (Eg. academic performance, completing assignments, attendance) [ ]
5. LEISURE TIME OR RECREATIONAL ACTIVITIES [ ]
6. ADJUSTING TO MAJOR LIFE STRESSES (Eg. separation, divorce, moving. new job / school, a death) [ ]
7. RELATIONSHIPS WITH FAMILY MEMBERS [ ]
8. GETTING ALONG WITH PEOPLE OUTSIDE OF THE FAMILY [ ]
9. ISOLATION OR FEELINGS OF LONELINESS [ ]
10. BEING ABLE TO FEEL CLOSE TO OTHERS [ ]
11. BEING REALISTIC ABOUT YOURSELF OR OTHERS [ ]
12. RECOGNISING AND EXPRESSING EMOTIONS APPROPRIATELY [ ]

... continued next page ...

BASIS - 32

WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY YOU HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0 no difficulty
1 a little difficulty
2 moderate difficulty
3 quite a bit of difficulty
4 extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, indi that there is NO DIFFICULTY (IE. '0')

A. BASIS - 32 CONTINUED ...

13. DEVELOPING INDEPENDENCE, AUTONOMY	[ ]
14. GOALS OR DIRECTIONS IN LIFE	[ ]
15. LACK OF SELF-CONFIDENCE, FEELING BAD ABOUT YOURSELF	[ ]
16. APATHY, LACK OF INTEREST IN THINGS	[ ]
17. DEPRESSION, HOPELESSNESS	[ ]
18. SUICIDAL FEELINGS OR BEHAVIOUR	[ ]
19. PHYSICAL SYMPTOMS (Eg. headaches, aches & pains, sleep disturbances, stomach aches, dizziness)	[ ]
20. CONFUSION, CONCENTRATION & MEMORY	[ ]
21. FEAR, ANXIETY OR PANIC	[ ]
22. DISTURBING OR UNREAL THOUGHTS OR BELIEFS	[ ]
23. HEARING VOICES, SEEING THINGS	[ ]
24. MANIC, BIZARRE BEHAVIOUR	[ ]
25. MOOD SWINGS, UNSTABLE MOODS	[ ]
26. UNCONTROLLABLE, COMPULSIVE BEHAVIOUR (Eg. eating disorder, hand washing, hurting yourself) Please specify _____	[ ]
27. SEXUAL ACTIVITY OR PREOCCUPATION	[ ]
28. DRINKING ALCOHOLIC BEVERAGES	[ ]
29. TAKING ILLEGAL DRUGS, MISUSING DRUGS	[ ]
30. CONTROLLING TEMPER (Eg. outbursts of anger or violence)	[ ]
31. IMPULSIVE, ILLEGAL OR RECKLESS BEHAVIOUR	[ ]
32. FEELING SATISFACTION WITH YOUR LIFE	[ ]

Office use only

TOTAL SCORE |__|__|__|

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

CLIENT RATINGS OF WITHDRAWAL

Research Use Only

Research No. [ ][ ][ ][ ]	Date [ ][ ].[ ][ ].[ ][ ][ ][ ]
Study Code [H][W][B][R] Site Code [T][P]	Client Initials [ ][ ] Staff Initials [ ][ ]

A. WHAT TREATMENT MEDICATION DID THE CLIENT RECEIVE? (please tick ✓)

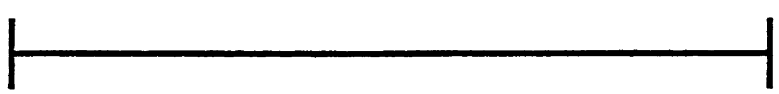
BUPRENORPHINE [ ] CLONIDINE [ ]

B. SEVERITY OF WITHDRAWAL EXPERIENCED DURING THIS EPISODE.

"How severe would you rate your discomfort you experienced during this withdraw episode?"

Please indicate on the following line by marking a slash through the line where you feel best represents the discomfort you experienced during this heroin withdrawal.

0 = no discomfort was experienced and
100 = the most severe discomfort you have ever experienced.



0 — 100

No Discomfort Experienced — Most Severe Discomfort Experienced

Research Purposes Only

Total mm [ ][ ][ ]

C. SATISFACTION WITH WITHDRAWAL PHARMACOTHERAPY

"Overall, how satisfied were you with your withdrawal medication? "

Please indicate on the following line by marking a slash through the line where you feel b
representstour staisfaction with the withdrawal medication you received.

0 = very unsatisfied
100 = very satisfied.

0 **100**

Very Unsatisfied

Very Satisfied

Research Purposes Only

Total mm |___|___|___|

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

ATTAINMENT OF CLIENT GOALS - day 8

Research Use Only

Research No. [ ][ ][ ][ ] Date [ ][ ].[ ][ ].[ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P] Client Initials [ ][ ] Staff Initials [ ][ ]

A. ATTAINMENT OF GOALS FOR THIS WITHDRAWAL EPISODE.

"To what extent have you achieved your goals for this withdrawal episode?"

Please indicate on the following line by marking a slash through the line where you feel best represents the attainment of your goals for this heroin withdrawal episode.

0 = no goals were attained
100 = all goals were attained.

0 — No goals were attained

100 — All goals were attained

Total mm [ ][ ][ ]

B. What treatment option do they intend to pursue following the withdrawal? (please tick ✓)

(a)	Methadone treatment	1[ ] Yes	0[ ] No
(b)	Naltrexone treatment	1[ ] Yes	0[ ] No
(c)	Buprenorphine treatment	1[ ] Yes	0[ ] No
(d)	Counselling	1[ ] Yes	0[ ] No
(e)	Self-help group (eg, NA)	1[ ] Yes	0[ ] No
(f)	Unsure	1[ ] Yes	0[ ] No
(g)	No ongoing treatment	1[ ] Yes	0[ ] No
(h)	Other	1[ ] Yes	0[ ] No

(please specify_____)

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

CLIENT SATISFACTION WITH MEDICATION

Research Use Only

Research No. |_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_|_| Staff Initials |_|_|_|

A. WHAT TREATMENT MEDICATION DID THE CLIENT RECEIVE? (please tick ✓)

BUPRENORPHINE [ ] CLONIDINE [ ]

B. RANKING OF AVAILABLE HEROIN WITHDRAWAL OPTIONS.

According to patient experience, rank the following heroin withdrawal options from best (1) to worst (8) using the card sorting technique. With the cards (each card containing the different treatment options listed below) ask the client to place in order, their experience of each treatment from best to worst. Transcribe this order into the boxes below. If the client has never attempted such withdrawal or does not know the answer mark with a '0'.

	Client Rank
• Combination Symptomatic - excluding Doloxene® / Panadeine forte® (eg. Brufen®, Maxalon®, Valium® etc)	☐
• Panadeine forte® or Doloxene®	☐
• Short Term Methadone (less than 2 weeks)	☐
• Benzodiazepines (only)	☐
• Other medications (Please specify _____)	☐
• Buprenorphine	☐
• Clonidine (Catapress®) - only	☐
• Rapid opiate withdrawal using naltrexone	☐

C. From your experience, what were the good things about using _____ for heroin withdrawal?

D. From your experience, what were the bad things about using _____ for heroin withdrawal?

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

CLIENT SATISFACTION WITH MEDICATION

Research Use Only

Research No. [ ][ ][ ][ ]	Date [ ][ ].[ ][ ].[ ][ ][ ]
Study Code [H][B][W][R] Site Code [T][P]	Client Initials [ ][ ] Staff Initials [ ][ ]

E. If it was available, would you choose _____ again for attempting Heroin withdrawal in the future?

No[ ]0 Yes[ ]1 Maybe[ ]2
(please ✓ appropriate section)

List 3 main reasons for this view

_____

_____

_____

_____

_____

_____

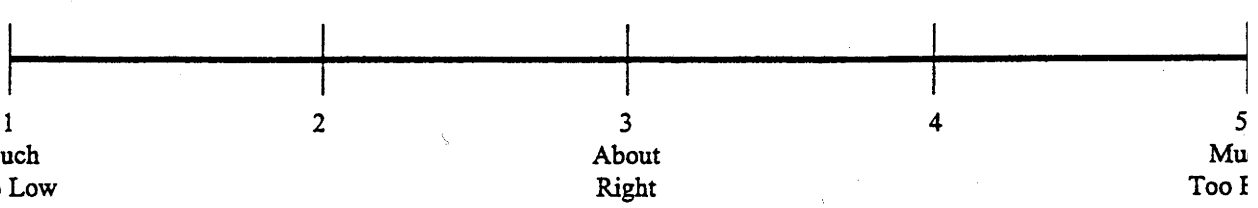
_____

F. ADEQUACY OF DOSES OF WITHDRAWAL MEDICATION.

"Overall, how adequate do you think your doses of the withdrawal medication were?

Please indicate on the following scale by circling the appropriate indicator.

1 = much too low,
3 = about right,
5 = much too high



Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Research Assessment
Day 35 Data Collection

- Opiate Treatment Index
- Leeds Dependence Questionnaire
- BASIS - 32
- Health Status Profile (SF-36)
- Attainment of Client Goals - day 35
- Previous Drug Treatments - day 35
- AQOL

1999

OPIATE TREATMENT INDEX

Research Use Only

Research No. _ _ _ _ _	Date _ _ . _ _ . _ _
Study Code H W B R Site Code T P	Client Initials _ _ Staff Initials _ _

SECTION II

NB: *For all categories, if the subject responds that their last use of the drug was more than a month ago, score zero for that category. Do not include use on the day of interview.*

Day this form was completed (circle)

MON TUE WED THUR FRI SAT SUN

HEROIN

Now I'm going to ask you some questions about heroin (smack, hammer, horse, scag).

1. On what day did you last use heroin? __________
2. How many hits/smokes/snorts did you have on that day? __________
3. On which day before that did you use heroin? __________
4. And how many hits/smokes/snorts did you have on that day? __________
5. And when was the day before that? __________

5a. What was the average cost of a **typical day's use** (or estimated cost if not purchased) $ __________

5b. On how many days in the past **four weeks** have you used any heroin? ________days

q1 = , q2 = , t1 = , t2 = Q ☐

POLY-DRUG USE

Other Opiates

These questions are about your use of opiates other than heroin (eg. street methadone/done, morphine, pethidin codeine).

6. On what day did you last use opiates other than heroin? (do not include legally obtained methadone) __________
7. How many pills, doses etc. did you have on that day? __________
8. On which day before that did you use opiates other than heroin? __________
9. And how many pills, doses etc. did you have on that day? __________
10. And when was the day before that? __________

10a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

NOTE: Include only cost of other opiods obtained illicitly - not on prescription.

q1 = , q2 = , t1 = , t2 = Q

Alcohol

These questions are about your use of alcohol.

11. On what day did you last drink alcohol? _____

12. How much alcohol did you drink on that day? _____

	Wine	Spirits	Beer	Fortified Wine
	Wine Gl. (120 ml)	Nips (30 ml)	Glasses (200 ml)	Port Gl. (60 ml)
	Bottles (750 ml)	Doubles (60 ml)	Pots (285 ml)	Bottles (750 ml)
	Flagons (1.5 lt)	Bottles (750 ml)	Cans/Stubbies (375 ml)	Flagons (1.5 lt)
	Casks (___lit.)			
No. Standard Drinks				

Total Standard Drinks _____

13. On which day before that did you drink alcohol? _____

14. And how much did you drink on that day? _____

	Wine	Spirits	Beer	Fortified Wine
	Wine Gl. (120 ml)	Nips (30 ml)	Glasses (200 ml)	Port Gl. (60 ml)
	Bottles (750 ml)	Doubles (60 ml)	Pots (285 ml)	Bottles (750 ml)
	Flagons (1.5 lt)	Bottles (750 ml)	Cans/Stubbies (375 ml)	Flagons (1.5 lt)
	Casks (___lit.)			
No. Standard Drinks				

Total Standard Drinks _____

15. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q

OPIATE TREATMENT INDEX

Cannabis

These questions ask you about your use of marijuana (dope, grass. hash. pot).

16. On what day did you last use marijuana? _____

17. How many joints, bongs, etc. did you have on that day? _____

18. On which day before that did you use marijuana? _____

19. And how many joints, bongs etc. did you have on that day? _____

20. And when was the day before that? _____

20a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Amphetamines

These questions ask you about your use of amphetamines (speed).

21. On what day did you last use amphetamines? _____

22. How many tablets/snorts/hits did you have on that day? _____

23. On which day before that did you use amphetamines? _____

24. And how many tablets/snorts/hits did you have on that day? _____

25. And when was the day before that? _____

25a. What was the average cost of **a typical day's use** (or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Cocaine

These questions ask you about your use of cocaine (coke, snow, crack)

26. On what day did you last use cocaine? _____

27. How many snorts/hits/smokes etc. did you have on that day? _____

28. On which day before that did you use cocaine? _____

29. And how many snorts/hits/smokes etc. did you have on that day? _____

30. And when was the day before that? _____

30a. What was the average cost of **a typical day's use**
(or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Tranquillisers (Benzodiazepines)

These questions ask you about your use of tranquillisers (eg. Serepax, Valium, Rohypnol, Mogadon)

31. On what day did you last use tranquillisers? _____

32. How many pills did you have on that day? _____

33. On which day before that did you use tranquillisers? _____

34. And how many pills did you have on that day? _____

35. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q

Hallucinogens

These questions ask you about your use of hallucinogens (eg. LSD/acid, ecstasy, magic mushrooms)

36. On what day did you last use hallucinogens? _____

37. How many tabs/pills etc. did you have on that day? _____

38. On which day before that did you use hallucinogens? _____

39. And how many tabs/pills etc. did you have on that day? _____

40. And when was the day before that? _____

40a. What was the average cost of **a typical day's use**
(or estimated cost if not purchased) $ _____

q1 = , q2 = , t1 = , t2 = Q

Inhalants

These questions ask you about your use of inhalants (eg. amyl nitrate/rush, glue, laughing gas, aerosols petrol)

41. On what day did you last use inhalants? _____

42. How many sniffs did you have on that day? _____

43. On which day before that did you use inhalants? _____

44. And how many sniffs did you have on that day? _____

45. And when was the day before that? _____

q1 = , q2 = , t1 = , t2 = Q [ ]

Tobacco

46. **Finally, if you smoke cigarettes, how many do you usually smoke each day?** _____

DRUG USE SUMMARY

Heroin Use Total [ ] Poly-drug use total [ ]

POLY- DRUG USE

Heroin	[ ]	Cocaine	[ ]
Other Opiates	[ ]	Tranquillisers	[ ]
Alcohol	[ ]	Hallucinogens	[ ]
Cannabis	[ ]	Inhalants	[ ]
Amphetamines	[ ]	Tobacco	[ ]

General Comments on Drug Use

LEEDS DEPENDENCE QUESTIONNAIRE

Research Use Only

Research No. [| | | | |]

Study Code [H | W | B | R] Site Code [T | P]

Date [| |] . [| |] . [| | | |]

Client Initials [| |] Staff Initials [| |]

In answering this questionnaire:

* think about the last week
* think specifically about your heroin use
* tick the answer most appropriate to you

B. LEEDS DEPENDENCE QUESTIONNAIRE

(✓Appropriate Box)

No.	Question	0= Never	1= Some-times	2= Often	3= Nea Alw
1	Do you find yourself thinking about when you will next be able to take Heroin?				
2	Is taking heroin more important than anything else you might do during the day?				
3	Do you feel that your need for heroin is too strong to control?				
4	Do you plan your day around taking heroin?				
5	Do you take heroin in a particular way in order to increase the effect it gives you?				
6	Do you take heroin morning, afternoon & evening?				
7	Do you feel that you have to carry on taking heroin once you have started?				
8	Is getting the effect you want more important than the heroin you use?				
9	Do you want to take more heroin when the effect starts to wear off?				
10	Do you find it difficult to cope with life without heroin?				
(Office use only)	SCORE FOR EACH COLUMN				
	TOTAL SCORE				

BASIS - 32

Research Use Only

Research No. [| | | |]
Study Code [H|W|B|R] Site Code [T|P]

Date [| |]. [| |]. [| | | |]
Client Initials [| |] Staff Initials [| |]

A. BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32) INSTRUCTIONS

Below is a list of problems and areas of life functioning in which some people experience difficulties. Using the scale below, WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY YO HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0	no difficulty
1	a little difficulty
2	moderate difficulty
3	quite a bit of difficulty
4	extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, indicate that there is NO DIFFICULTY (IE. '0')

Example

To what extent are you experiencing difficulty in the area of FRIENDSHIPS [2]

B. THE BEHAVIOUR & SYMPTOM IDENTIFICATION SCALE (BASIS - 32)

TO WHAT EXTENT ARE YOU EXPERIENCING DIFFICULTY IN THE AREA OF :

1. MANAGING DAY-TO-DAY LIFE (Eg. getting to places on time, handling money, making everyday decisions) [ ]
2. HOUSEHOLD RESPONSIBILITIES (Eg. shopping, cooking, keeping room clean, other chores) [ ]
3. WORK (Eg. completing tasks, performance level, finding/ keeping a job) [ ]
4. SCHOOL (Eg. academic performance, completing assignments, attendance) [ ]
5. LEISURE TIME OR RECREATIONAL ACTIVITIES [ ]
6. ADJUSTING TO MAJOR LIFE STRESSES (Eg. separation, divorce, moving. new job / school, a death) [ ]
7. RELATIONSHIPS WITH FAMILY MEMBERS [ ]
8. GETTING ALONG WITH PEOPLE OUTSIDE OF THE FAMILY [ ]
9. ISOLATION OR FEELINGS OF LONELINESS [ ]
10. BEING ABLE TO FEEL CLOSE TO OTHERS [ ]
11. BEING REALISTIC ABOUT YOURSELF OR OTHERS [ ]
12. RECOGNISING AND EXPRESSING EMOTIONS APPROPRIATELY [ ]

... continued next page ...

BASIS - 32

WRITE IN THE BOX THE NUMBER THAT BEST DESCRIBES THE DEGREE OF DIFFICULTY YOU HAVE BEEN EXPERIENCING IN EACH AREA IN THE PAST WEEK.

0	no difficulty
1	a little difficulty
2	moderate difficulty
3	quite a bit of difficulty
4	extreme difficulty

Please respond to each item. Do not leave any blank. If there is an area you consider to be inapplicable, ind that there is NO DIFFICULTY (IE. '0')

A. BASIS - 32 CONTINUED ...

13. DEVELOPING INDEPENDENCE, AUTONOMY	[ ]
14. GOALS OR DIRECTIONS IN LIFE	[ ]
15. LACK OF SELF-CONFIDENCE, FEELING BAD ABOUT YOURSELF	[ ]
16. APATHY, LACK OF INTEREST IN THINGS	[ ]
17. DEPRESSION, HOPELESSNESS	[ ]
18. SUICIDAL FEELINGS OR BEHAVIOUR	[ ]
19. PHYSICAL SYMPTOMS (Eg. headaches, aches & pains, sleep disturbances, stomach aches, dizziness)	[ ]
20. CONFUSION, CONCENTRATION & MEMORY	[ ]
21. FEAR, ANXIETY OR PANIC	[ ]
22. DISTURBING OR UNREAL THOUGHTS OR BELIEFS	[ ]
23. HEARING VOICES, SEEING THINGS	[ ]
24. MANIC, BIZARRE BEHAVIOUR	[ ]
25. MOOD SWINGS, UNSTABLE MOODS	[ ]
26. UNCONTROLLABLE, COMPULSIVE BEHAVIOUR (Eg. eating disorder, hand washing, hurting yourself) Please specify _____	[ ]
27. SEXUAL ACTIVITY OR PREOCCUPATION	[ ]
28. DRINKING ALCOHOLIC BEVERAGES	[ ]
29. TAKING ILLEGAL DRUGS, MISUSING DRUGS	[ ]
30. CONTROLLING TEMPER (Eg. outbursts of anger or violence)	[ ]
31. IMPULSIVE, ILLEGAL OR RECKLESS BEHAVIOUR	[ ]
32. FEELING SATISFACTION WITH YOUR LIFE	[ ]

Office use only

TOTAL SCORE |_|_|_|

HEALTH STATUS PROFILE (SF - 36)

Research Use Only

Research No. [ ] [ ] [ ] [ ] Date [ ] [ ] [ ] [ ] - [ ] [ ] [ ] [ ]

Study Code [H][W][B][R] Site Code [T][P] Client Initials [ ] [ ] Staff Initials [ ] [ ]

Instructions: *This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.*

Answer every question by selecting the appropriate answer. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better than 1 year ago 1
Somewhat better now than 1 year ago 2
About the same as 1 year ago 3
Somewhat worse now than 1 year ago 4
Much worse now than 1 year ago 5

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

circle one number in each row

		Yes Limited Alot	Yes Limited a little	No, not Limited at
a.	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c.	Lifting or carrying groceries	1	2	3
d.	Climbing **several** flights of stairs	1	2	3
e.	Climbing **one** flight of stairs	1	2	3
f.	Bending, kneeling, or stooping	1	2	3
g.	Walking **more than a kilometre**	1	2	3

HEALTH STATUS PROFILE (SF - 36)

continued from page 1

h.	Walking **several blocks**	1	2	3
i.	Walking **one block**	1	2	3
j.	Bathing or dressing yourself	1	2	3

4. During the **past four weeks**, have you had any of the following problems with your work or other regular dai activities **as a result of your physical health?**

		YES	NO
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Were limited in the **kind** of work or other activities	1	2
d.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past four weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

		YES	NO
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past four weeks, to what extent has your physical health or emotional problems interfered with you normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

HEALTH STATUS PROFILE (SF - 36)

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Non of th time
a.	Did you feel full of pep? (energy)	1	2	3	4	5	6
b.	Have you been a very nervous person?	1	2	3	4	5	6
c.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d.	Have you felt calm and peaceful?	1	2	3	4	5	6
e.	Did you have a lot of energy?	1	2	3	4	5	6
f.	Have you felt downhearted and blue?	1	2	3	4	5	6
g.	Did you feel worn out?	1	2	3	4	5	6
h.	Have you been a happy person?	1	2	3	4	5	6
i.	Did you feel tired?	1	2	3	4	5	6

HEALTH STATUS PROFILE (SF - 36)

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

11. How TRUE or FALSE is each of the following statements for you?

		Definitely True	Mostly True	Don't Know	Mostly False	Definit Fals
a.	I seem to get sick a little easier than other people	1	2	3	4	5
b.	I am as healthy as anybody I know	1	2	3	4	5
c.	I expect my health to get worse	1	2	3	4	5
d.	My health is excellent	1	2	3	4	5

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

ATTAINMENT OF CLIENT GOALS - day 35

Research Use Only

Research No. |_|_|_|_|

Study Code |H|W|B|R| Site Code |T|P|

Date |_|_|.|_|_|.|_|_|_|_|

Client Initials |_|_| Staff Initials |_|_|

A. ATTAINMENT OF GOALS FOR THIS WITHDRAWAL EPISODE.

"To what extent have you achieved your goals for this withdrawal episode?"

Please indicate on the following line by marking a slash through the line where you feel best represents the attainment of your goals for this heroin withdrawal episode.

0 = no goals were attained
100 = all goals were attained.

0 — No goals were attained

100 — All goals were attained

Research use only

Total mm |_|_|_|

OUTPATIENT HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

PREVIOUS DRUG TREATMENTS - DAY 35

Research Use Only

Research No. [ ][ ][ ][ ]

Study Code [H][W][B][R] Site Code [T][P]

Date [ ][ ].[ ][ ].[ ][ ]

Client Initials [ ][ ] Staff Initials [ ][ ]

INSTRUCTIONS - Ask the client to self-report the number of times since they enrolled in this study, they have participated in the following forms of treatment.

A. Previous Drug Treatment

TREATMENT OPTIONS :	Have you received this treatment?	Was the treatment at T/P or another service?	Are you currently in treatment
1. **Outpatient withdrawal with or without medication** (including attempts with GP, A&D Agency, Home Based Withdrawal etc.)	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
2. **Inpatient withdrawal** with or without medication	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
3. **Rapid Opiate withdrawal using Naltrexone**	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
4. **Cold Turkey** (unassisted withdrawal) with or without medication	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
5. **Methadone Maintenance**	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
6. **Naltrexone Maintenance treatment**	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
7. **Maintenance Treatment with other substitution pharmacotherapy** (eg. Buprenorphine, LAAM)	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
8. **Outpatient counselling** not as part of other listed treatment	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
9. **Residential Rehabilitation** (eg. Therapeutic Community)	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No
10. **Other** (Please specify _____)	1 [ ] Yes 2 [ ] No	1 [ ] Yes 2 [ ] No	1 [ ] Ye 2 [ ] No

Outpatient Heroin Withdrawal Using Buprenorphine

Randomised Control Trial

Termination From Study
(Day 1 - 35)

- Summary of Adverse Events
- Termination From the Study

1999

SUMMARY OF ADVERSE EVENTS
(BASED ON VA / NIDA FORM)

Research Use Only

Research No. |__|__|__|__|__| Date |__|__|.|__|__|.|__|__|__|__|

Study Code |__|__|__|__|__| Site Code |__|__| Client Initials |__|__|__| Staff Initials |__|__|__|

A. PERIOD OF REVIEW :

From Date |__|__|.|__|__|.|__|__|__|__| To Date |__|__|.|__|__|.|__|__|__|__|

B. WHAT TREATMENT MEDICATION DID THE CLIENT RECEIVE? (please tick ✓)

BUPRENORPHINE [ ]

CLONIDINE [ ]

C. ADVERSE EVENTS

Date of Onset	Nature of Illness, Event or Abnormal Lab Value	I. Type of Report	II. Relatedness	III. Level of severity	IV. Action Taken	V. Outcome	Date Resolv
	1.						
	2.						
	3.						
	4.						
	5.						
	6.						
	7.						
	8.						

I. Type of report	II. Relatedness	II. Severity	IV. Action Taken	V. Outcome
1 = Anticipated adverse event *2 = Unanticipated adverse event* *3 = Concomitant illness* *4 = Development of clinically significant abnormal lab value* *5 = Serious adverse event*	*1 = Definitely study drug related* *2 = Probably study drug related* *3 = Possibly study drug related* *4 = Unrelated to study drug*	*1 = Mild* *2 = Moderate* *3 = Severe***	*1 = None required* *2 = Prescription drug therapy* *3 = In-patient hospitalisation* *4 = Prescription drug therapy & hospitalisation* *6 = Medical specialty consultation required* *7 = Randomisation code broken* *8 = Other (please specify)*	*1 = Resolved* *2 = Unresolved* *3 = Resulted in chronic condition or severe / permanent disability*** *4 = Deceased*** *5 = Unknown*

*** Complete Serious Adverse Events Form (F10SAdv.Doc)*

Continued Next Page ....

SUMMARY OF ADVERSE EVENTS
(BASED ON VA / NIDA FORM)

C. Is a Serious Adverse Events form required? 1[ ] Yes 0[ ] No

Adverse Event Number (from table overleaf)	Date Serious Adverse Event form completed.
	__/__/____
	__/__/____
	__/__/____
	__/__/____

INFORM PRINCIPLE INVESTIGATOR WITHIN 12 HOURS OF SERIOUS ADVERSE EVENT

D. Comments : _____

_____

_____

_____

_____

* ***PLEASE FORWARD THIS FORM TO THE PRINCIPLE INVESTIGATOR AT TURNING POINT A.S.A.P.***

Principle Investigator's Signature and Date

_____ __/__/____

Principle Investigator's Comments : _____

_____

_____

_____

_____

_____

HEROIN WITHDRAWAL USING BUPRENORPHINE (RCT)

TERMINATION FROM THE STUDY

Research Use Only

Research No. |_|_|_|_|_| Date |_|_|.|_|_|.|_|_|_|_|

Study Code |_|_|_|_|_| Site Code |_|_| Client Initials |_|_| Staff Initials |_|_|

A. DURATION OF TREATMENT EPISODE

Date enrolled in the study (day 1) |_|_| / |_|_| / |_|_|_|_| (day / month / year)

Date Terminated from study |_|_| / |_|_| / |_|_|_|_| (day / month / year)

Total No. of days in study |_|_|

Did the client complete withdrawal treatment (8 days)? 1 [ ] yes 2 [ ] no

Did the client enter post-withdrawal treatment? 1 [ ] yes 2 [ ] no

Did the client complete post-withdrawal treatment (35 days)? 1 [ ] yes 2 [ ] no

B. REASONS FOR TERMINATION OF TREATMENT

	Please tick appropriate box			
1. COMPLETED TREATMENT (35 DAYS)	1[ ]	Yes	0[ ]	No
2. VOLUNTARY DISCHARGE	1[ ]	Yes	0[ ]	No
(a) client choosing to resume heroin use	1[ ]	Yes	0[ ]	No
(b) side effects to medication	1[ ]	Yes	0[ ]	No
(c) medication not holding (severe withdrawal discomfort experienced)	1[ ]	Yes	0[ ]	No
(d) inconvenience of attendance requirements	1[ ]	Yes	0[ ]	No
(e) entered other treatment (please specify .....)	1[ ]	Yes	0[ ]	No
(f) other	1[ ]	Yes	0[ ]	No
3. MEDICAL DISCHARGE	1[ ]	Yes	0[ ]	No
(a) due to adverse / severe / intolerable side effects	1[ ]	Yes	0[ ]	No
(a) client non-responsive to medication	1[ ]	Yes	0[ ]	No
4. ADMINISTRATIVE DISCHARGE	1[ ]	Yes	0[ ]	No
(a) due to non-compliance with conditions of the Clinical Services	1[ ]	Yes	0[ ]	No
(b) non-attendance at clinic (where appropriate)	1[ ]	Yes	0[ ]	No
(d) missed > 2 consecutive days for dosing	1[ ]	Yes	0[ ]	No

DISCHARGE FROM THE STUDY

3. POST-WITHDRAWAL LINKAGES / REFERRALS

Please indicate post treatment linkages / referrals. (Including provision of continuing care for clients at compl
of study - Naltrexone / Buprenorphine / Methadone clients)

4. OTHER RELEVANT ISSUES

Please describe any other issues relating to the use of the study medications with this client (include aspects
regarding safety, convenience, extent to which medication alleviated withdrawal discomfort, client satisfaction

Staff Name & signature _____

APPENDIX 2

APPENDIX 2

Cost of Clinical Services Associated the Randomised Controlled Trial of Outpatient Heroin Withdrawal

Trial related staffing costs

Position	**Hourly salary**	**Hourly salary + On-costs @ 16%**
Turning Point Alcohol & Drug Centre		
Clinical Nurse	$20.26	$23.50
Medical practitioner	$32.77	$38.01
Pharmacist	$22.69	$26.32
A&D worker	$20.62	$23.92
Allied Health	$19.97	$23.17
The Langton Centre		
Clinical Nurse	$21.00	$ 24.36
Medical practitioner	$45. 00	$ 52.20
Pharmacist	$26.70	$ 30.97

Medication Costs (trial and non-trial related)

	Cost per tablet / unit ($AUS)[1]
Trial medications	
Clonidine 100 mcgm	0.184
Clonidine 150 mcgm	0.2948
Diazepam 5 mg tabs	0.165
Temazepam 10 mg	0.12
Nitrazepam 5 mg	0.08
Metoclopramide 10 mg	0.0664
Ibuprofen 400 mg	0.0774
Quinine sulphate 300 mg	0.1064
Hyoscine butylromide (Buscopan®) 10 mg	0.174
Lomotil	0.083
Imodium	0.1375
Buprenorphine (Subutex®)[2] 2 mg	1.54
Buprenorphine (Subutex®) 8 mg	4.62
Non – trial medications	
Fluoxetine 20 mg tabs	0.964
Moclobomide 300 mg tabs	0.416
Venlafaxine 30 mg	0.628
Oxazepam 30 mg tabs	0.056
Modecate12.5mg (IM ampoule)	11.00
Benztropine (Cogentin®) 1mg (IM ampoule)	12.66
Sodium valproate (Epilim®) 500mg tablets	0.298
Codeine 30 mg tabs	0.134
Difflam® oral lozenges	0.284
Cipramil® 30 mg	0.964
Augmentin duoforte® (875 mg)	1.21
Daivonex® topical cream (psoriasis)	17.25 for 30g
Monofeme® oral contraceptive	0.333
Paracetamol 500 mg tabs	0.029

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[1] Prices refer to wholesale pharmacy prices. Subsidised prices are included for medications listed under the Pharmaceutical Benefits Scheme.

[2] Subutex® prices are based upon Australian wholesale pharmacy price (from Reckitt Benckiser)

Non-trial related health services[3]

Item	Cost / service	Rationale / reference
Outpatient hospital attendance (no admission)	$141.48	Victorian Ambulatoy Costs S3 Outpatient Mean (1998-1999)
General Practitioner	$25.85	Medical Benefits Scheme Item 23, Level B; (November 1999). Assume 100% of consultation charged to Medicare
Dentist	$106.38	Victorian Ambulatory Cost (Department of Human Services 1999-2000)
Naturopath / masseuse Clairvoyant	$ 45	Naturopath Practitioners Association
Individual counselling provided by psychologist / social worker	$85	National schedule of recommended fees (Australian Psychologist Association)

[3] Fee schedules provided by the Centre for Economic Health Evaluation, Monash University

APPENDIX 3

National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence

National Drug Strategy

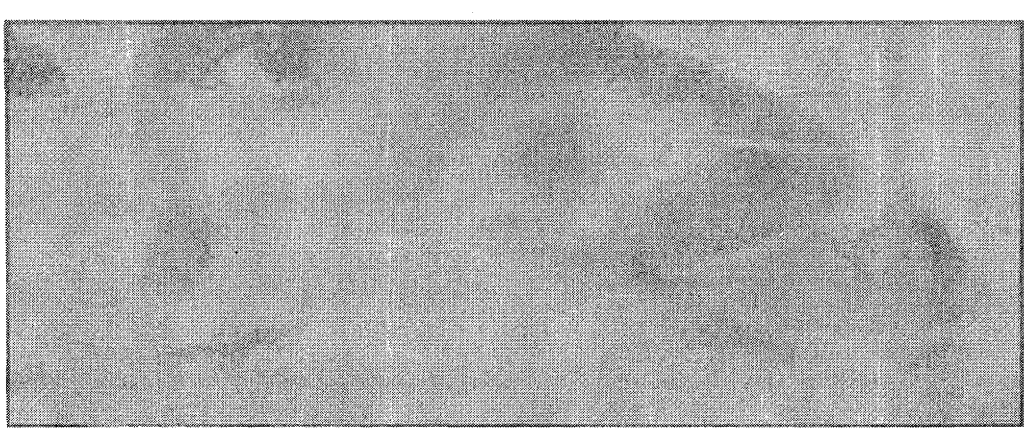
National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence

Authors

Lintzeris N, Clark N, Muhleisen P, Ritter A

Ali R, Bell J, Gowing L, Hawkin L, Henry Edwards S, Mattick RP, Monheit B, Newton I, Quigley A, Whicker S, White J

Medical Editor
Elizabeth Vorrath



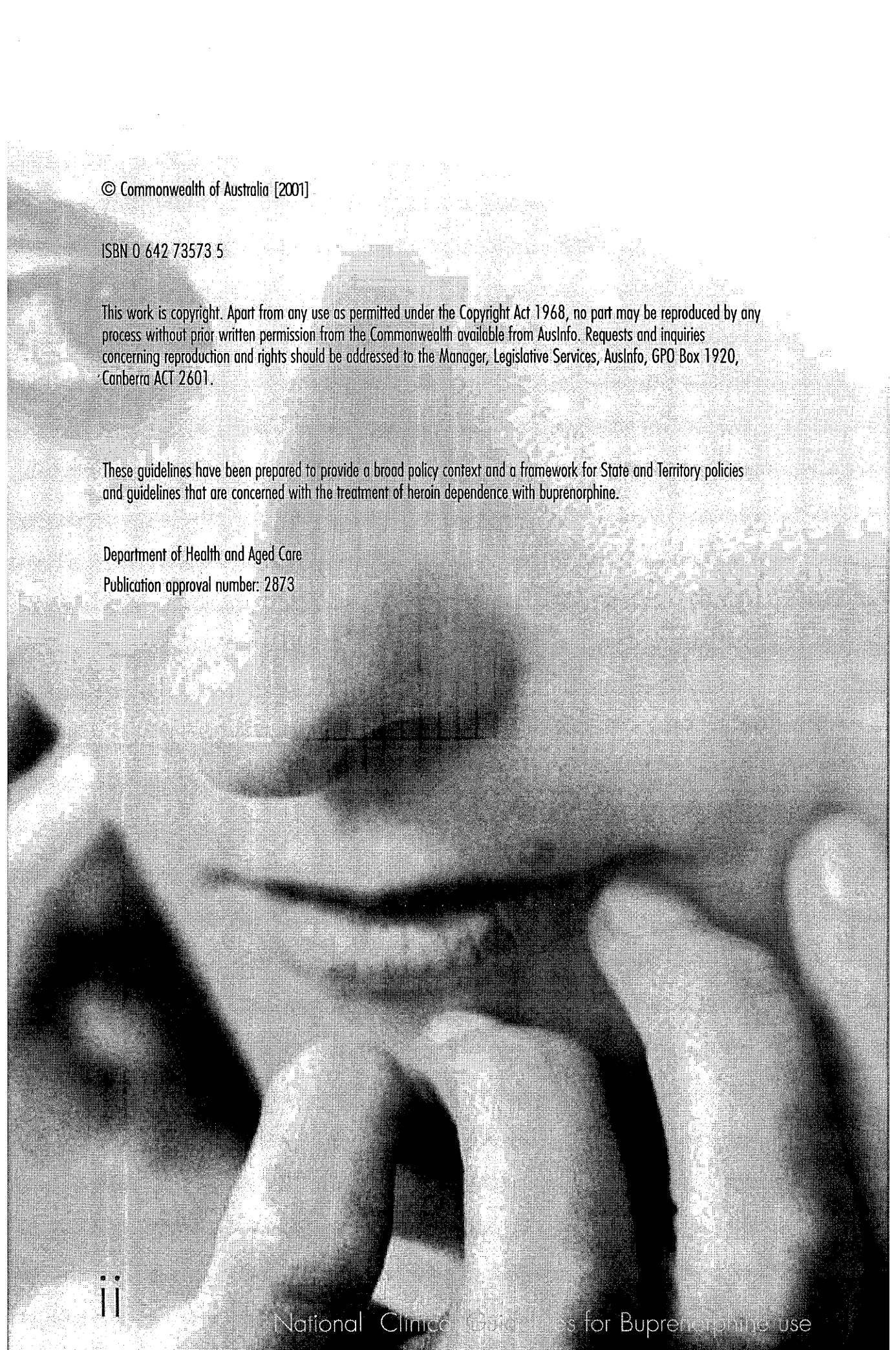
March 2001

ISBN 0 642 73573 5

These guidelines have been prepared to provide a broad policy context and a framework for State and Territory policies and guidelines that are concerned with the treatment of heroin dependence with buprenorphine.

Department of Health and Aged Care

Publication approval number: 2873



Introduction

Buprenorphine, in sublingual tablet form (Subutex®), has recently been registered in Australia for the management of opioid dependence including maintenance and detoxification, within a framework of medical, social and psychological treatment. This preparation is effective both in the long-term, as a maintenance treatment program, and in the short-term as part of a heroin withdrawal program. To assist in the safe and effective implementation of buprenorphine treatment in Australia, the following national guidelines have been commissioned by the Commonwealth Department of Health and Aged Care under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID).

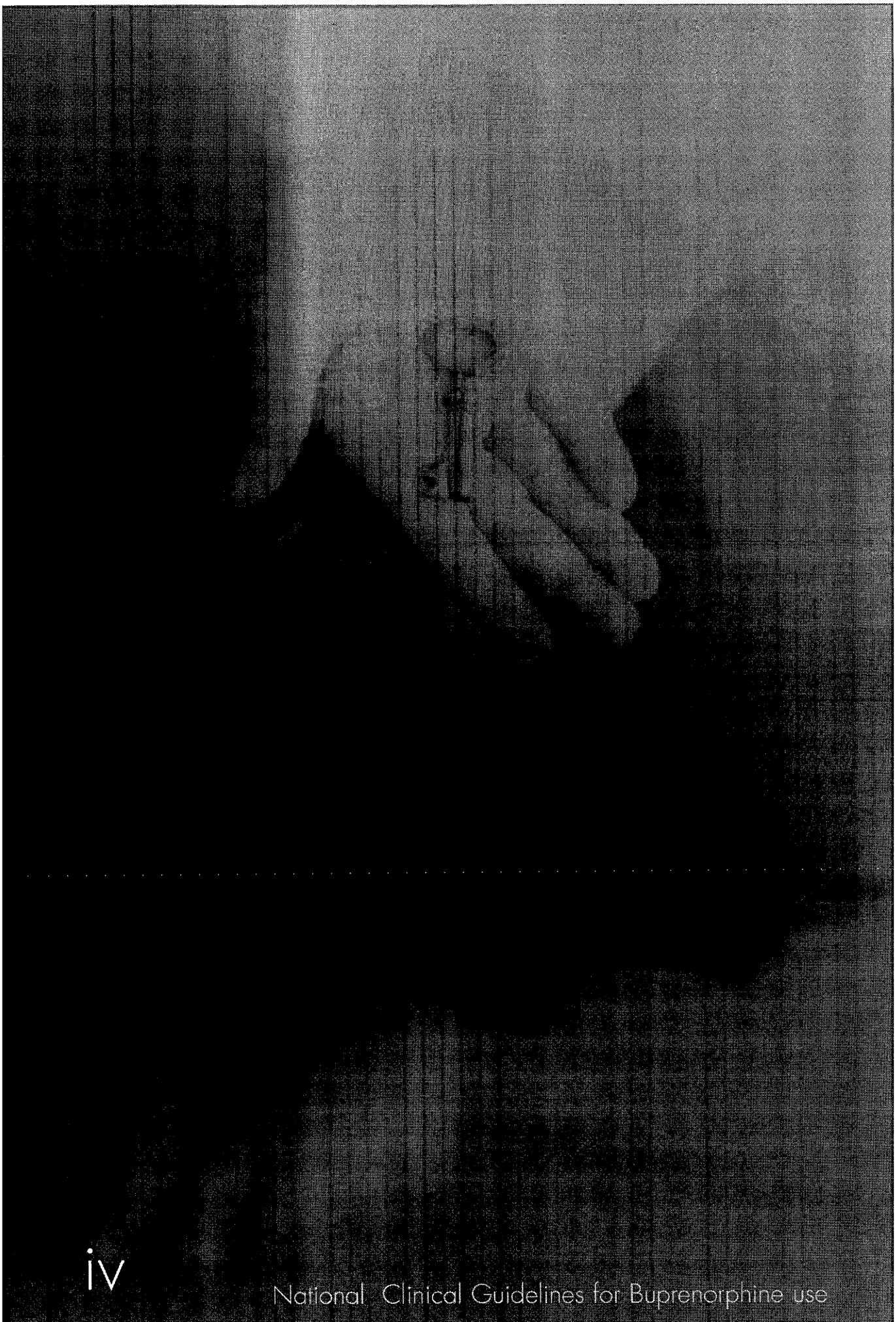
These guidelines cover both the maintenance and withdrawal programs using buprenorphine. Section 1 explains the clinical pharmacology of the preparation; Section 2 covers the commencement of buprenorphine treatment; Section 5, complications and adverse events; and Section 6 discusses prescribing and dispensing issues. In all of these sections, both maintenance and withdrawal programs are covered. In Sections 3 and 4, however, guidelines and procedures are set out separately for each program: for maintenance treatment in Section 3, and withdrawal programs in Section 4.

This set of guidelines has been developed through a consensus process by a working party of senior Australian clinicians and researchers who have experience in the use of buprenorphine in a variety of jurisdictions. The original draft of the maintenance guidelines for this project was developed as part of the Buprenorphine Implementation Trial by the Turning Point Alcohol and Drug Centre. The Clinical Guidelines for the Buprenorphine Implementation Trial were piloted by over 20 medical practitioners (both specialists and general practitioners) and 30 pharmacies involved in delivering buprenorphine maintenance treatment. In addition to the participants (patients, doctors, pharmacists and researchers) of the Buprenorphine Implementation Trial, the following individuals have contributed to the development of these clinical guidelines:

In the USA: Paul Fudala, Alice Huber, Ed Johnson, Surita Lao, Walter Ling, Laura McNicholas, Boris Meandzija, Charles O'Brien, Richard Rawson, Richard Schottenfeld, George Woody. **In France:** Marc Auricombe **In the UK:** Fergus Law, Judith Myles, David Nutt, Chris Chapleo, Don Walter. **And in Australia:** Louise Rushworth, Reckitt Benkizer; Gabriele Bammer, National Centre for Population Health and Epidemiology; Adrian Dunlop, Nadine Ezard, Alan Gisbjers, Sandra Hocking, Jozica Kutin, Paul Murray, and Greg Whelan.

The guidelines have been endorsed by the Royal Australian College of General Practitioners, the Royal Australian College of Physicians and the Australian Professional Society on Alcohol and other Drugs.

The contribution of Ms Elizabeth Vorrath, Medical Editor, in ensuring that the guidelines are clear and easy to read is gratefully acknowledged.



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SECTION 1. CLINICAL PHARMACOLOGY

General Information

What is Buprenorphine?

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a *partial opioid agonist* at the μ opioid receptors in the nervous system. It is also a κ (kappa) opioid receptor antagonist. It has low intrinsic agonist activity, only partially activating μ opioid receptors, thus producing a milder, less euphoric and less sedating effect than full opioid agonists such as heroin, morphine and methadone. Nevertheless, its activity is usually sufficient to diminish cravings for heroin, and prevent or alleviate opioid withdrawal in dependent heroin users. Buprenorphine also has a high affinity for μ opioid receptors, binding more tightly to these receptors than full opioid agonists. It therefore reduces the impact of additional heroin (or other opioid) use, by preventing heroin from occupying these receptors. By its dual effects of producing opioid responses while blocking the effects of additional heroin use, buprenorphine reduces the self-administration of heroin.

What form does it come in?

The buprenorphine product registered in Australia for treating opioid dependence is Subutex®, a sublingual tablet preparation of buprenorphine hydrochloride in 0.4, 2, and 8 mg strengths. Buprenorphine is also registered in Australia for the management of short term (not more than one week) relief of moderate to severe pain, including post–operative and terminal and chronic pain as Temgesic® sublingual tablets and ampoules for intramuscular or subcutaneous injection. Sublingual buprenorphine tablets have approximately 30-35% of the bioavailability of intravenous buprenorphine preparations[1]. Buprenorphine undergoes extensive first pass metabolism when taken orally.

How is it metabolised?

Peak plasma concentrations are achieved 1 - 2 hours after sublingual administration. Buprenorphine has a distribution half-life of 2 - 5 hours. It is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-de-alkylation. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and urine.

Buprenorphine has an elimination half-life of 24 - 37 hours. It is long-acting, relative to the dose administered. Peak clinical effects occur 1 - 4 hours after sublingual administration, with continued effects for up to 12 hours at low doses (2 mg), but as long as 48 - 72 hours at higher doses (16 or 32 mg). The extended duration of action of buprenorphine is thought to relate to three factors:

- its very high affinity for opioid μ receptors (once bound to these receptors it is dislodged only slowly);
- its high lipophilicity (low levels of buprenorphine are released slowly from fat stores, particularly with chronic dosing).
- Reabsorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite.

The prolonged duration of effect at high doses enables alternate-day, and even 3-days-a-week dispensing regimes.

[1] The majority of early studies using sublingual buprenorphine used a liquid solution of buprenorphine in 30% aqueous ethanol, with a bioavailability of approximately 40% of subcutaneous preparations. The commercial sublingual tablet preparation of buprenorphine (Subutex®) is reported as having 50 - 80% of the bioavailability of the ethanol solution (Shuh and Johansen 1999; Ajir et al 2000). In practice, sublingual tablet doses should be approximately 50% greater than sublingual solution doses referred to in earlier research studies (for example, 8 mg sublingual solution corresponds approximately to a 12 mg sublingual tablet dose).

TABLE 1
ONSET AND DURATION OF RESPONSE TO BUPRENORPHINE

Onset of effects	30 - 60 minutes
Peak clinical effects	1 - 4 hours
Duration of effects	8 - 12 hours at low dose (e.g. < 4 mg)
	24 - 72 hours at high dose (e.g. >16 mg)

Buprenorphine also exhibits antagonist effects at the κ opioid receptor. The role of these receptors in humans is still poorly understood, but excess endogenous κ agonist activity appears to be implicated in both affective and psychotic conditions. Buprenorphine's antagonist effects at the κ receptor are thought to produce anti-depressant and anti-psychotic effects in some people. However, as further research is needed into these effects, buprenorphine is not currently indicated for these conditions.

Withdrawal syndrome from buprenorphine

Its partial agonist properties, along with its slow dissociation from opioid receptors, are thought to explain why opioid withdrawal syndrome is milder with the cessation of buprenorphine treatment, than with heroin, morphine or methadone. Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within 3 – 5 days of the last dose, and mild withdrawal features continue for up to several weeks. Treatment with opioid antagonists (eg naltrexone) can be commenced within days of the cessation of low-dose buprenorphine treatment without precipitating severe opioid withdrawal. This enables patients to transfer promptly to naltrexone treatment, and avoid relapse and treatment drop-out. By contrast, naltrexone is not usually started until 10 - 14 days after the cessation of methadone *(Bell et al 1999 : Interim National Naltrexone Guidelines)*.

Withdrawal is milder and transfers to alternate treatments are more rapid

Safety and side effects

High doses: Dose response studies show that, because of its ceiling effects, high doses (16 mg daily or more) do not result in substantially greater peak opioid effects than lower doses (8 or 12 mg). Doses many times greater than normal therapeutic doses appear to be well-tolerated, and rarely result in clinically-significant respiratory depression, even in non-opioid-tolerant individuals.

Buprenorphine is safer in high doses than full opioid agonists

Combined with other drugs: The safety of buprenorphine mixed with high doses of other sedative drugs, such as alcohol or benzodiazepines, is still unclear, with several deaths having been reported. Naloxone is of limited use in resuscitating individuals who have overdosed on high doses of buprenorphine (See section 5.2 on Management of Overdose).

Precaution should be exercised when buprenorphine is administered concomitantly with CYP 3A4 inhibitors (eg protease inhibitors, some drugs in the class of azole antimycotics such as ketoconazole, calcium channel antagonists such as nifedipine, and macrolide antibiotics) as this may lead to increased plasma concentrations of buprenorphine.

Not safe mixed with high doses of other sedatives

Side effects: The side effects of buprenorphine are similar to those of other opioids, the most common being:

- constipation
- disturbed sleep
- drowsiness
- sweating
- headaches
- nausea.

Many patients report less sedation on buprenorphine than on methadone. Like all opioid medications, buprenorphine may affect the capacity of patients to drive or operate machinery during the early stages of treatment or following dose increases. It appears to have minimal impact on hepatic function, although its effects in very high doses remain unclear.

Side effects - similar to other opioids

Under certain circumstances, buprenorphine may precipitate opioid withdrawal symptoms 1 - 4 hours after the first dose. It has a higher affinity and lower intrinsic activity than agonists such as methadone, morphine or heroin. Consequently, buprenorphine displaces agonists from opioid receptors and, in the short term, may not produce sufficient agonist effects to compensate for the displaced methadone or heroin, producing opioid withdrawal as the buprenorphine reaches its peak effects (approx. 1 - 4 hours after initial administration). The phenomenon of precipitated withdrawal has particular clinical relevance during the induction of heroin users and methadone patients (see Section 3.2).

May induce rapid opioid withdrawal

Drug Interactions

The principal drug interactions of buprenorphine relate to its opioid activity.

- *other sedatives.* Buprenorphine exerts additive sedative effects when used in conjunction with other sedating medications. These include other opioids, benzodiazepines, alcohol, tricyclic antidepressants, sedating anti-histamines, and major tranquillisers. **A number of deaths have been reported involving the combination of buprenorphine with benzodiazepines and other sedatives.**
- *opioid antagonists (naloxone and naltrexone).* Buprenorphine has higher affinity for m opioid receptors than the opioid antagonists. In the event of overdose of buprenorphine, very high doses of naloxone are required to reverse its effects (10-35 mg have been reported). Naltrexone can precipitate a delayed withdrawal reaction in patients on buprenorphine.
- *opioid agonists.* Buprenorphine exerts a degree of blockade to the effects of full agonist opioids, which may complicate the use of additional opioids for analgesia. The initial dose of buprenorphine can precipitate opioid withdrawal in patients with high levels of neuroadaptation to full opioid agonists.
- *hepatic enzyme inducers and inhibitors.* Buprenorphine is metabolized by the hepatic microsomal enzyme system (CYP 3A4). While current evidence is inconclusive, it is thought that the concurrent use of medications which induce or inhibit microsomal enzyme activity will have minimal clinical impact on buprenorphine dosing requirements.

TABLE 2
SUMMARY OF THE PHARMACOLOGICAL AND CLINICAL PROPERTIES OF BUPRENORPHINE

Property	Clinical implication
Produces opioid effects	Reduces cravings for heroin and enhances treatment retention. Less sedating than full agonists (heroin, morphine or methadone).
Prevents or alleviates heroin withdrawal symptoms	Can be used for maintenance or withdrawal treatment.
Diminishes the effects of additional opioid use (e.g. heroin)	Diminishes psychological reinforcement of continued heroin use. May complicate attempts at analgesia with other opioids (e.g. morphine).
Long duration of action	Allows for once-a-day to three-times-a-week dosing schedules.
Ceiling on dose response effect	Higher doses (e.g. >16 mg) may not increase the opioid agonist effects, while prolonging the duration of action. Safer in overdose, as high doses in isolation rarely result in fatal respiratory depression.
Sublingual preparation	Safer in accidental overdose (e.g. in children) as poorly absorbed orally. More time involved in supervised dispensing.
No severe withdrawal precipitated by opioid antagonists.	Treatment with naltrexone can be commenced within days of buprenorphine. May complicate management of heroin overdose requiring high naloxone doses.
Side effect profile similar to other opioids	Generally well tolerated, with most side effects transient.

SECTION 2. ENTRY INTO BUPRENORPHINE TREATMENT

2.1 Suitability for treatment with buprenorphine

The following guidelines should be taken into account when considering a person's suitability for treatment with buprenorphine in either the maintenance or the withdrawal program.

Indications

1. Buprenorphine treatment is only indicated for those who are opioid-dependent.

What is opioid dependence?

Diagnostic Definition of Opioid Dependence (DSM IV)

"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."

- *Tolerance* as defined by either of the following:
    - A need for markedly increased amounts of opioids to achieve intoxication or desired effect;
    - Markedly diminished effect with continued use of the same amount of opioids.
- *Withdrawal* as manifested by either of the following:
    - The characteristic withdrawal syndrome for opioids;
    - Opioids, or a closely related substance, being taken to relieve or avoid withdrawal symptoms.
- Impaired control over use: Opioids often taken in larger amounts or over longer period than intended.
- *Wish to quit:* A persistent desire or unsuccessful attempts to cut down or control opioid use.
- *Time factor:* A great deal of time regularly spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
- *Life-style changes:* Important social, occupational, or recreational activities given up or reduced because of opioid use.
- *Consciousness of damage being out of control:* The opioid use continued, despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

NEUROADAPTATION TO OPIOIDS

Evidence of neuroadaptation (or physical dependence):

- tolerance of the opioid;
- onset of withdrawal syndrome on stopping or decreasing use.

Note: Neuroadaptation is not a prerequisite for the diagnosis of drug-dependence. However, in the absence of neuroadaptation, the prescribing medical practitioner must clearly demonstrate potential benefits to the individual's health and well-being that outweigh the potential disadvantages of buprenorphine treatment, and alternative treatment options should be carefully considered.

2. **The patient must be at least 18 years of age.** The prescribing doctor should seek a second or specialist opinion before treating anyone under 18 years of age. (Note: While buprenorphine has been registered for administration to people aged 16 and over caution should be exercised in prescribing a drug of dependence for anyone in the 16-17 age group.)
3. **The patient must be able to provide proof of identity - a requirement for treatment with any S8 medication.**
4. **The patient must be capable of giving informed consent to treatment with buprenorphine.**

Suitability for Buprenorphine Treatment
opioid-dependent
18 years or older
proof of identity
capable of informed consent

Contraindications

1. Anyone with known hypersensitivity and/or severe side-effects from previous exposure to buprenorphine is ineligible for buprenorphine treatment.
2. Pregnant women and nursing mothers are also ineligible at this stage, as there is insufficient evidence that it is safe for either the developing fetus or the breast-fed neonate, and there is evidence in other species of harms. Developmental toxicity studies of buprenorphine in pregnant rats and rabbits have shown fetotoxicity, including post-implantation loss, and decreased post-natal survival with no evidence of teratogenicity. The described effects occurred at systemic exposures similar to the maximum anticipated human dose of 32 mg/day.. In addition, maternal oral administration at high doses (80 mg/kg/day) during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.In humans, there is currently not sufficient data to evaluate potential teratogenic or fetotoxic effects of buprenorphine in pregnancy. However, high doses, even for short durations, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates.
3. Animal studies indicate buprenorphine has the potential to inhibit lactation. Buprenorphine passes into the mother's milk, therefore breast-feeding while using buprenorphine is contra-indicated until its safety has been fully established.
4. Severe respiratory or hepatic insufficiency.

Precautions

Particular caution should be exercised when assessing the suitability of buprenorphine treatment for anyone with any of the following clinical conditions.

1. *High-risk polydrug use.* All opioid substitution treatments should be approached with caution in individuals using other drugs, particularly sedative drugs such as alcohol, benzodiazepines or antidepressants. Particular emphasis should be given to assessing the level of neuroadaptation to opioids, the likelihood of continued use of other sedative drugs, and overdose risk.

2. *Concomitant medical conditions.* Buprenorphine is an opioid medication and caution should be exercised in using it in the following situations:
   - *Recent head injury or increased intracranial pressure.*
   - *Compromised respiratory function.* Buprenorphine, like other opioids, should be used with caution in patients with chronic obstructive airways disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnea. **In such patients, even normally safe therapeutic doses of opioids may decrease respiratory drive whilst simultaneously increasing airways resistance to the point of apnoea.**
   - *Acute abdominal conditions.*
   - *Severe hepatic disease.* Caution needs to be taken in considering buprenorphine treatment for people with clinically significant hepatic failure. Severe hepatic disease may alter the hepatic metabolism of the medication. However, the presence of elevated enzyme levels on liver function testing, in the absence of clinical evidence of liver failure, does not exclude someone from treatment with buprenorphine.
   - *Special risk patients. Opioids should only be given with caution, and at a reduced initial dose, to patients with any of the following conditions:*

     advanced age or debilitation;

     prostatic hypertrophy or urethral stricture;

     pre-existing diabetes mellitus or a pre-disposition to it, with the possibility of increases in serum glucose on buprenorphine;

     severe renal disease. (Pharmacokinetic studies have not been conducted on this group, so methadone should be the first option.)

3. *Concomitant psychiatric condition.* Opioid substitution treatment should not be initiated in anyone with acute psychosis, severe depression, or other psychiatric conditions which severely compromise the capacity to give informed consent. The first priority should be an attempt to manage and stabilise the psychiatric condition. People at moderate or high risk of suicide should not be commenced on buprenorphine without adequate supervision, and specialist advice should be sought.

4. *Chronic Pain.* Buprenorphine can be used as an analgesic in the management of acute and chronic pain conditions (although it is not registered for this purpose), but at much lower doses than for heroin dependence. Ideally, chronic pain is best managed under the supervision of a specialist multidisciplinary team, and appropriate referral or consultation should be considered.

5. *Transfer from methadone maintenance.* Buprenorphine may cause difficulties in transferring from methadone by precipitating withdrawal (see Section 3.2). This is most likely to occur in patients on high doses of methadone, and attempts to reduce the methadone dose to below 60 mg (and preferably below 40 mg) should be made before initiating buprenorphine. **Methadone patients who relapse into regular heroin use following the reduction of their methadone dose are likely to find transition to buprenorphine difficult, if not unachievable.**

EXERCISE CAUTION

With patients in any of the following categories

high-risk polydrug use

concomitant medical conditions (see list above)

concomitant psychiatric conditions

suffering chronic pain

transfer from methadone maintenance

2.2 Assessment procedures

A careful assessment should be conducted at the outset of buprenorphine treatment. The following issues should be addressed:

History

- Heroin and other opioid use:
  - quantity and frequency (amount, cost, number of times used per day);
  - duration;
  - route of administration (injected/non-injected);
  - when last used;
  - features and severity of dependence.
- Use of other drugs (including benzodiazepines, alcohol, cannabis, psychostimulants) and assessment of degree of dependence to each drug class.
- Participation in high-risk drug behaviours, particularly overdoses, self-injury, or polydrug intoxication.
- History of prior attempts at withdrawal, maintenance and other treatment - what has worked and not worked before.
- Social circumstances, including home environment, social supports, employment, and barriers to change.
- Medical and psychiatric history, with particular attention to unstable or active conditions which might potentially complicate treatment.
- Pregnancy and contraception.
- Motivations and goals for treatment. Finding the right approach requires an understanding of the **reasons for seeking treatment** and of **patient goals and expectations.**

Examination

- Vital signs (blood pressure, pulse, respiratory rate);
- Evidence of intoxication or withdrawal from heroin or other drugs;
- Evidence of complications of injecting drug use, including injection site problems, hepatic disease, lymphadenopathy, systemic infections.

Investigations

- Urinary drug screens can be helpful in clarifying or confirming an unclear drug use history. However, delays in getting the results of routine urine tests often limits their usefulness at initial assessment.
- **Liver function tests and viral serology** (HIV, Hepatitis B and C) should be considered at some stage with appropriate pre- and post-test counselling. (This is advisable after stabilisation, when the patient is better able to understand the significance and consequences of testing).

A comprehensive assessment for buprenorphine treatment can rarely be completed at the initial appointment, and generally needs to be conducted over several sessions. Initially, clinicians should target key issues important in the selection and initiation of treatment, and assess indications, contraindications and precautions. Referral or consultation with a specialist is recommended for patients with complex presentations.

2.3 Informed Consent and Patient Literature

The participation of an informed patient in the clinical decision-making process is important in the treatment of all opioid dependence. It is particularly important when incorporating opioid medications - such as buprenorphine or methadone - as part of the treatment plan. In considering the commencement of buprenorphine for maintenance or withdrawal treatment, the service provider should also explore alternative treatment options with the patient (including alternative approaches to withdrawal or substitution maintenance treatment, self-help, residential rehabilitation programs, counselling, and naltrexone).

All patients commencing treatment with buprenorphine must give their informed consent to treatment. This process requires fully informed patients and their opportunity to discuss with the service provider the following topics:

- what is buprenorphine, how does it work, and what are its advantages & disadvantages?
- what is the duration of treatment; its cost; its associated 'routines', including urine-testing, "take-aways", transfers?
- what are the known side-effects?
- what about pregnancy and contraception issues?
- what are the dangers of additional drug use, overdose?
- what is the potential impact on driving, and on employment?
- what are the conditions of involuntary discharge?

Specific patient literature should be provided prior to the commencement of treatment. It is recommended that consent be documented and that patients be given their own copies of the documents they have signed.

Buprenorphine may affect the capacity of patients to drive or operate machinery during the early stages of treatment, after an increase in dose, or when patients are also taking other drugs. Warn patients about this effect before entry into treatment, when the dose of buprenorphine is increased, or when the use of other drugs is suspected.

2.4 Permits and Registration of Patients

Buprenorphine is registered as a Schedule 8 medication. Each jurisdiction is responsible for a system of authorising medical practitioners to prescribe buprenorphine to a particular patient. (See Appendix 3)

SECTION 3. GUIDELINES FOR MAINTENANCE TREATMENT

3.1 Selecting maintenance pharmacotherapies

Current evidence suggests that key treatment outcomes for maintenance buprenorphine and methadone treatment are comparable under optimal treatment conditions. Whilst there is no evidence of the greater efficacy of one treatment over the other, patients or clinicians may develop personal preferences. These might reflect:

- **Response to treatment.** Ultimately, the continued use of a medication should depend on its ability to meet the aims and objectives of treatment. This requires the identification of treatment goals by the patient and the individual service provider, and decisions about how the treatment outcomes will be assessed.

Where these goals are *not* being met, a review of treatment strategies should occur, including:

- the role of psychosocial interventions,
- levels of supervision, monitoring and review,
- dose of a substitution opioid,
- the role of adjuvant interventions, and – ultimately –
- a review of alternative opioid pharmacotherapies. For example, patients who cannot stabilise their continued use of heroin, even on high doses of buprenorphine, may be better suited to high doses of an agonist treatment (methadone).

- **Individual variation in absorption, metabolism and clearance.** There may be considerable pharmacokinetic and pharmacodynamic differences between individuals in their response to different opioid substitution pharmacotherapies.
- **Adverse events.** Individuals experiencing significant side-effects from one opioid medication may benefit from treatment with an alternative medication. In particular, buprenorphine may be preferred by individuals complaining of continued sedation under methadone.
- **Logistics of participating in treatment,** including issues such as ease of access for participants, frequency of dispensing, convenient location of treatment services and the costs to patients, service providers and funding bodies. Once stabilised on a daily dosing regime, the majority of patients on buprenorphine will be able to switch to an alternate-day, or three-times-a-week dosing regime. This should be more convenient for patients and reduce the need for regular take-away doses. Not all patients will be comfortable on alternate-day buprenorphine dosing, and may require daily doses.
- **Ease of withdrawal from maintenance buprenorphine treatment.** A limiting factor for many patients considering maintenance treatment is the problem of dependence on the maintenance opioid. As it is only a partial agonist and dissociates slowly from receptors, buprenorphine appears to have a milder withdrawal syndrome than methadone. Nevertheless, current research indicates that relapse rates to heroin use are comparable for patients discontinuing maintenance treatment from either opioid.
- **Patient (and clinician) expectancy.** Expectations of any medication may impact seriously on its perceived outcomes. The introduction of new pharmacotherapies for heroin dependence may give rise to unrealistic expectations in patients, their families, and even service providers.
- **Capacity for transfer from methadone maintenance.** Some patients require high doses of methadone to stabilise their heroin use, and a marked reduction can cause a relapse to regular heroin use. For patients who cannot reduce below high doses of methadone (i.e. 60 mg) without becoming destabilised, transfer to buprenorphine should not be recommended unless it is part of a broader plan of gradual withdrawal from maintenance substitution treatment.

FACTORS TO CONSIDER WHEN SELECTING MAINTENANCE PHARMACOTHERAPIES

- Response to treatment
- Individual variation in absorption, metabolism & clearance rates
- Adverse effects
- Logistics of participating in treatments
- Ease of withdrawal from maintenance buprenorphine treatment
- General expectations of the treatment
- Capacity for transfer from methadone maintenance

3.2 Induction to buprenorphine treatment

Commencing buprenorphine from heroin use

The initial dose of buprenorphine should be between 2 and 8 mg. The initial dose should not be greater than 8mg.

The following factors must be taken into consideration when considering the initial dose of buprenorphine:

- **Degree of neuroadaptation to opioids.** Patients with a low degree of neuroadaptation to opioids (low opioid tolerance) should be commenced on a dose of 2 or 4 mg. In instances where the doctor is uncertain of the degree of neuroadaptation, the patient should be commenced on a dose of 4 mg. Patients with high levels of neuroadaptation should commence on 6 or 8 mg.
- **Extent of heroin withdrawal at the time of first buprenorphine dose.** Patients experiencing considerable opioid withdrawal at the time of the first dose require higher doses of buprenorphine to alleviate withdrawal symptoms. Patients with little or no indication of opioid withdrawal at the time of the first dose should be prescribed a lower dose, or be asked to re-present at a later time (see rationale below).
- **The perceived likelihood of concurrent drug abuse,** including alcohol consumption, unauthorised use of prescription sedative drugs (particularly benzodiazepines), or illicit drug use. In such instances, lower doses of buprenorphine should be prescribed, with frequent reviews.
- **Concurrent medical conditions** (particularly impaired hepatic function and interactions with other medications) warrant the use of lower initial doses of buprenorphine with regular monitoring (see Section I **"Clinical pharmacology"** and Section 2.1 **"Precautions"**).

The first dose of buprenorphine should be administered at least 6 hours after last heroin use.

Care should be taken by prescribing doctors, pharmacists and nursing staff, not to administer the first dose to a patient within 6 hours of heroin use, and especially not to patients intoxicated on opioids. If they do, the patient may experience opioid withdrawal, as the buprenorphine displaces heroin from the opioid receptors. Buprenorphine-precipitated withdrawal typically begins 1- 4 hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. If this happens, patients may require symptomatic withdrawal medication, and should be directed to see their doctor.

Subsequent doses of buprenorphine (taken the following day) should result in light or minimal withdrawal discomfort if the patient has not used heroin during the intervening period. Patients who continue to use heroin between their first and second doses of buprenorphine may have difficulty stabilising on the treatment, with ongoing features of opioid withdrawal. They should be advised to cease heroin use at least 6 hours prior to the next dose of buprenorphine.

Transferring from methadone maintenance treatment

Buprenorphine has a higher affinity for m opioid receptors than methadone, but a weaker action (lower intrinsic activity) at these receptors. When methadone patients take a dose of buprenorphine, the methadone is displaced from the μ opioid receptors by buprenorphine. Patients on low doses of methadone (e.g. less than 30 mg) generally tolerate this transition with minimal discomfort. **However, patients on higher doses of methadone may find the replacement of methadone with buprenorphine precipitates transient opioid withdrawal.**

This has a number of clinical implications. Wherever possible, patients in methadone treatment should have their methadone dose reduced and should be stabilised on this low dose prior to transferring to buprenorphine, in order to minimise any opioid withdrawal features. The following table describes key factors in the development of precipitated withdrawal.

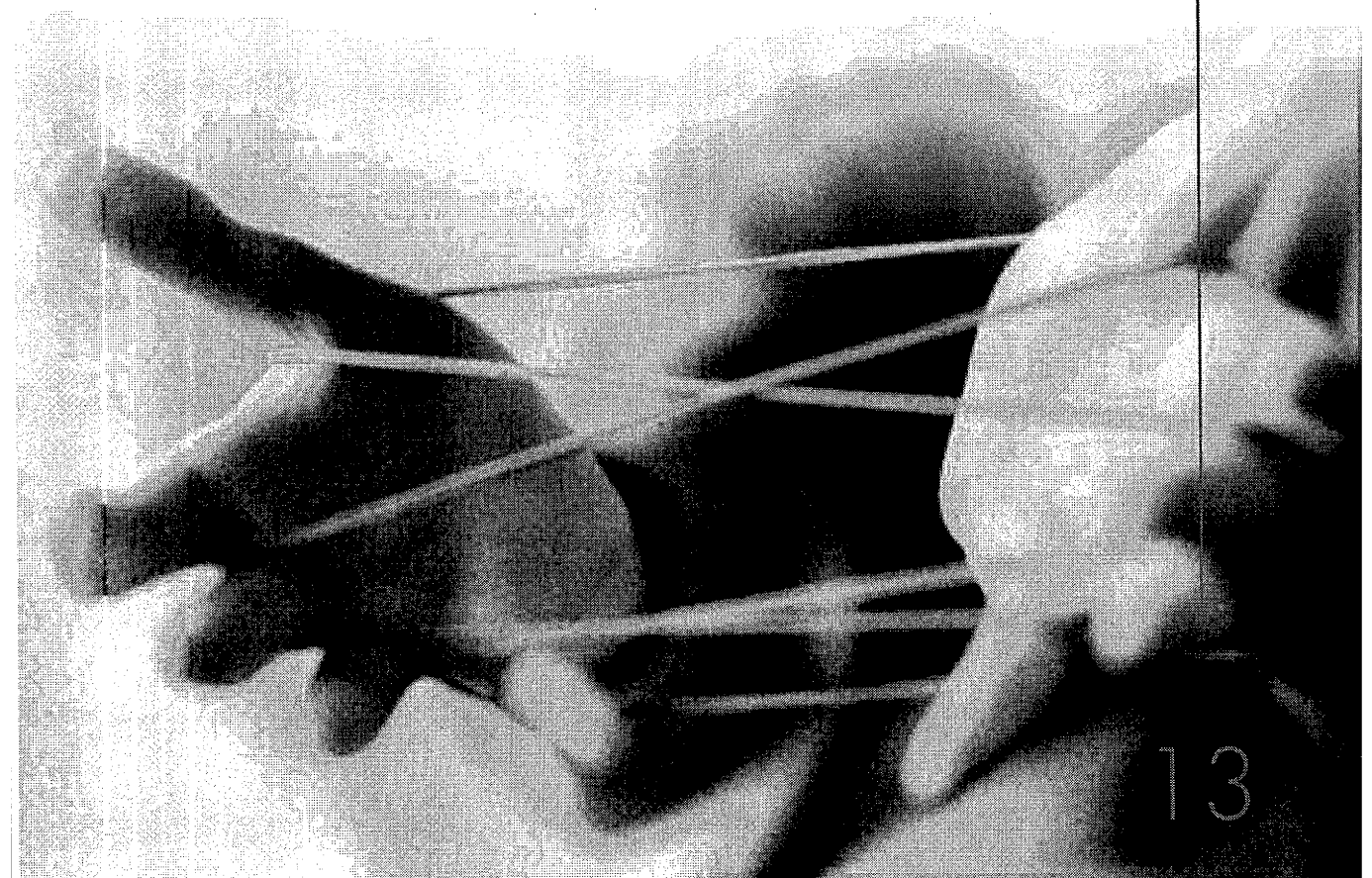


TABLE 3
KEY FACTORS AFFECTING PRECIPITATED WITHDRAWAL

Factor	Discussion	Recommended strategy
Dose of methadone	Doses greater than 30 mg of methadone are more often associated with precipitated withdrawal. In general, the higher the methadone dose, the more severe the withdrawal experienced.	Attempt transfer from low dose of methadone (e.g. < 40 mg where possible). Patients on > 60 mg methadone should not attempt transfer.
Time between last methadone dose and first buprenorphine dose	Buprenorphine should not be taken within 24 hours of last methadone dose. Increasing the interval between last dose of methadone and first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.	Cease methadone and delay first dose of buprenorphine until patient is experiencing features of methadone withdrawal
Dose of buprenorphine	Very low doses of buprenorphine (e.g. 2 mg) are generally inadequate to substitute for methadone (unless the methadone dose is very low). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal, as there is greater displacement of methadone from the receptors. *This is a common mistake by inexperienced prescribers.*	First dose of buprenorphine should generally be 4 mg, with review of the patient 2 - 4 hours later (or early the following day)
Patient expectancy	Patients who are not prepared for the possibility of precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment drop-out, abuse of other medications).	Inform patients fully (and carers where relevant). Provide written information. Prepare a contingency management plan for severe symptoms.
Use of other medications	Symptomatic medication (eg clonidine) can be useful in relieving any precipitated withdrawal.	Prescribe and dispense in accordance with a management plan

Transferring to buprenorphine from doses of methadone of 40 mg or less:

Wherever possible, patients should be on a methadone dose of less than 40 mg (and preferably 30 mg or less) for at least one week prior to receiving their first dose of buprenorphine. Indeed, it is preferable for patients to be experiencing a mild degree of methadone withdrawal prior to converting to buprenorphine. For many patients, the optimal methadone dose prior to transferring to buprenorphine may be below 30 mg of methadone.

The following conversion rates should be used when converting from low-dose methadone to buprenorphine.

Last Oral Methadone Dose (mg)	Initial Buprenorphine Dose (mg) (S/L tablet)	Day 2 Buprenorphine Dose (mg) (S/L tablet)
20 - 40 mg	4 mg	6 to 8 mg
10 - 20 mg	4 mg	4 to 8 mg
1 - 10 mg	2 mg	2 to 4 mg

The first dose of buprenorphine should be administered at least 24 hours after the last methadone dose, and at least 6 hours after last heroin use.

The likelihood of precipitating withdrawal on commencing buprenorphine is reduced as the time interval between the last methadone dose and the first buprenorphine dose increases. A precipitated withdrawal may be avoided by ensuring the last dose of methadone is taken early in the morning, and the first dose of buprenorphine is taken late the following day.

e.g. Last dose of methadone – early morning; 1st dose buprenorphine – late next day

Features of a precipitated withdrawal following the first dose of buprenorphine are typically mild to moderate in severity, which can distress the unprepared patient. Symptoms commence 1 - 4 hours after the first buprenorphine dose and last for up to 12 hours before subsiding. Patients experiencing discomfort may re-present to the prescribing doctor later in the day and require symptomatic withdrawal medication (eg clonidine 100 mcg 3 - 4 hourly). Subsequent doses of buprenorphine (the following day) are less likely to precipitate withdrawal symptoms.

Transferring to buprenorphine from doses of methadone greater than 40 mg (ie where there is a risk of relapse to heroin on lower dose)

Most patients in methadone treatment require maintenance doses of greater than 40 mg of methadone to achieve abstinence from heroin, and are unable to reduce their dose of methadone to 40 mg or less without considerable withdrawal discomfort or relapse to heroin use. As it may be difficult to get these patients' doses of methadone below 40 mg, transfer to buprenorphine may need to be considered at higher methadone doses, with the inherent risks associated with such a procedure explained fully to the patient.

It is possible to transfer to buprenorphine from methadone doses of 40 - 60 mg for those patients who choose to do so. *The general principle is to cease methadone dosing, and delay the initiation of buprenorphine treatment until the patient experiences significant, observable features of opioid withdrawal. This generally means that buprenorphine is not commenced until 48 - 96 hours after the last dose of methadone.* Patients should be warned that the use of heroin or other opioids at this stage increases the likelihood of a difficult initiation to buprenorphine. Symptomatic withdrawal medication may be prescribed to ease the discomfort of methadone withdrawal, although the quantities of medications, such as benzodiazepines or clonidine, should be limited. Medications containing codeine or d-propoxyphene should be avoided.

Prepare the patient for withdrawal symptoms

Patients should have the possibility of precipitated withdrawal explained, as well as the relevant strategies for dealing with its symptoms. Transfer should be organised for a time when the patient has no significant work or other commitments, and the doctor is available for review.

Patients should be reviewed by their prescriber immediately prior to commencing buprenorphine, to ensure they are indeed in opioid withdrawal.

The first dose of buprenorphine should be 4 mg.

After first dose, later the same day (approximately 3 - 4 hours after the first dose of buprenorphine): Review by medical practitioner.

- If patient is experiencing no increase in withdrawal severity, either subjectively or objectively, give another 2 or 4 mg of buprenorphine.
- If patient is experiencing a worsening of withdrawal, give no further dose that day. Symptomatic withdrawal medication may be required for the rest of the day (eg clonidine 100 mcg 3 - 4 hourly).

Note: Peak withdrawal discomfort is experienced during the first day of buprenorphine treatment.

Second day: Review by the prescriber prior to dosing on the following day.

Dose can generally be increased to 6 or 8 mg.

Subsequent days: Subject to review of the patient by the prescriber, further increases.

Patients may not feel entirely comfortable during the whole first week. The recommended procedure for transferring patients from medium doses of methadone (e.g. 40 - 60 mg) to buprenorphine is summarised in the following table.

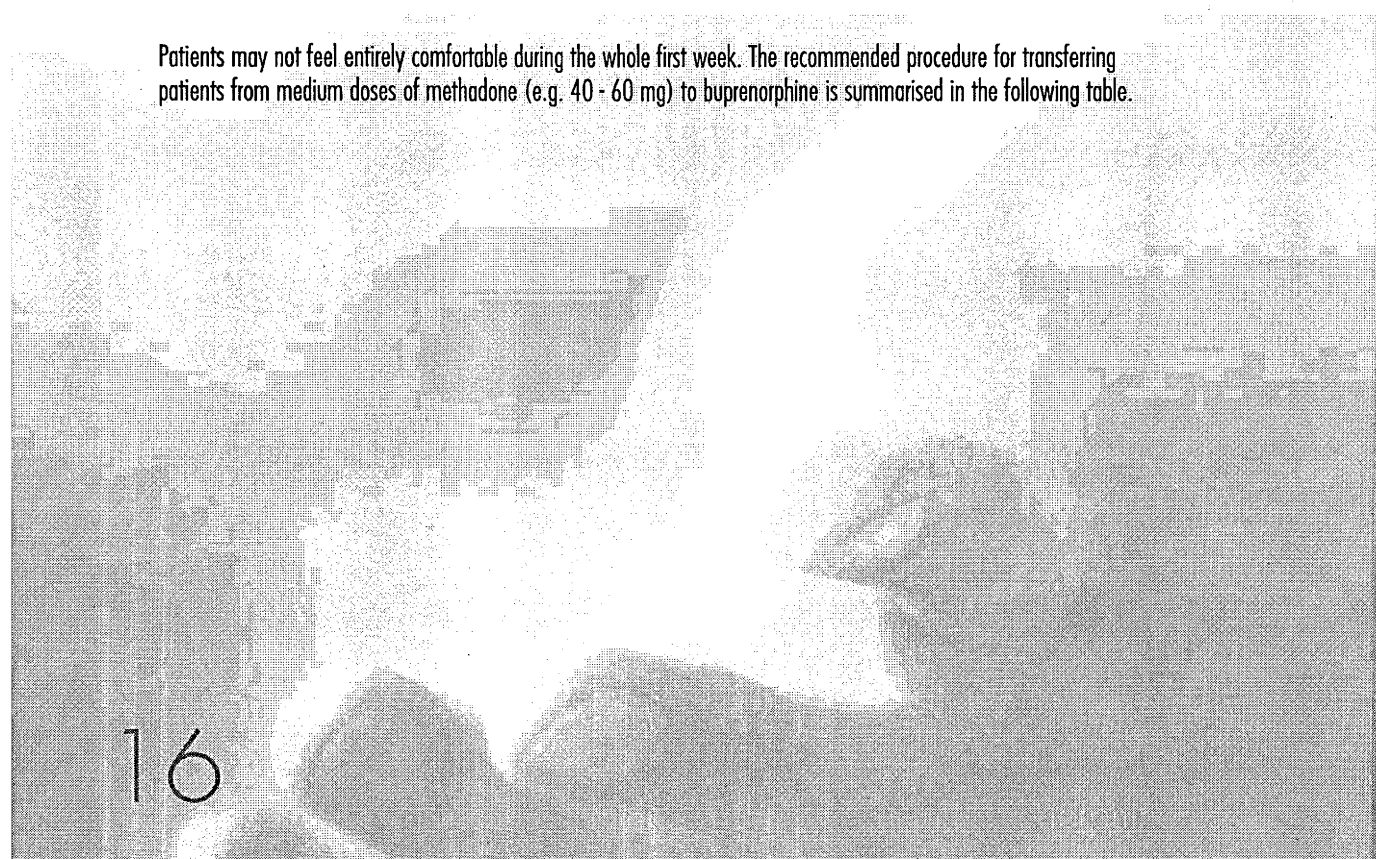


TABLE 4

SUMMARY OF PROPOSED PROCEDURES FOR MEDIUM DOSE METHADONE (40 - 60 MG) TO BUPRENORPHINE TRANSFER

1. Prepare the patient for the transition. Provide information, organise supports, communicate with pharmacist and/or other staff.
2. Cease methadone dose and delay first buprenorphine dose until the patient experiences significant withdrawal discomfort (generally 48 - 96 hours after last methadone dose). Symptomatic medication (limited amounts) may be required.
3. Administer first dose of 4 mg buprenorphine in the morning or early afternoon.
4. Review the patient 2 - 4 hours after first buprenorphine dose:
   - Worsening of withdrawal following first dose ▸ provision of symptomatic medication for opioid withdrawal for remainder of the day;
   - no worsening, or an improvement, in withdrawal following the first dose ▸ a further 2 to 4 mg of buprenorphine dispensed that afternoon / evening.
5. Review the patient prior to dosing on the following day. Titrate the dose of buprenorphine to 6 - 10 mg, according to response on previous day.
6. Review frequently and titrate dose until stable. Patients may continue to describe mild withdrawal features and/or dysphoria for one to two weeks after transfer.

It is strongly recommended that patients on methadone doses of greater than 60 mg reduce their dose to 60 mg or less prior to attempting transfer. Patients unable to reduce to these levels of methadone should not attempt transfer to buprenorphine.

3.3 Stabilisation

The optimal maintenance dose needs to be individualised according to the patient's response to buprenorphine. People's responses vary considerably, according to the following factors:

1. rates of absorption or metabolism of buprenorphine;
2. levels of opioid neuroadaptation and dependence;
3. experience of side-effects;
4. continued use of other drugs.

These variations require the clinician to titrate the buprenorphine dose to optimise treatment objectives.

Early doses can be test doses. Initial doses of buprenorphine can serve as 'test doses' to enable both patient and clinician to monitor responses to the medication. In some people they may not be adequate to prevent withdrawal over a 24-hour period, while they may make some people feel sedated or 'drugged' (due to additional drug use, or to the initial dose of buprenorphine being too high).

Prompt results. Equilibrium levels with buprenorphine are achieved quickly, and the effects of a dose-change should become apparent within 2 - 3 days. Consequently, dose levels of buprenorphine can be more rapidly titrated according to patient response, than can methadone.

TO ACHIEVE STABILISATION OF BUPRENORPHINE DOSE:

Regular patient review for first few weeks: adequacy of dose; withdrawal symptoms, side-effects, any additional drug use (see below for minimal schedule of prescriber reviews).

Increase dose only as indicated by reviews (see below for guidance on titration of doses)

Regular patient review

Frequent reviews by the prescriber are required in the first few weeks:

- to titrate the individual optimal doses of buprenorphine,
- to make a more comprehensive overall assessment of the patient;
- to further discuss treatment plans.

As treatment progresses, the prescribing doctor should review the patient 2-3 times a week until stabilised:

- to establish adequacy of dose;
- to inquire about withdrawal symptoms or side-effects;
- to monitor any additional drug use.

Maintenance buprenorphine doses should be achieved within the first one or two weeks of treatment, subject to the patient's use of heroin, or other drugs.

The following minimal schedule of reviews is recommended by treating doctors or their nominees[2]:

- *The day after the 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 2 - 4 *days until stabilisation.*
- *Every week during the following 4 – 6 weeks.*
- *Every two weeks during the following 6 – 8 weeks.*
- *Monthly reviews thereafter, although the prescriber may wish to extend reviews to up to 3 months for very stable patients.*

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

[2]In practice, a suitably trained nurse or pharmacist often undertakes these reviews, with reference to the prescribing doctor where necessary.

Dose increases should be made only after review of the patient by the prescribing doctor.

If daily reviews can be organised by the prescriber, daily increases can be accommodated. Practically, however, most prescribers may not be able to review the patient more than every two or three days (eg because of sessional practice or weekends). A period of 2 - 3 days on a specific dose allows the patient time to get a 'feel' for their current dose, and the opportunity to modify behaviour appropriately prior to further dose changes. The buprenorphine dose may be decreased where there are concerns regarding the patient's safety (e.g. where there are reports of intoxication or overdose).

Changes in buprenorphine dose

The dose response curve of buprenorphine indicates that small increments have a greater impact at low doses, whereas at higher doses, larger changes are required for a substantial change of effect. The following increments are proposed:

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

Titrating the dose of buprenorphine

At each review, the buprenorphine dose should be titrated according to the following parameters:

- features of intoxication or withdrawal over preceding 24 hours (self-report, examination);
- cravings for heroin use;
- additional drug use (heroin and other drugs), and reason stated by patient for using;
- side-effects or other adverse events (including intoxicated presentations, overdoses);
- adherence with dosing regime (attendance for dosing, route of administration);
- patient satisfaction with buprenorphine dose and treatment.

The following should guide prescribers in determining the buprenorphine dose.

Decrease buprenorphine dose	Maintain buprenorphine dose	Increase buprenorphine dose
Features of intoxication to buprenorphine (eg sedation) particularly at peak effect times (1 – 4 hours after dosing)	No features of withdrawal or intoxication	Features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose
		No features of intoxication to buprenorphine, particularly at peak effect times (1 - 4 hrs after dosing)
	Low cravings for heroin or other drugs	Intense cravings for heroin in past 24 hrs or heroin use to avert withdrawal
Severe or intolerable side effects	Nil / mild and tolerable side effects	Nil / mild and tolerable side effects

Regular and high risk use of heroin

Stabilisation with prescribed opioids is hard to achieve if the patient is in the habit of using additional opioids (eg heroin, codeine preparations), as they complicate the interpretation of withdrawal or intoxication effects. In particular, patients who continue to use heroin during the first few doses of buprenorphine may experience difficulties in stabilising on the new medication. The patient should be encouraged to make every effort to avoid heroin, or any other opioid, in the period prior to dosing.

Alternative regime for rapid induction onto buprenorphine

Evidence from overseas trials indicates that a faster rate of induction may be safely undertaken and that this may reduce the risk of early drop out from the program. The alternative regime achieves maintenance doses within 2-3 days using the following dose increments:

- Day 1 8 mg
- Day 2 16 mg
- Day 3 24 mg

Prescribers who undertake this regime should review patients daily, looking particularly for signs and symptoms of toxicity (especially nausea and dizziness). If there is evidence of toxicity dose increases should be slowed.

3.4 Maintenance dosing

Dose levels

Buprenorphine doses need to be individually titrated according to the patient's response to treatment. Effective maintenance doses, resulting in reduced heroin use and improved treatment retention, are achieved with high buprenorphine doses in the range of 12 - 24 mg per day. Some patients may be satisfactorily maintained on daily doses of 8 - 12 mg, while doses of 4 mg or less will not be as effective in retaining patients in treatment or reducing heroin use (similar to, or worse than, the outcomes associated with methadone doses of 20 mg). There is little evidence to suggest that daily doses higher than 24 mg will result in improved outcomes or effects, and little is known regarding the nature of adverse events at maintenance daily doses greater than 32 mg. **The maximum daily dose of buprenorphine routinely recommended is 32 mg.**

Effective maintenance doses, which reduce heroin use and improve treatment retention, are achieved with buprenorphine doses in the range of 12 - 24 mg per day.

People wishing to reduce their use of heroin, or other opioids, can do so with increases in the substitution dose of buprenophine, as higher doses of this substance produce more effective antagonist reactions, blocking the effects of additional heroin use.

However, this only succeeds up to a point. Continued heroin use despite adequate daily doses of buprenophine may indicate that the patient needs more intensive psychosocial interventions, and/or an alternative opioid substitution (e.g. methadone).

Frequency of dosing: alternate-day and three-times-a-week dosing regimes

Buprenorphine dosing begins on a daily basis. Most clinical studies with this therapy have examined daily dosing regimes, but recent studies indicate that many patients who are stabilised on buprenorphine can be maintained on alternate-day dosing, some even on three-times-a-week dosing, without experiencing features of intoxication or withdrawal.

The convenience of reduced-frequency dosing should be considered for all patients found suitable for a trial of alternate-day dosing, i.e. if they meet the following conditions:

- on a stable dose of buprenorphine for at least two weeks;
- having no high-risk drug use (high-risk drug use refers to frequent abuse of other sedatives including alcohol, benzodiazepines, heroin or other opioids, intoxicated presentations to the pharmacy or medical practitioner, or recent history of overdose).

However, not all patients will be suited to an alternate-day, or three-times-a-week, dispensing regime, as some will experience increased cravings or features of withdrawal on the non-dosing days.

Estimates suggest that about 15% of patients are more comfortable and more effectively maintained on daily, rather than alternate-day, dosing regimes. It is recommended that suitable patients initially be trialed for two weeks on an alternate-day dosing regime of buprenorphine. If this is successful, the patient can then be trialed on a three-times-a-week regime. If a patient cannot be stabilised on such dosing regimes due to the onset of withdrawal, cravings, side-effects or features of intoxication, they should be returned to a more frequent dosing regime.

Alternate-day or four-times-a-week regime. This involves attending the pharmacy for dosing on alternate days (i.e., a dose every 48 hours), or attending four times a week (with 3 x 48 hour doses and 1 x 24 hour dose each week (e.g. Mon; Tues; Thurs; Sat)). The advantage of the latter approach (4 times a week) is that the patient is on a regular attendance each week, with less likelihood of attendance errors on the patient's part and dosing errors by the pharmacist.

The dose dispensed for a 48-hour period is initially double the normal daily (24 hour) buprenorphine dose (to a maximum of 32 mg dosed at a time). The patient should be reviewed following the first or second 48-hour dose, and the dose titrated according to the response:

- If the patient reports features of intoxication from the buprenorphine during its peak effects (within the first 24 hours), the 48-hour dose should be reduced.
- If the patient reports that the dose does not prevent the onset of opioid withdrawal or cravings over a 48-hour period, then the 48-hour buprenorphine dose should be increased.

Three-times-a-week regime. Some patients may tolerate three-times-a-week dosing with buprenorphine, reducing the inconvenience and costs of treatment further. This should be attempted after a two-week trial on four-days-a-week dosing has been shown to be successful. The recommended regime for a three-day dose is:

3-day dose = 3 times the normal 24 hr dose if 24 hr buprenorphine dose < 12 mg

3-day dose = 32 mg when 24 hr buprenorphine dose ≥ 12 mg

The patient should be reviewed in the week following the first 72-hour dose, and the dose titrated accordingly. If a patient cannot be stabilised on a three-times-a-week dosing regime, the four-times-a-week dosing regime should be considered.

TABLE 5
Buprenorphine S/L dose (mg)

Daily dose (24 hrs)	Two day dose (48 hrs)	Three day dose (72 hrs)
2	4	6
4	8	12
6	12	18
8	16	24
10	20	30
12	24	32
14	28	32
16	32	32
18	32	32
20	32	32
22	32	32
24	32	32
26	32	32
28	32	32
30	32	32
32	32	32

Some patients attempting alternate-day dosing may benefit from doses greater than 32 mg, however, there is limited evidence regarding the safety of higher doses, and buprenorphine is registered in Australia with a maximum recommended dose of 32 mg. Practitioners should be aware of the medico-legal implications of off-label prescribing before they prescribe doses of greater than 32 mg. **Frequent clinical and hepatic monitoring is recommended under such circumstances.**

3.5 Take-away doses

The take-away policy for buprenorphine will be determined by each jurisdiction. (See Appendix 3). "Take-away" is medication not administered by the dispensing clinician, but given to the patient for administration at a later time.

The benefits of take-away opioid doses:

1. they emphasise and promote patients' responsibility for their own treatment ;
2. they enhance the patients' integration into the community by cutting time and travel costs associated with the treatment;
3. they tend to promote patient retention by minimising the inconvenience of regular attendance for doses. (Studies show take-away policies produce better retention rates than programs which restrict take-away doses).
4. They benefit pharmacists by reducing the inconvenience and cost of daily dispensing.

Concerns regarding take-away doses of opioid medications:

1. **Possible overdose or accidental dose:** Take-aways increase the risk of deliberate or accidental overdose by the patient or others, particularly children and other non-tolerant individuals, and by any one of these in combination with other sedative drugs.
2. **Injection of take-aways**, resulting in overdose, damage to veins or other health consequences.
3. **Doubtful or poor compliance:** Diversion to others of take-aways, resulting in poor outcomes for patient (poor compliance with treatment regime), and abuse by other individuals.
4. **Diversion** of buprenorphine to heroin-dependent individuals or methadone maintenance patients and precipitation of withdrawal
5. **Bad 'publicity'** over treatment regime - "just another drug being bought and sold".

Uncontrolled access to take-aways
▸ more diversion and increased adverse consequences.

The main issues regarding the safety of take-aways are:

a) **Discerning suitability.** Close monitoring by the provider is vital to decide which patients are suitable for take-aways, and this monitoring is not always achievable in community programs.

b) **Education of the patient** regarding safe and responsible handling of the take-away doses.

Absence from pharmacy in patients ineligible for take-away doses

The "one-off" supervised multiple dose. In circumstances where a patient is ineligible for buprenorphine take-aways (eg recently commenced treatment, high-risk drug use), but is unable to attend for dosing for one or two days, it is possible to organise a one-off supervised multiple-dose of buprenorphine (as administered to patients engaged in alternate-day or three-times-a-week dispensing). In this way, the dose of buprenorphine can be doubled in circumstances where the patient is away from the pharmacy for one day, or increased by 3 times the daily dose (to maximum of 32 mg) where the patient cannot attend the pharmacy for 2 consecutive days.

3.6 Ancillary interventions

People with a background of heroin dependence often have a range of social problems (e.g. financial, employment, parenting, legal, accommodation) and psychological difficulties (e.g. depression, anxiety). The stability afforded by long-term substitution treatment provides an opportunity for these issues to be addressed. It is one of the key roles of treating clinicians to assist in this process, either as direct service providers, or as case managers referring the patient on to appropriate services for other areas of their lives.

There has been considerable debate over the role of counselling in maintenance substitution programs. The evidence from methadone treatment studies suggests that counselling should be available to all patients, and that patients should be positively encouraged to avail themselves of counselling services. However there is no real place for mandatory attendance at counselling sessions, and all ancillary services should be offered on the basis of the patient freely consenting to be involved.

Counselling approaches, such as motivational interviewing, relapse prevention and social skills training, which are based on cognitive behavioural therapies, are frequently used and found to be effective. More intensive psychotherapy can be beneficial to people with concomitant affective disorders (e.g. anxiety, depression).

3.7 Continued high-risk drug use

People are said to be in continued high-risk drug use when there are frequent intoxicated presentations or overdoses of heroin or other substances, chaotic drug-related behaviours, or deteriorating medical or mental states due to drug use.

- Attempts should be made to stabilise such patients. A review is required of their psychosocial interventions and supports, precipitants to continued drug use, and medication regimes.
- An adequate dose of buprenorphine should be prescribed; and the clinician must ensure that the patient is taking the buprenorphine as prescribed, which may require:
  - × ceasing take-away doses;
  - × ensuring supervised consumption; and
  - × daily dosing regimes.

  Increases in the dose of buprenorphine may assist patients to reduce their heroin use.
- Transfer to another pharmacotherapy (e.g. methadone) may be indicated if:

  (a) there is little or no response to an increase in medication;

  (b) the patient is already on a high dose of medication; or

  (c) an increase in dose is considered 'unsafe' by the prescriber.
- Alternatively, non-pharmacotherapeutic treatment options should be considered (e.g. therapeutic communities, counselling and support), and the patient withdrawn from prescribed opioid medication.

3.8 Missed Doses

Single dose missed

Sometimes a patient who is on an alternate-day or three-times-a-week regime misses a 'dosing day', attending on the following ('non-dosing') day. **When this happens, a lower dose of buprenorphine should be prescribed and dispensed in order to tide the patient over until the next scheduled dose.**

The following procedures are recommended:

- The pharmacist should contact the prescriber. The buprenorphine dose prescribed should be sufficient to last until the next scheduled dose (if this is 24 hours, then prescribe a 24-hour dose; if 48 hours - a 48-hr dose).
- In circumstances where the pharmacist cannot contact the prescribing doctor, no buprenorphine can be dispensed (as there is no valid prescription). However, this increases the risk that the patient will drop out of treatment. To prevent this happening, the prescriber can issue a prescription of buprenorphine to be administered by the pharmacist as a **one-off dose**, for use if the patient on a three- or four-times-a-week regime misses the scheduled dosing day and presents on a non-scheduled day.

This prescription **must not be greater than the usual 24-hour dose.** The prescriber may wish to limit the maximum level of such an 'emergency dose' to a lower than usual dose in order to discourage such occurrences.

- Patients who repeatedly miss doses under these circumstances should be reviewed by their prescribing doctor to find out why, and whether these issues can be addressed. Alternatively, consideration might be given to a more feasible dosing regime.

Multiple doses missed

Patients who have erratic attendance for dosing are unlikely to achieve optimal outcomes. Patients who have missed more than five consecutive days of buprenorphine must be reviewed by their prescribing doctor prior to receiving a further dose, to ensure their safety.

The recommended recommencement doses of buprenorphine are:

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

Patients can be brought up to their usual maintenance doses over subsequent days (using dosing increments discussed earlier) if clinician and patient think this is appropriate.

3.9 Cessation of buprenorphine maintenance treatment

Withdrawal from buprenorphine maintenance treatment

Nature of withdrawal from buprenorphine maintenance treatment

There is some clinical and anecdotal evidence that withdrawal from buprenorphine is less prolonged and less severe than methadone withdrawal, but the research on this is not conclusive. Withdrawal does appear to be milder during buprenorphine dose reductions, and the rate of buprenorphine dose-reduction is normally more rapid than with methadone. The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids.

Common pattern of long-term withdrawal of buprenorphine treatment:

- The onset of symptoms is usually around 24 - 72 hours after the last 24-hour dose.
- Symptoms peak around days 3 - 5 following short maintenance courses of buprenorphine treatment (weeks / months), or days 5 - 14 for longer-term treatment.
- Duration of withdrawal from buprenorphine maintenance treatment has not been established, although mild to moderate withdrawal symptoms (particularly cravings, sleep and mood disturbances associated with protracted withdrawal) are likely to persist for weeks. One study described mild but ongoing withdrawal features 30 days after the last buprenorphine dose. Longer-term follow up has not been reported.

Voluntary withdrawal from buprenorphine maintenance treatment

Evidence from methadone research suggests that long-term outcomes of treatment are enhanced by:

- **Longer treatment episodes.** Evidence from methadone research suggests that long-term outcomes are enhanced by longer treatment episodes (for example, more than 12 months).
- **A more stable and supportive lifestyle.** The longer treatment episode allows the opportunity for the patient to establish a lifestyle away from heroin and other drug use prior to withdrawing from methadone treatment. Premature withdrawal from methadone (before the patient has achieved a degree of stability in social circumstances and drug use) is more likely to be associated with a relapse into dependent heroin use.

The likelihood of premature withdrawal from maintenance treatment is reduced by:

- **A well-informed patient, with all the facts about the maintenance program.** A patient may wish to withdraw from maintenance treatment for a range of reasons, e.g. the need for interstate travel, concerns about side-effects or about remaining in treatment 'too long'. The clinician should address issues regarding the duration of treatment and withdrawal early in the treatment program, and provide information regarding the process of withdrawal. Patient literature is now available regarding withdrawal from methadone treatment (Dunlop et al 1996), and parallels can be made with withdrawal from buprenorphine. Despite withdrawal from buprenorphine being frequently described as milder than from other opioids, patients should be informed of the likely withdrawal profile.

Except in the case of involuntary withdrawal (see below), withdrawal from buprenorphine should occur only 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 proposed, although reductions can occur both more rapidly and more slowly:

TABLE 6
RATES OF DOSE REDUCTION

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

An increase in heroin or other drug use, or a worsening of the patient's physical, psychological or social well-being, may warrant a temporary cessation or slowing-down of the reduction rate.

Supportive Care

Patients should be aware of their dose, except where an agreement has been reached between patient and service provider to the administration of a 'blind dose'. Increased supportive counselling, as well as information and education, should be available for patients withdrawing from buprenorphine. There may be a role for other medication for symptomatic relief. These include clonidine, NSAIDs, anti-emetics, anti-diarrhoeal agents, hypnotics, and smooth muscle relaxants (eg hyoscine) for patients experiencing severe withdrawal. However, caution should be applied regarding the use of potential drugs of abuse (eg benzodiazepines).

Involuntary withdrawal (without patient consent or against patient's wishes)

The conditions for involuntary termination usually concern behaviour which the service provider finds intolerable, and will vary from program to program. These may include:

- threatened or actual abuse of other patients or staff ;
- illegal activities, such as theft, property damage, or drug-dealing, in or near the service;
- diversion of medications.

The rate of reductions under circumstances of involuntary treatment cessation can be faster (e.g. up to 4 - 8 mg reductions every 3 - 4 days). Patients who pose a considerable risk to the safety of other patients or staff may be abruptly terminated without a graduated dose reduction.

Transfer to other service providers should always be considered as an alternative to rapid involuntary discharge.

The use of buprenorphine to assist withdrawal from methadone maintenance programs

Many patients on long-term methadone maintenance programs experience considerable difficulties in conventional approaches to withdrawing from methadone, including a prolonged period of withdrawal discomfort and/or relapse to heroin use. Consequently, there is considerable interest in finding alternative methods of withdrawing from methadone maintenance programs.

Two approaches have been recently proposed:

1. the use of opioid antagonists (rapid opioid withdrawal techniques), and
2. transfer to buprenorphine.

The latter approach entails a reduction in the dose of methadone, transfer to buprenorphine, and subsequent withdrawal from buprenorphine. *As there is limited experience or evidence to support these approaches, they cannot be generally recommended at this time.*

Commencing naltrexone following buprenorphine maintenance treatment

There is limited experience in commencing naltrexone following the cessation of maintenance buprenorphine treatment. The initiation of naltrexone must be delayed until several days after the last dose of a full opioid agonist (generally 7 days after heroin use and 10 - 14 days after methadone use). However, naltrexone can generally be initiated within days of the last dose of buprenorphine. The following procedures are recommended.

- In circumstances where the last dose of buprenorphine was 2mg (or less) for at least one week, naltrexone can be initiated 4 - 5 days after the last dose of buprenorphine (providing there has been no heroin use in the previous 7 days).
- Where the last dose of buprenorphine was greater than 2 mg, and to reduce the likelihood of precipitating withdrawal symptoms, the first dose of naltrexone can be delayed until more than 7 days after the last buprenorphine dose.
- The initial dose of naltrexone (12.5 mg orally) should be administered in the morning. The patient should be monitored for up to 3 hours after the first dose of naltrexone for features of opioid withdrawal.
- Symptomatic withdrawal medication should be available for the patient to use in the 12 hours after the first dose of naltrexone, including clonidine (up to 150 mg 3 - 4 hourly), benzodiazepines (eg diazepam up to 5 - 10 mg every 3 - 4 hours as needed), metoclopramide, hyoscine butylbromide and NSAIDS.
- Subsequent doses of naltrexone can be 25 mg for a further 2 - 3 days and then 50 mg per day as usually recommended. Clinical guidelines regarding the use of naltrexone should be consulted (Bell et al 1999).

The high receptor affinity of buprenorphine complicates the interpretation of a naloxone challenge test prior to commencing naltrexone in patients transferring from buprenorphine:

- a negative naloxone challenge test does not preclude the onset of withdrawal on commencing naltrexone;
- a positive naloxone challenge test is likely to reflect recent use of other opioids, and indicates that naltrexone induction should be delayed.

Given the potential for patients to use heroin or other opioids following the cessation of buprenorphine and prior to the commencement of naltrexone, some objective test should be conducted prior to commencing naltrexone in order to exclude recent opioid use. **The naloxone challenge test or appropriate urine drug screening are recommended.**

Transferring to methadone

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

1. **Intolerable side effects to buprenorphine.**
2. **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 clinician as treatment goals. In such instances, treatment with an alternative substitution pharmacotherapy should be considered
3. **Where buprenorphine is not available.** As buprenorphine is a relatively new drug, it may not be available in certain jurisdictions, when the patient is overseas, during periods of incarceration and 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.
4. **Complications with antagonists and analgesics.** In patients who have frequent overdoses, the use of buprenorphine may complicate resuscitation efforts with naloxone. Such patients should be taken off substitution pharmacotherapies or transferred to methadone. Patients requiring frequent additional analgesia for recurrent acute or chronic pain conditions may be better stabilised on full agonists, such as methadone.

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

Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of up to 40mg.

Patients transferring from low doses of buprenorphine (e.g. 4 mg or less) should be commenced on lower doses of methadone (e.g. 20 mg methadone or less). The methadone dose can then be titrated accordingly. Care should be taken not to increase the dose of methadone too quickly, as buprenorphine can diminish the effects of methadone for several days (blockade effect), and there should be adequate time to allow "wash out" of buprenorphine prior to marked increases in methadone dose.

SECTION 4. GUIDELINES FOR THE MANAGEMENT OF HEROIN WITHDRAWAL

4.1 Heroin withdrawal in context

Heroin withdrawal defined

Drug withdrawal is a substance-specific syndrome due to the cessation or reduction of heavy and prolonged drug use. This syndrome causes clinically significant distress and impairment in social, occupational, or other important areas of functioning (DSM IV, 1994). The characteristic features of heroin withdrawal are shown in the following table.

TABLE 7
CLINICAL FEATURES OF THE HEROIN WITHDRAWAL SYNDROME

Increased sweating, lacrimation, rhinorrhoea, urinary frequency.
Diarrhoea, abdominal cramps, nausea, vomiting.
Muscle spasm leading to headaches, back aches, leg cramps, twitching, arthralgia
piloerection, pupillary dilatation, elevated blood pressure, tachycardia.
Anxiety, irritability, dysphoria, disturbed sleep, increased cravings for opioids

Physical symptoms generally commence 6 - 24 hours after last use, peak in severity during days two to four, and generally subside by day seven, while the psychological features of dysphoria, anxiety, sleep disturbances and increased cravings may continue for weeks or even months. Heroin withdrawal is unpleasant, though rarely, if ever, life-threatening. It can, however, significantly complicate concomitant medical or psychiatric conditions.

Objectives of withdrawal services

Heroin users present for withdrawal services for a range of reasons and motivations, and the goals of individual patients may vary considerably. Withdrawal services should not be seen as a stand-alone treatment resulting in prolonged periods of abstinence. Indeed, research suggests that withdrawal treatment alone has little, if any, long-term impact on levels of drug use1 - 4. Unfortunately, many patients, families, friends, and health and welfare professionals hold unrealistic expectations regarding the outcomes of withdrawal services. Many are disappointed when people in these programs either cannot give up their heroin use in the first place, or recommence regular heroin use soon after a withdrawal attempt.

[1-4] Mattick, R.P., & Hall, W. (1996). Are detoxification programmes effective?. *Lancet* 1996; 347: 97-100.

Hubbard, R.L., Marsden, M.E., Rachal, J.V., Harwood, H.J., Cavanaugh, E.R., & Ginzburg, H.M. (1989). Drug abuse treatment a national study of effectiveness. University of North Carolina Press: North Carolina.

Vaillant , G.E. (1988). What does long term follow up teach us about relapse and prevention of relapse in addiction. *British Journal of Addiction*, 83, 1143-57.

Simpson, D.D. & Sells, S.B. (1982). Effectiveness of treatment for drug abuse: An overview of the DARP research program. *Advances in Alcohol and Substance Abuse*, 2, 7-29.

A realistic set of objectives for withdrawal services would be:

1. *To alleviate distress.* Palliation of the discomfort of heroin withdrawal symptoms is an important reason for patients presenting for treatment, and one of the primary aims of withdrawal services.
2. *To prevent severe withdrawal sequelae.* Although heroin withdrawal on its own is almost never life-threatening, withdrawal can present various serious problems:
   - Complication of concomitant medical or psychiatric conditions, e.g. precipitation of an acute psychotic episode in a patient with schizophrenia in remission, or dehydration in an individual with poor baseline nutritional status.
   - Increased risk of overdose following withdrawal. This can occur with resumption of heroin use following the reduction in opioid tolerance that accompanies withdrawal, and due to the combined sedative effects of heroin use and medications used for the management of heroin withdrawal (e.g. benzodiazepines).
3. *To break a pattern of heavy and regular drug use.* Many patients want treatment to end their heroin use completely during the withdrawal episode, intending to stay off it for a set period of time afterwards. However, giving up entirely is not the goal of every patient. Many see withdrawal as a means of reducing levels of heroin use, the severity of their dependence and some of its associated harms. So, although the cessation of heroin use is an optimal outcome, a reduction in heroin use during a withdrawal attempt may still represent a very positive outcome for patients.
4. *To get patients help with any other problems.* Withdrawal services are essentially acute services with short-term outcomes, whereas heroin dependence is a chronic relapsing condition, and positive long-term outcomes are more often associated with longer participation in treatment. Consequently, an important role of withdrawal services is to provide links with post-withdrawal services for those with other physical problems, or psychological or social needs. Optimally, they should have automatic access to drug treatment services, such as 'drug-free' counselling; naltrexone treatment; residential therapeutic communities; self-help programs; or substitution maintenance programs with methadone or buprenorphine. But while some people will be unwilling or unable to continue in ongoing drug treatment programs, they may need - and be grateful for - contacts with welfare services (e.g. accommodation); general support and case management services (e.g. outreach workers); or primary or specialist health services.

4.2 Non-pharmacological aspects in managing heroin withdrawal

As well as the use of medications (pharmacotherapy) the delivery of withdrawal services entails:

- assessment,
- treatment-matching,
- planning for withdrawal, *and*
- supportive care.

The assessment of patients presenting for treatment was discussed in Section 2.3.

Treatment selection

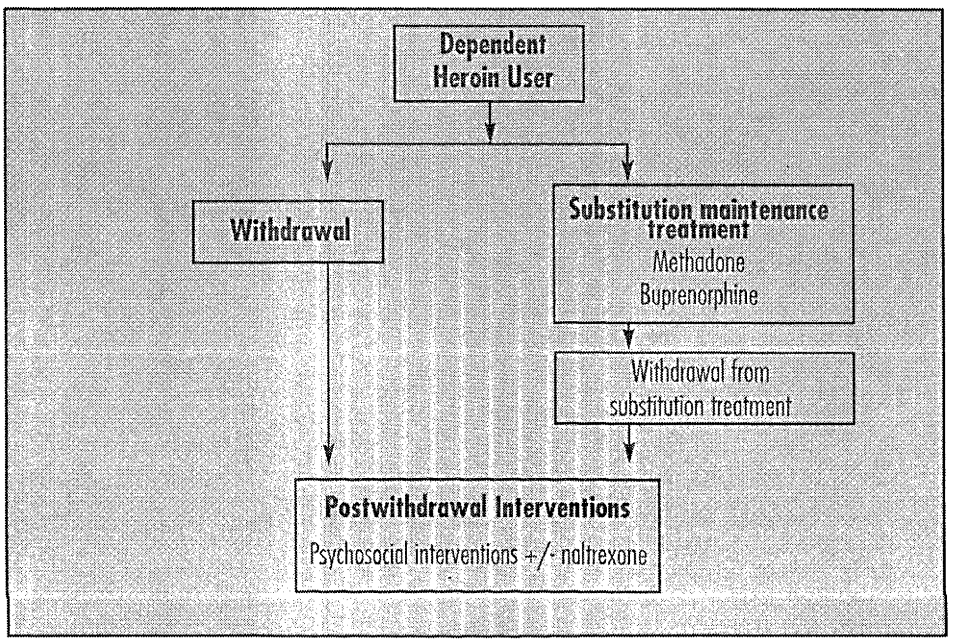
Range of Treatments

Treatment selection is a synthesis of:

- **assessment** of the patient;
- **examination** of the available treatment options and likely outcomes; and
- **negotiation** with the patient around a suitable treatment pathway.

In considering possible modalities, it is important to remember that many people come for treatment with misconceptions and/or inadequate information about the two major options available. These treatment pathways for dependent heroin users are set out in Figure 1.

FIGURE 1
TREATMENT PATHWAYS FOR DEPENDENT HEROIN USERS



In general, withdrawal treatment (such as naltrexone, residential rehabilitation programs, counselling or 12-step programs), is appropriate for those who are considering abstinence-oriented, post-withdrawal treatment, or for those who are not interested in longer-term treatment, and merely want a 'break' from dependent heroin use.

However, maintenance substitution treatment (with methadone or buprenorphine) may be more appropriate for those with significant heroin dependence who will not accept residential rehabilitation or naltrexone treatment, but nevertheless want to stop or permanently reduce their heroin use and all the damage it is causing them. Clinical decision-making should have an evidentiary basis, and patients should be presented with the relative evidence, i.e. the merits and the limitations of treatment outcomes associated with each approach. Within such a framework, there is widespread evidence suggesting that maintenance substitution remains the 'gold standard' treatment for most people with chronic heroin dependence, by virtue of its success in keeping patients in treatment, and reducing drug-related harms.

Once it is established that withdrawal is to be attempted, consideration must be given to the services needed to achieve the best outcome. An optimal setting and adequate supports should be found for each patient, and monitoring arranged for their personal requirements and medication needs.

The optimal setting for withdrawal

Withdrawal can occur in a continuum of settings, ranging from intensive residential (e.g. inpatient withdrawal unit or hospital) to outpatient (e.g. ambulatory or home-based withdrawal services). Most heroin withdrawal attempts can occur in outpatient settings, usually with the assistance of a general practitioner, alcohol and drug worker, or other health professional. However, there are circumstances where a residential setting is indicated (see Table 2).

Some patients may wish to persevere with an outpatient withdrawal, despite unsuitable home environments or having repeatedly 'failed' as outpatients before. Such attempts at outpatient withdrawal may still be the way to go, if it's what the patient really wants. However, clinicians should first negotiate with their patient some mutually agreed criterion of failure (e.g. no significant progress within a week) at which point a switch will be made to an alternative treatment pathway.

TABLE 8
COMPLEX PRESENTATIONS REQUIRING RESIDENTIAL WITHDRAWAL SERVICES

Criteria for intensive residential settings (e.g. inpatient withdrawal unit)
• Unstable medical / psychiatric condition; • Polydrug dependence and withdrawal from multiple drugs; • Unclear medical, psychiatric or drug-use histories requiring close monitoring in a supervised environment.
Criteria for supported residential setting (e.g. community withdrawal unit)
• Unsupportive home environment, such as with other drug users, or without anyone reliable to supervise and support the patient; • Repeated failure at outpatient withdrawal.

Getting organised for withdrawal

Residential withdrawal settings generally provide the full range of services needed for a withdrawal episode. They set out to be drug-free, with support available from staff and fellow patients, and the capacity for continuous monitoring. They usually have access to medical staff and medications. Unfortunately, such inpatient services often have waiting-lists of days or weeks, and the patient may need short-term support in the interim.

Commencing an outpatient withdrawal requires planning, and the mobilisation of the necessary supports and services. Patients should prepare themselves and their environment in advance, to maximise their chance of 'success'. For example, it is very hard to get through withdrawal in the company of others still using heroin.

A safe environment should be organised at the beginning of the withdrawal episode.

A 'safe' place is one where there won't be any drugs easily accessible, and where patients will not be confronted by other drug users. It is important to have caring people to support a patient during withdrawal, and these support people themselves need guidance and information about the process, and suggestions as to what they can reasonably do to help.

Supportive care

Provision of information and strategies for coping.

Patients need information regarding:

- the nature and duration of withdrawal symptoms;
- strategies for coping with symptoms and cravings;
- strategies to remove high-risk situations;
- the role of medication.

Patients often have limited concentration during withdrawal, and information may have to be repeated, perhaps even re-phrased, to be fully understood and absorbed. Written information is valuable in these circumstances, and is also recommended for support people (contact the local drug and alcohol authority for relevant literature).

Counselling during the withdrawal episode should be aimed specifically at supporting the patient through problems associated with withdrawal and in facilitating post-withdrawal links.

Many patients will want to deal with a range of personal, emotional or relationship problems during the withdrawal episode, but they should be persuaded to defer all this until later. Attempting to work through such issues will almost certainly be emotionally painful and anxiety-provoking, which just intensifies cravings and puts the whole withdrawal program in jeopardy. Furthermore, patients in withdrawal tend to be irritable, agitated, tired and run-down; they can suffer from mood swings and poor sleep patterns, as well as difficulty in concentrating. This is definitely not the optimal frame of mind in which to try to solve significant, long-standing life problems. Assure your patients that you understand that they have many important issues to work through to get their lives together again, but it is best to take one step at a time. There will be opportunities for these wider problems to be addressed as part of their ongoing rehabilitation after they get through withdrawal. On the other hand, crisis intervention may be required during a withdrawal episode to ensure adequate accommodation, food or other urgent welfare issues.

In addition to supportive counselling from health professionals and the support of family, friends and peer workers, heroin users may also benefit from 24-hour telephone counselling services for help when others are unavailable. Each state in Australia has telephone alcohol and drug services (see Appendix 3).

Monitoring

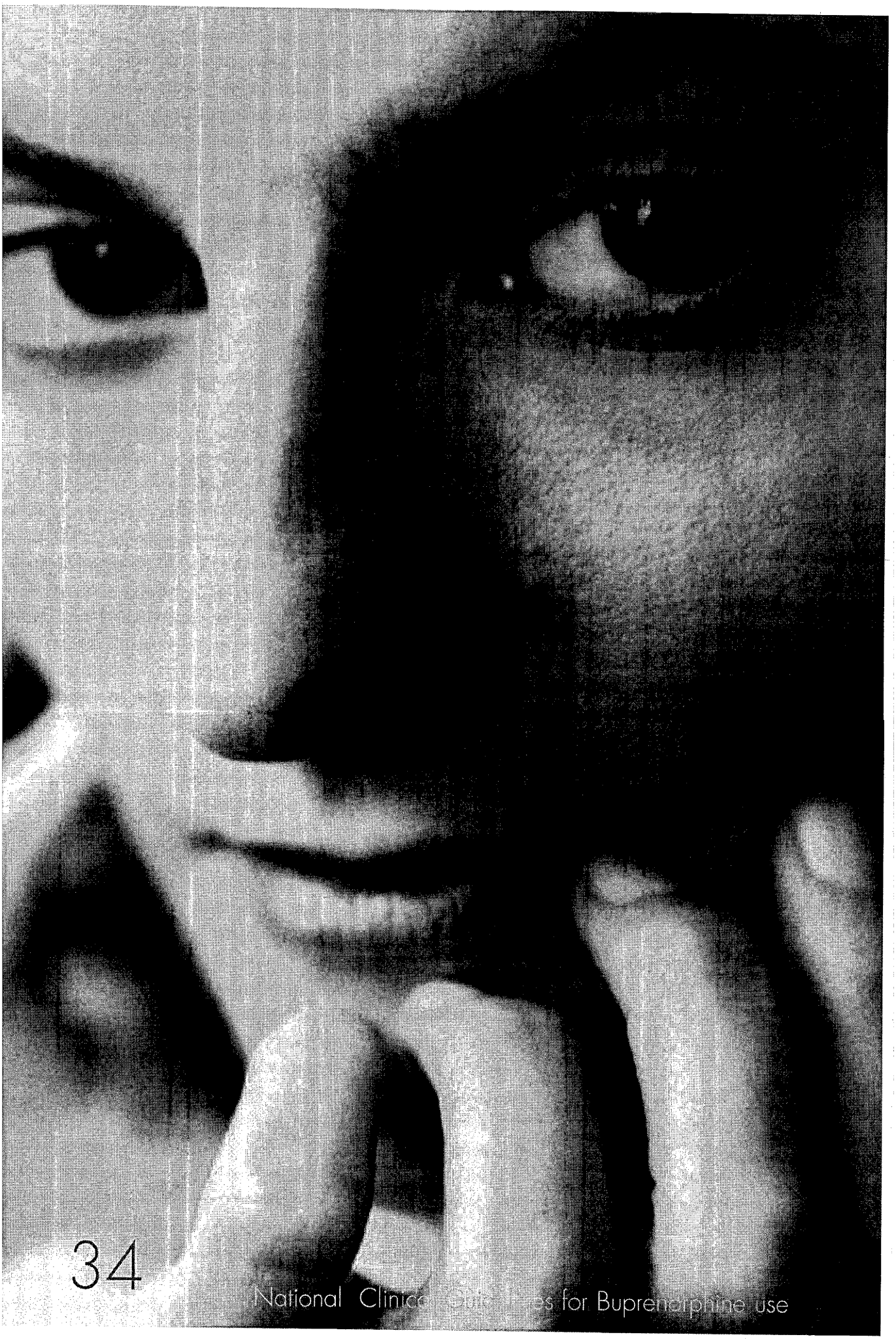
An important part of withdrawal service is regular and frequent monitoring, to check:

- general progress;
- drug use;
- response to the medication(s);
- severity of withdrawal symptoms (which can be facilitated by the use of withdrawal scales);
- complications or difficulties;
- ongoing motivation levels.

Doses of medication can then be adjusted according to the patient's progress. It is recommended that patients undergoing outpatient withdrawal be reviewed by a health professional (eg alcohol and drug worker, general practitioner, or experienced pharmacist) at least daily during the first few days of treatment.

Objective and Subjective Withdrawal Scales

There are various opioid withdrawal scales available to refer to. Subjective scales are far more sensitive to changes in withdrawal severity, and are better predictors of patient outcomes. Objective scales are not only less sensitive, but usually need to be administered by a health professional. They may nevertheless be useful in corroborating subjective ratings, particularly in individuals who are thought to be over- or under- rating their withdrawal severity. Copies of the *Subjective Opioid Withdrawal Scale* and Objective Opioid Withdrawal Scale are provided in Appendix 2.



4.3 Overview of buprenorphine in the management of heroin withdrawal

Efficacy of buprenorphine compared to other withdrawal medication regimes (literature review)

The efficacy of buprenorphine in the management of heroin withdrawal has been compared to other withdrawal approaches in several randomised controlled trials conducted in inpatient [1-3] and outpatient settings [4-6].

In general, these studies have demonstrated buprenorphine to be:

- more effective than symptomatic medications in reducing withdrawal symptoms[1, 2, 3, 5, 6],
- more effective in retaining patients through the withdrawal episode and in post-withdrawal treatment[6]; and
- more effective in reducing heroin use in outpatient settings[6].

Readers are referred to the *Cochrane Review on Buprenorphine for Opiate Withdrawal.*

In the medically ill. Controlled trials comparing buprenorphine with other withdrawal medications for the management of heroin withdrawal in medically-ill patients have not been conducted. Nevertheless, uncontrolled studies have reported favourably on the use of buprenorphine in these circumstances. Furthermore, the sublingual preparation is well suited to individuals who cannot tolerate oral medications. Caution should be used in using buprenorphine or other opioids in individuals with certain medical conditions (see Section 2.1).

The role of buprenorphine in withdrawal

The aim of medication in withdrawal is the reduction of withdrawal symptoms and cravings; it is not the complete removal of all symptoms or the intoxication of the patient.
The clinician should discuss patients' expectations of the medication with them, and address any misconceptions.

In particular, the following principles regarding doses should be understood by the patient:

- Buprenorphine doses that are too high can result in increased rebound withdrawal, prolonged duration of symptoms, increased side-effects, and increased cost of the medication.
- Alternatively, use of doses that are too low can result in unnecessary withdrawal discomfort, continued heroin use and treatment drop-out.
- Continued heroin use or cravings may not be due to inadequate doses of medication. For example, patients who continue to associate with other heroin users, and are present when others are acquiring or using heroin, can expect to have cravings regardless of their dose of buprenorphine.

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1 Cheskin LJ, Fudala PJ, & Johnson RE (1994). A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug and Alcohol Dependence, 36*(2), 115-21;

2 Nigam AK, Ray R, & Tripathi M. (1993). Buprenorphine in opiate withdrawal: A comparison with clonidine. *Journal of Substance Abuse Treatment,* 10, 391-394;

3 O'Connor PG, Carroll KM, Shi J, Schottenfeld RS, et al (1997). Three methods of opioid detoxification in a primary care setting. *Annals of Internal Medicine 127(7)* 526-530;

4 Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, et al (1988). A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. *Clinical Pharmacology & Therapeutics, 247,* 47-53;

5 Schneider U, et al. Buprenorphine and carbanazepine as a treatment for detoxification of opioid addicts with multiple drug misuse: a pilot study. *Addiction Biology 2000,* 5(1) 65-69; and

6 Lintzeris N, Bell J, Bammer G, Rushworth L et al (2000) A randomised controlled trial of buprenorphine for the management of outpatient heroin withdrawal. paper presented at the November 2000 National Methadone Conference, Melbourne, Australia.

Buprenorphine dosing in withdrawal
Over-dosing doesn't help
Under-dosing doesn't help
Problems encountered may not be the fault of the medication dose

Preventing precipitated withdrawal on commencing buprenorphine

Buprenorphine can precipitate opioid withdrawal in someone who has recently used heroin (within the past 6 hours) or methadone (See Section 3.2). Buprenorphine-precipitated withdrawal typically commences 1- 4 hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. Patients experiencing severe discomfort may benefit from symptomatic withdrawal medication (eg clonidine 100 mcg 3 - 4 hourly as required), and should be directed to see their prescribing doctor.

Patients should not receive the first dose of buprenorphine if they are experiencing heroin effects. In practice, it is recommended that patients wait at least 6 hours after their last use of heroin prior to receiving their first buprenorphine dose. It is preferable to withhold the first dose until the patient is beginning to experience the early features of withdrawal. If there are doubts or concerns, the patient should be asked to come back for dosing later in the day, or alternatively, a lower initial dose can be dispensed (e.g. 2 or 4 mg) as it is less likely to precipitate withdrawal than a high initial dose.

Preventing precipitated withdrawal on commencing buprenorphine

No heroin for at least 6 hours: severe discomfort may need palliation.

No methadone for at least 24 hours.

No buprenorphine if there are obvious heroin effects : wait for withdrawal signs , or send away to return next day.

Use of ancillary medications in conjunction with buprenorphine

Buprenorphine provides general relief of withdrawal symptoms, so that other symptomatic medications for opioid withdrawal are not routinely required. An exception to this rule is when patients experience difficulty sleeping during withdrawal, and may benefit from the limited use of benzodiazepines as a hypnotic. However, benzodiazepines should not be used routinely from the outset of the withdrawal episode, but rather should be added, as required, following clinical review of the patient. Low doses of a hypnotic (eg temazepam 10-20 mg nocte, oxazepam 15-30 mg nocte or nitrazepam 5-10 mg nocte) are recommended, with daily dispensing from the pharmacy (or supervised by a responsible adult). Under normal circumstances, benzodiazepines should not be continued beyond several days, with non-pharmacological approaches being encouraged (sleep hygiene strategies).

Continued use of heroin and other drugs

Patients who keep on using heroin during buprenorphine treatment may have difficulty stabilising on the medication, and may continue to experience features of precipitated withdrawal after each dose.

It is very important for patients to abstain from heroin use until they are stabilised on buprenorphine.

Persistent features of precipitated withdrawal discomfort may be grounds for transfer to methadone, or other withdrawal medications.

The unsupervised use of other sedative drugs, such as benzodiazepines, alcohol, other opioids, and tricyclic antidepressants, in combination with buprenorphine, can be extremely dangerous, resulting in respiratory depression, coma and death.

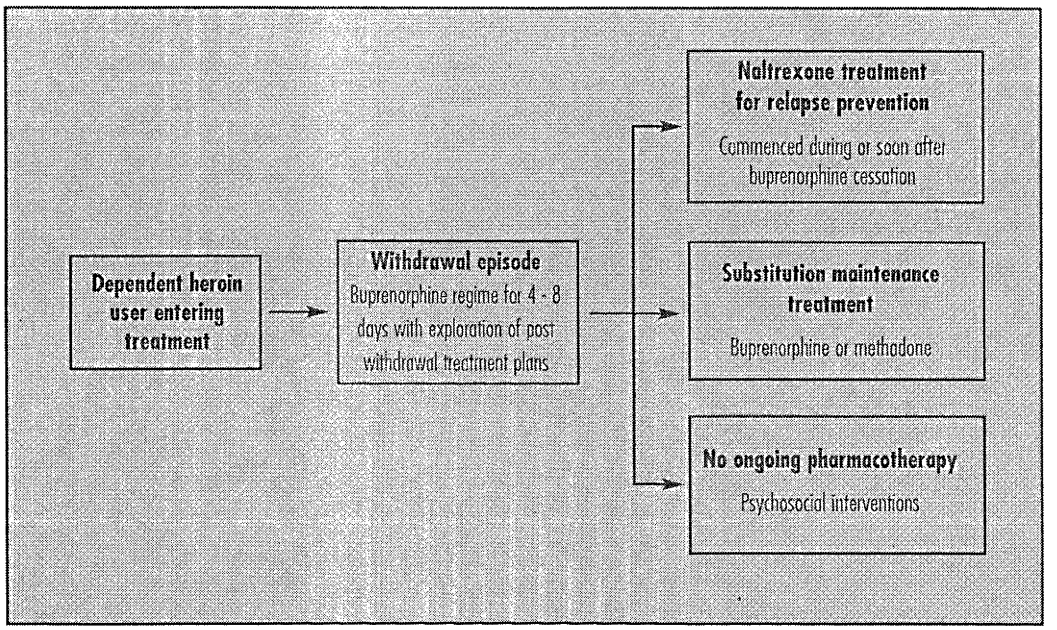
All patients should be informed verbally and in writing of these risks. Intoxicated patients should not be dosed with buprenorphine or sedative medications.

Gateway model of treatment with buprenorphine

Buprenorphine is particularly useful in managing heroin withdrawal, in that it is not only effective during the withdrawal period, but also facilitates links to post-withdrawal treatment. Many patients entering withdrawal treatment do so without necessarily having considered all their treatment options, simply 'hoping' that an attempt at withdrawal will be sufficient to stop heroin use.

The use of buprenorphine for several days generally alleviates withdrawal symptoms without significant sedation, thereby allowing patients and clinicians to examine post-withdrawal issues relatively early on in the withdrawal episode. (On many other withdrawal medications, such as benzodiazepines or clonidine, patients are either so psychologically distressed or so heavily sedated that this would not be possible.) A formal review of treatment plans should be structured several days into the withdrawal episode, at which time treatment can be tailored accordingly. For those patients who have successfully refrained from heroin use during withdrawal, and who are considering longer-term naltrexone treatment, naltrexone can be initiated either during buprenorphine administration or after a short course is ceased. Patients who are not interested in ongoing pharmacotherapy treatment can cease a short course of buprenorphine with minimal rebound discomfort. Alternatively, those patients who want to extend the duration of their withdrawal program, or have reconsidered the role of a maintenance treatment program, can continue buprenorphine treatment over a longer period of time. Care should be exercised in transferring patients with short histories of heroin dependence from short-term withdrawal programs on to long-term substitution maintenance programs.
These treatment pathways are shown in Figure 2.

FIGURE 2
GATEWAY MODEL OF TREATMENT WITH BUPRENORPHINE



4.4 Buprenorphine regimens in outpatient withdrawal settings

Buprenorphine is long-acting, and so is well suited to outpatient withdrawal settings, allowing for once-a-day supervised dosing.

Take-away doses are not recommended during the initial treatment period, and are subject to jurisdictional regulations.

Patients unable to attend an authorised pharmacy daily for supervised dispensing should consider alternative withdrawal medications.

The recommended duration of treatment with buprenorphine for the management of heroin withdrawal is 4 - 8 days. This short regime ensures the treatment covers the time when heroin withdrawal symptoms are most severe (typically up to 4 or 5 days), and then is promptly discontinued, thereby minimising rebound withdrawal phenomena and limiting the duration of withdrawal discomfort.

There is no conclusive evidence of an optimal buprenorphine dosing regime for heroin withdrawal. In general, daily buprenorphine doses of 4 - 16 mg appear to be most effective in reducing withdrawal severity and heroin use. The reader is referred to the Cochrane Review, for an analysis of relevant studies. The following short-term outpatient withdrawal regime is recommended:

TABLE 9
RECOMMENDED SHORT OUTPATIENT REGIMES

	Proposed regime	Recommended lower and upper limits
Day 1	6 mg	4 to 8 mg
Day 2	8 mg	4 to 12 mg
Day 3	10 mg	4 to 16 mg
Day 4	8 m	2 to 12 mg
Day 5	4 mg	0 to 8 mg
Day 6		0 to 4 mg
Day 7		0 to 2 mg
Day 8		0 to 1 mg
Total dose	36 mg	

Some flexibility is allowable in doses to accommodate a range of factors, such as amount of heroin use and psychological condition, impacting on each patient's individual dosing requirements and withdrawal severity.

Review by a trained health professional is recommended on a daily basis during the first few days of the withdrawal regime. This is important so that doses can be adjusted, if necessary, and any difficulties being experienced on the medication can be addressed. It is also needed to ensure provision of appropriate support care and monitoring.

Titration: Buprenorphine doses should be titrated against severity of withdrawal features and cravings for heroin use, actual use of heroin or other drugs, and occurrence of side-effects.

Flexible dosages Doctors may choose to prescribe a fixed daily dose (e.g. Day 1: 6 mg, Day 2: 8 mg, Day 3: 10 mg etc) or, alternatively, prescribe a flexible regime with upper and lower limits on any particular day and instructions for the pharmacist or withdrawal worker regarding dose titration (e.g. Day 1: 6 mg, Day 2: 6-10 mg; Day 3: 8-12 mg etc).

It is a good idea to attempt a short-term regime, and schedule a formal review of progress within a few days. At this review, the clinician and patient can together consider the available post-withdrawal treatment options (see Section 4.6).

Those patients who remain ambivalent about long-term post-withdrawal treatment, and have not been able to cease their heroin use, may need referral to an inpatient supervised withdrawal program. Alternatively, an extension of the withdrawal regime over several weeks may be warranted.

However, there are good reasons for not prolonging buprenorphine treatment:

- Intake for more than several days commonly produces rebound withdrawal when ceased, typically starting 1 - 3 days after the last dose of buprenorphine, peaking 2 - 5 days after the last dose, and with some symptoms persisting several weeks.
- Prolonged, probably unsuccessful, attempts at withdrawal can be demoralising for the patient, resulting in lowered capability, self-esteem, and/or confidence in the treatment provider. For this reason, a limit on the time spent on a gradual reduction regime should be discussed with the patient early in the program.

Longer-term maintenance substitution treatment (with buprenorphine or methadone) should be recommended to patients who:

- cannot stop, or markedly reduce, their heroin use during the withdrawal episode;
- relapse into regular heroin use as the dose of buprenorphine is reduced or ceased;
- do not feel confident about maintaining abstinence but do not want to relapse to dependent heroin use and the associated harms.

It is recommended that such patients stabilise on a maintenance substitution medication for a longer period of time before coming off their maintenance treatment, to give them the opportunity to first distance themselves from heroin use and possibly to address any problematic psychological and social issues which may be distressing them.

4.5 Buprenorphine for heroin withdrawal in residential settings

Buprenorphine is well suited to use in inpatient withdrawal settings, given its ability to alleviate the discomfort of withdrawal symptoms without significantly prolonging their duration.

It is recommended that an interval of at least 2 - 3 days be available from the time of the last buprenorphine dose to the time of planned discharge.

Duration of dosing will be determined by the length of admission available. e.g. in a 7-day admission, treatment will be limited to the first 4 - 5 days.

Approaches to dispensing in inpatient settings will depend on the level of supervision and staffing available. Titration regimes generally require nursing staff who can administer withdrawal scales and S8 medications, so places with limited access to nursing staff may be better suited to fixed regimes with the option of additional 'rescue' doses as required.

The additional rescue doses should only be administered:

- at least 4 hours after the earlier dose; and
- if the patient is experiencing moderate or severe withdrawal discomfort.

Buprenorphine doses in inpatient settings can generally be lower:

- outpatient regimes must accommodate higher cravings and exert blockade effects;
- outpatient regimes are generally limited to once-a-day dosing.

An evening dose (between 5 PM and 10 PM) is recommended, to allow relief of withdrawal symptoms until the morning. *N.B Buprenorphine should not be administered if there are any features of intoxication or sedation.*

The following regime is recommended for an admission time of approximately one week, and can be tailored accordingly:

TABLE 10
PROPOSED INPATIENT WITHDRAWAL REGIME

Day	Buprenorphine S/L tablet regime	Total daily dose
Day 1	4 mg at onset of withdrawal, & additional 2 to 4 mg evening dose prn	4 to 8 mg
Day 2	4 mg mane, with additional 2 to 4 mg evening dose prn	4 to 8 mg
Day 3	4 mg mane, with additional 2 mg evening dose prn	4 to 6 mg
Day 4	2 mg mane prn; 2 mg evening prn	0 to 4 mg
Day 5	2 mg prn	0 to 2 mg
Day 6	no dose	
Day 7	no dose	
		Total proposed dose = 12 to 28 mg

This regime serves as a guide only, and considerable individual variation in withdrawal severity and medication requirements should be expected.

Post-withdrawal options should be explored prior to discharge (see next section).

- Naltrexone: Patients commencing naltrexone treatment should do so during their admission.
- Buprenorphine: Patients wishing to commence buprenorphine maintenance treatment should continue their buprenorphine as inpatients until transfer to a community-based provider can be organised.

4.6 Transition to post-withdrawal treatment

Transition to maintenance treatment

Buprenorphine maintenance treatment

Transition to a buprenorphine maintenance treatment program simply requires the continuation of treatment, often with upward titration of the dose to achieve optimal maintenance dose levels (eg. 12 - 24 mg per day). The reader is referred to Section 3.

Methadone maintenance treatment

The transition to methadone maintenance treatment requires the cessation of buprenorphine, with the first dose of methadone given at least 24 hours later. The reader is referred to Section 3.9 of these guidelines.

Commencing naltrexone treatment after short duration buprenorphine withdrawal

Seven-day abstinence: One of the difficulties for many heroin users in commencing naltrexone treatment is staying off heroin for a whole week before the first dose, to avoid the precipitation of withdrawal. The recommended 7-day opioid-free period (Bell et al 1999) also limits the use of opioids (such as methadone, codeine or d-propoxyphene) as withdrawal medications, as they delay even further the initiation of naltrexone treatment.

The pharmacology of buprenorphine allows the commencement of naltrexone without major delays. This is thought to be because buprenorphine has a higher affinity for opioid receptors than naltrexone, so the naltrexone does not significantly displace buprenorphine or cause the precipitation of severe opioid withdrawal.

From buprenorphine to naltrexone: Researchers are yet to determine the optimal method of inducting on to naltrexone from buprenorphine treatment, but two general procedures have been used:

1. commencing low doses of naltrexone whilst continuing buprenorphine;
2. ceasing buprenorphine and commencing naltrexone several days later.

Sample dosing regimes for the two approaches are shown in the following table.

TABLE 11
NALTREXONE INDUCTION REGIMES

Day	Sample buprenorphine regime (S/L tablets)	Early NTX induction regime (oral)	Delayed NTX induction regime (oral)
1	6 mg	0	0
2	10 mg	0	0
3	8 mg	12.5 mg	0
4	6 mg	12.5 mg	0
5	4 mg	25 mg	0
6		50 mg	0
7		50 mg	0
8		50 mg	0 or 12.5 mg
9		50 mg	12.5 mg
10		50 mg	25 mg
11		50 mg	50 mg

dvantages and disadvantages of each approach are explored in Table 12 below.

Which procedure is best?

Both procedures result in an increased severity of opioid withdrawal following the first dose of naltrexone. This typically commences 90 minutes to 4 hours after the first naltrexone dose, peaks around 3 – 6 hours after the naltrexone dose, and generally subsides in severity within 12 – 24 hours. The withdrawal is frequently experienced as moderate to severe at its peak. Subsequent doses of naltrexone produce considerably less severe withdrawal discomfort.

Most patients undergoing this procedure request symptomatic medication, and clonidine (100 – 150 mcg every 3 – 4 hours as required) and a benzodiazepine (eg diazepam 5 mg 3 – 4 hourly, maximum of 30 mg in a day, as required) should be prescribed.

Most patients find either procedure tolerable.

All patients need supervision and access to the prescribing doctor.

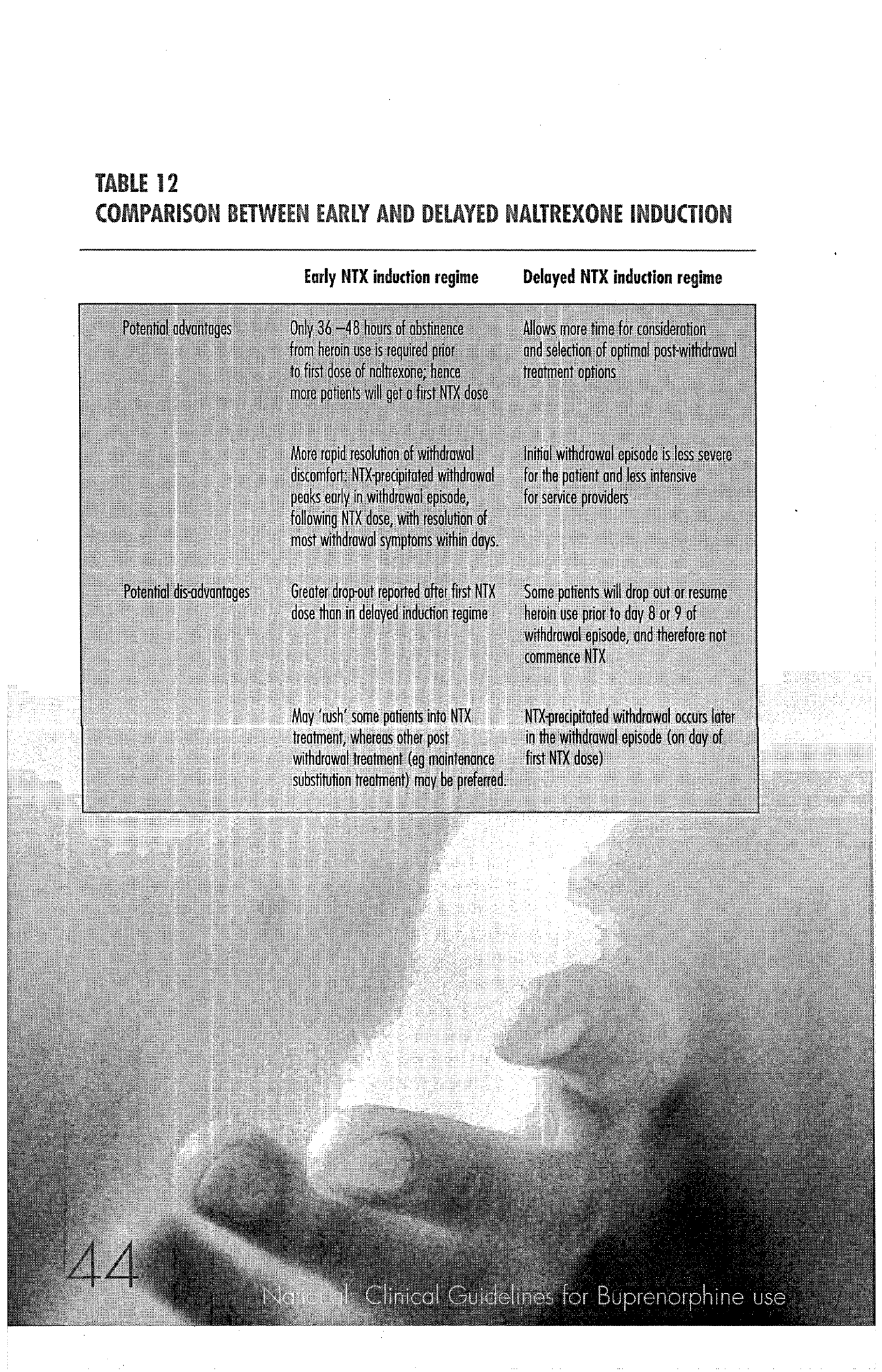
Outpatient setting is suitable only:

- where there is a suitable and responsible person to support the patient where they live, and to supervise medications; and
- if the prescribing doctor is available to address any potential complications.

PREPARE IN ADVANCE
for the increase in withdrawal severity, the role of medications, and the risks of using heroin to overcome the withdrawal symptoms

TABLE 12
COMPARISON BETWEEN EARLY AND DELAYED NALTREXONE INDUCTION

	Early NTX induction regime	Delayed NTX induction regime
Potential advantages	Only 36 –48 hours of abstinence from heroin use is required prior to first dose of naltrexone; hence more patients will get a first NTX dose	Allows more time for consideration and selection of optimal post-withdrawal treatment options
	More rapid resolution of withdrawal discomfort: NTX-precipitated withdrawal peaks early in withdrawal episode, following NTX dose, with resolution of most withdrawal symptoms within days.	Initial withdrawal episode is less severe for the patient and less intensive for service providers
Potential dis-advantages	Greater drop-out reported after first NTX dose than in delayed induction regime	Some patients will drop out or resume heroin use prior to day 8 or 9 of withdrawal episode, and therefore not commence NTX
	May 'rush' some patients into NTX treatment, whereas other post withdrawal treatment (eg maintenance substitution treatment) may be preferred.	NTX-precipitated withdrawal occurs later in the withdrawal episode (on day of first NTX dose)



SECTION 5. COMPLICATIONS OR ADVERSE EVENTS WITH BUPRENORPHINE TREATMENT

5.1 Side Effects

Similar to those of other opioids

The reported side-effects of buprenorphine are qualitatively similar to those of other opioids used in maintenance treatments (methadone, morphine, LAAM). An adverse drug reaction is any undesired or unintended effect of drug treatment. Adverse drug reactions may be predictable (on the basis of the drug's known actions) or unpredictable (eg allergic drug responses, idiosyncratic drug reactions).

Most common is opioid withdrawal

In large, multicentre trials of buprenorphine maintenance treatment, the most common adverse event (reported in over 30% of patients) has been opioid withdrawal symptoms, and these reports have been most common in patients on low doses of buprenorphine (eg 1 mg daily). Other commonly reported adverse events reported by the manufacturer are shown in the following table.

TABLE 13
COMMONLY REPORTED SIDE EFFECTS TO BUPRENORPHINE

Adverse event	Proportion of patients reporting adverse event	Relation to dose
Headache	8.7 %	Appears unrelated to dose
Constipation	7.5 %	More common on higher doses
Insomnia	7.3 %	Appears unrelated to dose
Asthenia	6.1 %	Appears unrelated to dose
Somnolence	4.3 %	Appears unrelated to dose
Nausea	3.5 %	More common on doses > 8 mg
Dizziness	2.7 %	More common on higher doses
Sweating	2.7 %	Appears unrelated to dose

Most are mild

In general, most adverse events to buprenorphine are mild, well tolerated, and typically occurring early in treatment with symptoms subsiding over time.

Management of the side-effects, which will depend on their nature and severity, should be negotiated between patient and clinician. Conventional strategies should be adopted to manage opioid-related side effects (eg constipation) (see Table next page).

TABLE 14
COMMON SIDE EFFECTS WITH OPIOID MAINTENANCE DRUGS

Not all of these may occur with Buprenorphine

Side effect	Common causes	Things that you can do
Feeling drowsy after taking dose	• Dose too high	Lower the maintenance dose and review other medications the patient may be taking
	• Other drug use (legal or illegal)	Review use of sedative and other drugs affecting cognition
Withdrawal symptoms maximal before next dose	• Dose too low	Raise maintenance dose or review other drugs patient is taking
	• Changes in legal or illegal drugs that patient may be using.	
Withdrawal precipitated by buprenorphine dose	• Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (eg heroin methadone, morphine)	Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal
Headache	• Common in first week of buprenorphine particularly if buprenorphine dose too high.	Side effect is transient and generally treatment. mild. Consider aspirin or paracetamol.
	• Other causes of headache	Exclude other causes
Nausea	• Common early in treatment,	Side-effect usually transient (days). Avoid rapid dose increases.
	• Usually mild and transient.	Consider dose-reduction if persistent
Constipation	• All opioids do this. Will be made worse by lack of dietary fibre, fluid intake or exercise	Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise.
Weight gain, particularly for women	• Fluid retention caused by opioids - more likely on high doses	Lower dose
	• Eating more while in treatment; high salt intake	Reduce fat and salt in diet, exercise regime
Poor sleep	• Dose too low and causing withdrawal at night; or	Review maintenance dose and review other medications
	• Dose too late at night, causing stimulation at time of peak effects	Follow sleep hygiene recommendations.
	• Other drugs (particularly stimulants in the evening, such as coffee, nicotine, amphetamines)	
	• General anxiety or irregular sleep pattern	

Amenorrhoea or oligomenorrhoea	• All opioids can do this • May be related to lifestyle stressors, poor diet, and general poor health	Periods may return after cessation of heroin use, or following withdrawal from opioids. Address other causes
Lowered sex drive	• More common with a high dose • Can be many other psychological factors (such as anxiety, poor relationship with partner etc...)	Review dose
Dental problems	• All opioids reduce saliva flow • Poor diet, dental hygiene	Encourage teeth hygiene, dental floss and use of sugar free gum. Dental check-up. Reduce intake of sugary drinks and sweet food

Modified from Dunlop et al (1996) Getting Through Methadone Withdrawal. Turning Point ADC: Fitzroy

5.2 Overdose

Less risk of lethal overdose: The risk of lethal overdose on buprenorphine in an opioid-tolerant individual is less than that associated with the use of other opioid medications, such as methadone. This is due to the ceiling dose response effects of buprenorphine.

Risk present with the opioid-naïve: An opioid-naïve individual may overdose with a high dose of buprenorphine, All patients should be commenced on low doses (2 - 8mg), and even lower doses (2 or 4 mg) should be considered where there is some doubt regarding the degree of neuroadaptation prior to commencing treatment.

Safer around children: The poor bioavailability of buprenorphine when taken orally reduces the risk of accidental overdose by children.

Risk increases when mixed with other sedatives: While overdose on buprenorphine is relatively uncommon, there is a greater risk when it is combined with other sedative drugs, such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and major tranquillisers. ***Several such deaths have been reported.***

High doses of antagonist needed for overdose reversal: Buprenorphine has a high affinity for μ opioid receptors, and is not easily displaced by the antagonist, naloxone. *Doses of 10 - 30 times the normal naloxone doses used to reverse heroin overdose (up to 10 - 35 mg/70 kg) may be required to reverse the effects of buprenorphine toxicity.*

In the event of depression of respiratory or cardiac function:

1. **re-establish patient airway**
2. **begin assisted or controlled ventilation.**

   Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.
3. **the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.**

5.3 Intoxicated presentations

Intoxicated patients should not be dosed with buprenorphine, and patients should be made aware of this prior to the commencement of treatment. They may re-present later in the day (or the following day) for dosing. The prescribing medical officer must be notified prior to the next dose being administered.

Patients with a history of repeated intoxicated presentations should be reviewed by the treating doctor and the treatment plan re-considered.

5.4 Incorrect dose administered

The risks associated are not as severe with an incorrect dose of buprenorphine as with other opioid medications. In the event of an incorrect dose being administered:

1) the dispensing pharmacist (or nursing staff) should immediately notify the patient and medical officer of the error;
2) the patient should be warned of the likely consequences (increased sedation / drowsiness may occur for several hours afterwards), and warned against any additional drug use, and driving or operating machinery, for the rest of the day;
3) the patient should be monitored for at least 6 hours after an incorrect dose by trained health professionals or in the Accident & Emergency Department of a hospital, if any of the following circumstances apply:
   a) the patient is sedated following the dose (for any reason);
   b) the patient is new to substitution treatment (within the first 2 weeks of maintenance treatment);
   c) the regular daily buprenorphine dose is ≤ 4 mg, and the patient was incorrectly administered a dose of ≥ 16 mg.
   d) a buprenorphine dose of ≥ 64 mg was incorrectly administered (regardless of routine daily dose)

The patient should be reviewed by the prescribing medical officer prior to the next dose of buprenorphine. It may be that a lower dose is required the following day (in effect, a two-day dose has been administered), or no dose.

5.5 Diversion of buprenorphine

Easily diverted. As buprenorphine is a sublingual tablet, it can easily be diverted by patients. They may try to avoid taking their buprenorphine as directed, at the pharmacy, for the following reasons:

- to take sublingually at a later time;
- to inject (or snort) the medication instead of the sublingual route of administration;
- to give or sell to another person.

There are potential risks associated with these practices.

1. Patients not taking their full dose of buprenorphine may be more likely to use heroin.
2. Injection of buprenorphine is associated with risks of venous thrombosis, thrombophlebitis and other local infections; and of systemic fungal or bacterial infections (particularly in circumstances where patients inject buprenorphine that has already been in their mouth).
3. Diversion of the medication to other people can result in overdose (through combination with other sedating drugs) or precipitation of withdrawal (e.g. when taken by a patient on a high dose of methadone).

To minimise the risks of diversion, the following safeguards are recommended:

- Pharmacists should note carefully whether the full number of buprenorphine tablets have been taken sublingually by the patient, who should not be allowed to handle the tablets prior to dosing.
- Pharmacists (or their assistants) should supervise the patient closely until the tablets have dissolved (about 3 - 7 minutes). However, inevitably there will be times when this is just not possible.

In circumstances where diversion of buprenorphine is a possibility (for example, where there is inadequate time for supervision), the following strategies are recommended.

- The pharmacist and medical practitioner should warn the patient of the potential health risks associated with misuse of the medication.
- The pharmacist should crush the tablets, administering a fine powder sublingually to reduce the time required for absorption and the potential for medication to be removed from the patient's mouth. While the effect of crushing tablets on the bioavailability of the sublingual preparation has not been examined, it is thought to have little clinical impact.

Where there is ongoing misuse of the medication, patients should be warned that they may have to be transferred from buprenorphine treatment to methadone, which is easier to supervise.

5.6 Investigations

Urine testing: Urine tests reveal someone's drug use in the preceding 48 - 72 hour period. This is an expensive investigation and should be conducted only if the results are likely to be important.

At the time of writing, Australian pathology laboratories do not routinely test for buprenorphine in the urine, and it will not be detected as an opioid.

The only possible indications for buprenorphine urine screening are:

- to confirm whether a patient has taken the take-away doses;
- to see if a patient (not in treatment) is abusing buprenorphine;

5.7 Analgesia requirements for patients on buprenorphine

Patients maintained on buprenorphine will have a diminished response to opioids prescribed for analgesia. This is because of the 'blocking' effect of the buprenorphine on full opioid agonists. Consequently, patients on buprenorphine who suffer severe or chronic pain will require considerably higher doses of opioid analgesia than individuals not in buprenorphine treatment.

The principles of analgesic management are:

1. **Use non-opioid analgesics** where possible (such as aspirin, NSAIDS, paracetamol).
2. **Maintain buprenorphine dose if acute or subacute analgesia is required.** A temporary increase in buprenorphine dose may provide additional analgesic cover. *Patients who develop chronic pain which is not responding to buprenorphine, and who require ongoing additional analgesia, may require transfer to methadone treatment.*
3. **Where additional opioid analgesia is required**, the dose of opioid (eg morphine) should be clinically titrated according to clinical response. The dose of analgesic should be closely monitored if buprenorphine is reduced or stopped. The concern is that high morphine doses will be required while buprenorphine is exerting 'blockade'

effects, but as the buprenorphine levels reduce (with a corresponding reduction in the 'blocking' effects of buprenorphine), there is the potential for over-sedation - or even overdose - from the high morphine doses. If buprenorphine treatment stops completely (eg due to the hospital pharmacy not having the drug, doctor ignorance or patient non-cooperation), the dose of morphine needs to be closely monitored every day for at least 4 - 5 days after the last buprenorphine dose. It will probably have to be reduced over time, to avoid an overdose.

5.8 Pregnancy and lactation

Inadequate research has been conducted on the effects of buprenorphine during pregnancy and lactation in humans. For this reason, and because of certain adverse effects reported in animal trials, buprenorphine is contra-indicated for both pregnant and lactating women.

BUPRENORPHINE IS CONTRA-INDICATED FOR PREGNANT AND BREASTFEEDING WOMEN

Buprenorphine is a Category C drug, which has implications for pregnancy.

ADEC states that this group of drugs "has caused, or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible." Opioid analgesics are capable of causing respiratory depression in the neonate, and withdrawal symptoms have been reported in cases of prolonged use.

Any woman patient seeking maintenance treatment who might become pregnant should be counselled on the potential risks of buprenorphine during pregnancy, with this information being reinforced and presented to them in writing.

Any woman patient seeking maintenance treatment who might become pregnant should be counselled on the potential risks of buprenorphine during pregnancy, with this information being reinforced and presented to them in writing.

Women wanting to become pregnant are better advised to consider methadone maintenance, or alternative forms of treatment for the management of their heroin dependence.

Reliable forms of contraception should be recommended to women not wishing to become pregnant.

The pregnant heroin user not in treatment

Heroin-dependent women who become pregnant should be advised to commence maintenance substitution treatment, with methadone the preferred option.

The patient who becomes pregnant while in buprenorphine treatment.

If this happens, advice should be sought from a specialist multi-disciplinary unit providing obstetric and paediatric services for chemically-dependent women and their babies. Counselling should be provided regarding treatment options, and support offered when a choice of action is made.

- **The continuation of pregnancy and transfer to methadone maintenance treatment.** This is the preferred option for the woman who wishes to continue with her pregnancy. She should be admitted to hospital for transfer to methadone, allowing for close observation of both her and the fetus, for evidence of withdrawal or distress.

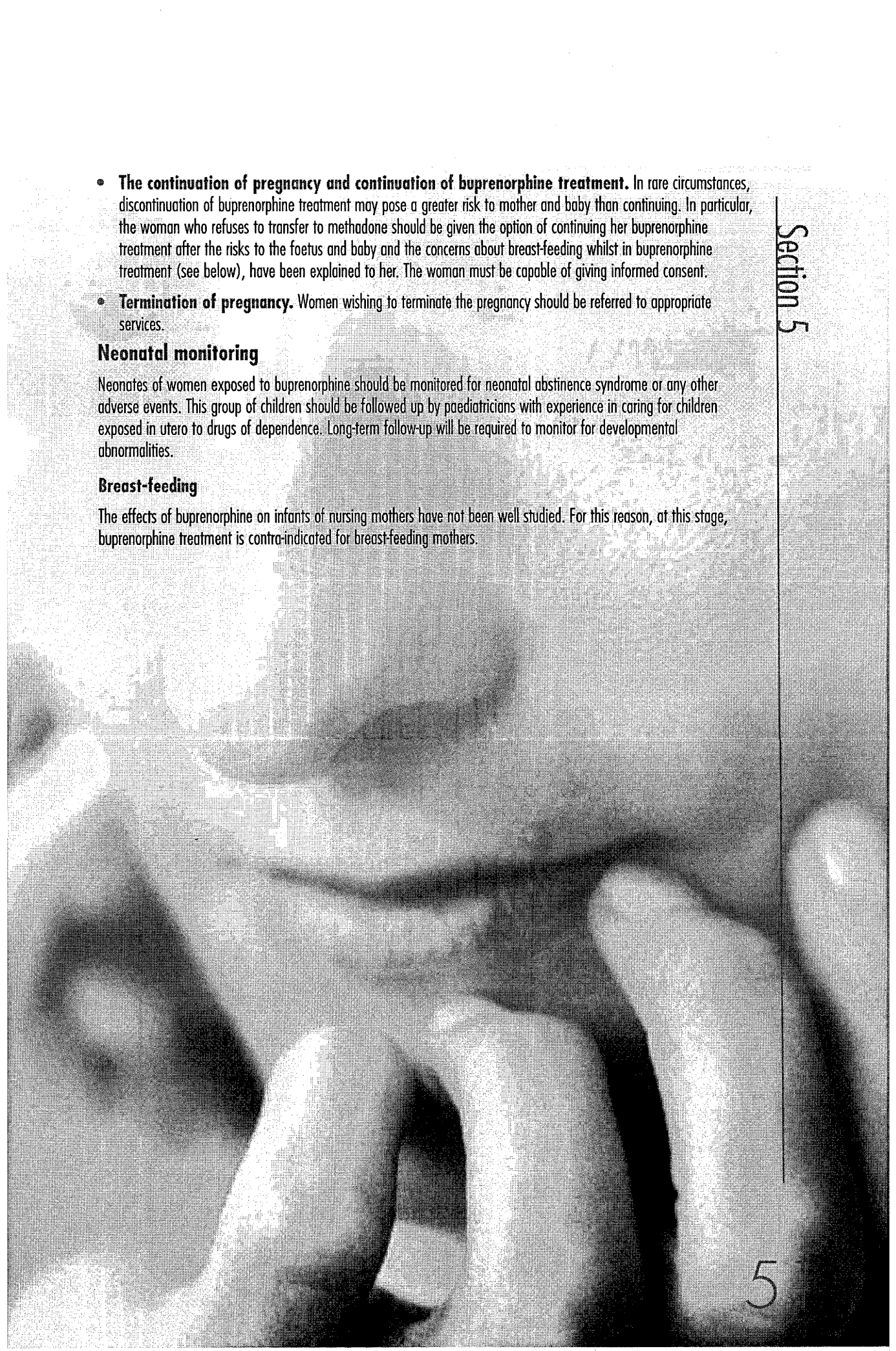
- **The continuation of pregnancy and continuation of buprenorphine treatment.** In rare circumstances, discontinuation of buprenorphine treatment may pose a greater risk to mother and baby than continuing. In particular, the woman who refuses to transfer to methadone should be given the option of continuing her buprenorphine treatment after the risks to the foetus and baby and the concerns about breast-feeding whilst in buprenorphine treatment (see below), have been explained to her. The woman must be capable of giving informed consent.
- **Termination of pregnancy.** Women wishing to terminate the pregnancy should be referred to appropriate services.

Neonatal monitoring

Neonates of women exposed to buprenorphine should be monitored for neonatal abstinence syndrome or any other adverse events. This group of children should be followed up by paediatricians with experience in caring for children exposed in utero to drugs of dependence. Long-term follow-up will be required to monitor for developmental abnormalities.

Breast-feeding

The effects of buprenorphine on infants of nursing mothers have not been well studied. For this reason, at this stage, buprenorphine treatment is contra-indicated for breast-feeding mothers.



SECTION 6. WRITING PRESCRIPTIONS & DISPENSING BUPRENORPHINE

Buprenorphine is an opioid and is registered as an S8 medication. Special precautions should be taken by clinicians in the prescribing, handling, dispensing and storage of the medication.

6.1 Writing Prescriptions

Prescriptions for buprenorphine may be on a standard prescription form. A valid prescription must specify the following:

- the name and address of the prescribing doctor who has been issued with the permit to prescribe;
- the patient's name and address;
- the date of the prescription;
- the preparation to be dispensed (buprenorphine sublingual tablets);
- the dose of buprenorphine to be dispensed in mg (words and numbers);
- different dose schedules must be written separately (ie 24-hour doses, 2-day or 3-day doses), specifying the days of the week the patient is to be dosed;
- the beginning and end dates of the prescription.

It is strongly recommended that the name of the pharmacy be included on the prescription.

6.2 Protocols for administering buprenorphine

Procedures prior to dosing

Staff authorised to administer buprenorphine include a pharmacist, a medical practitioner or two registered nurses.

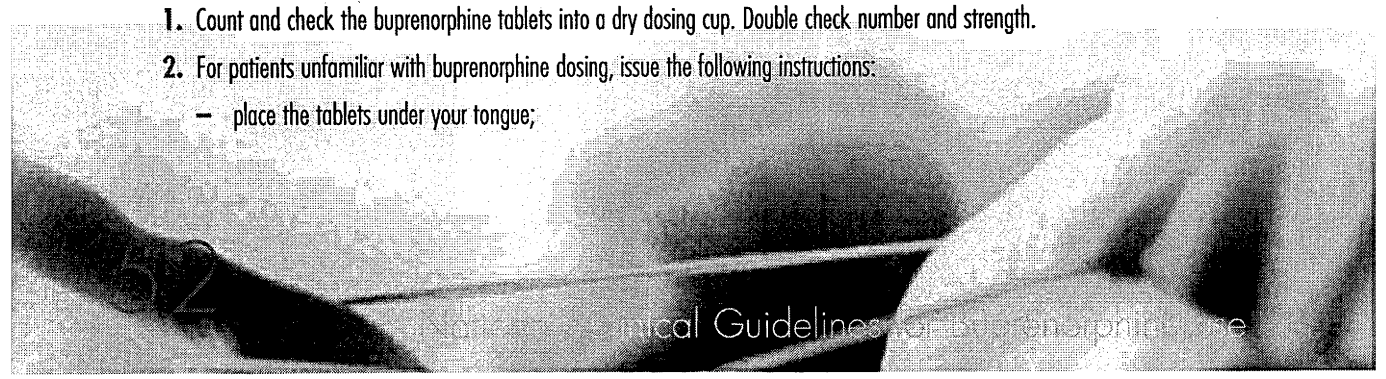
Prior to administering the medication, staff must:-

- Establish the identity of the patient;
- Confirm that the patient is not intoxicated;
- Check currency and amount of prescription. A patient cannot be dosed if a prescription is not current;
- Check that the current day is a dose day on the patient's regime;
- Confirm the dose for the current day if it is an alternate-day or three-times-a-week regime;
- Record the dose in the Drug of Addiction recording system.

Administering buprenorphine

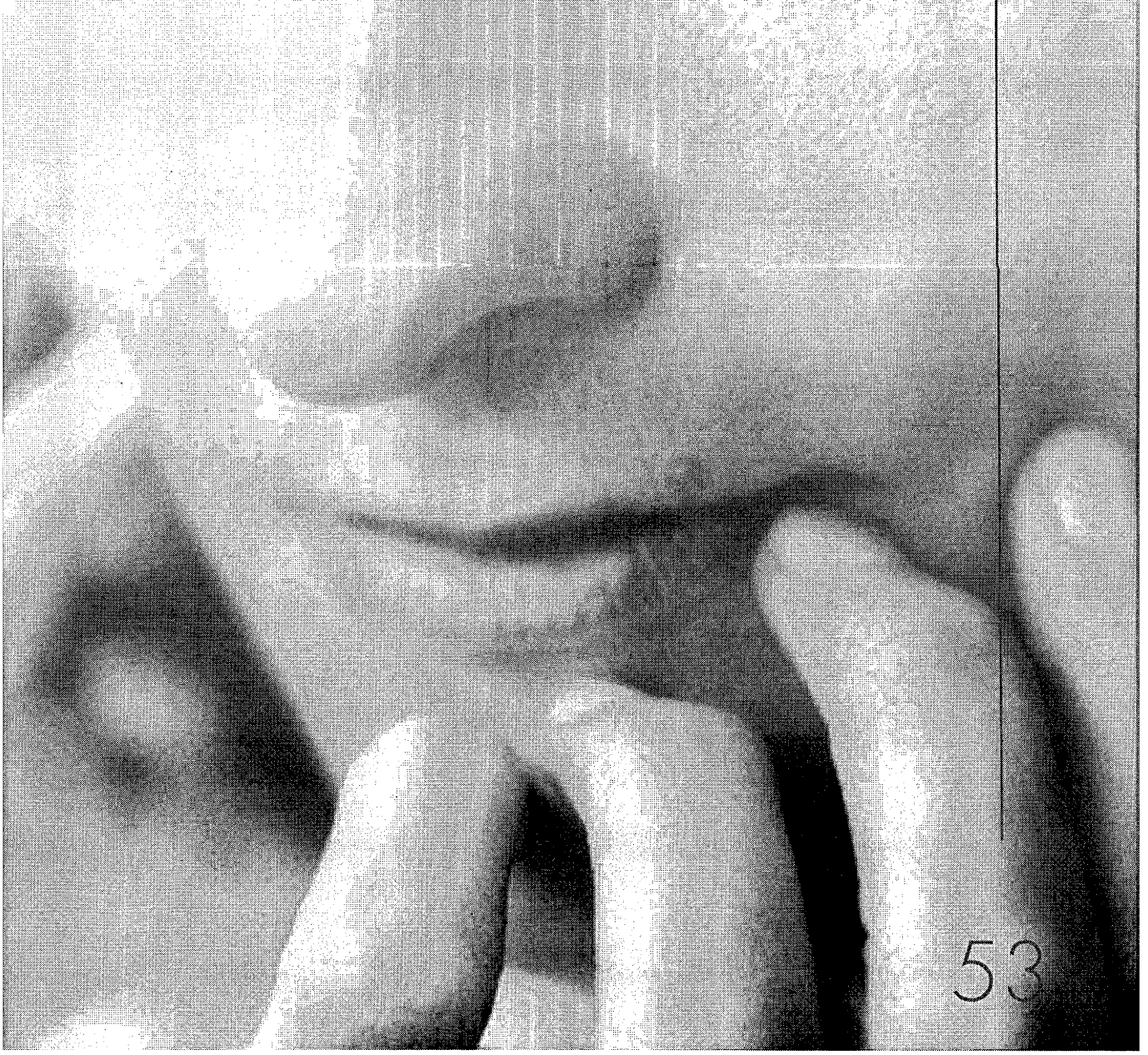
After recording dose details in the necessary Drug of Addiction recording system, the following procedures should be observed.

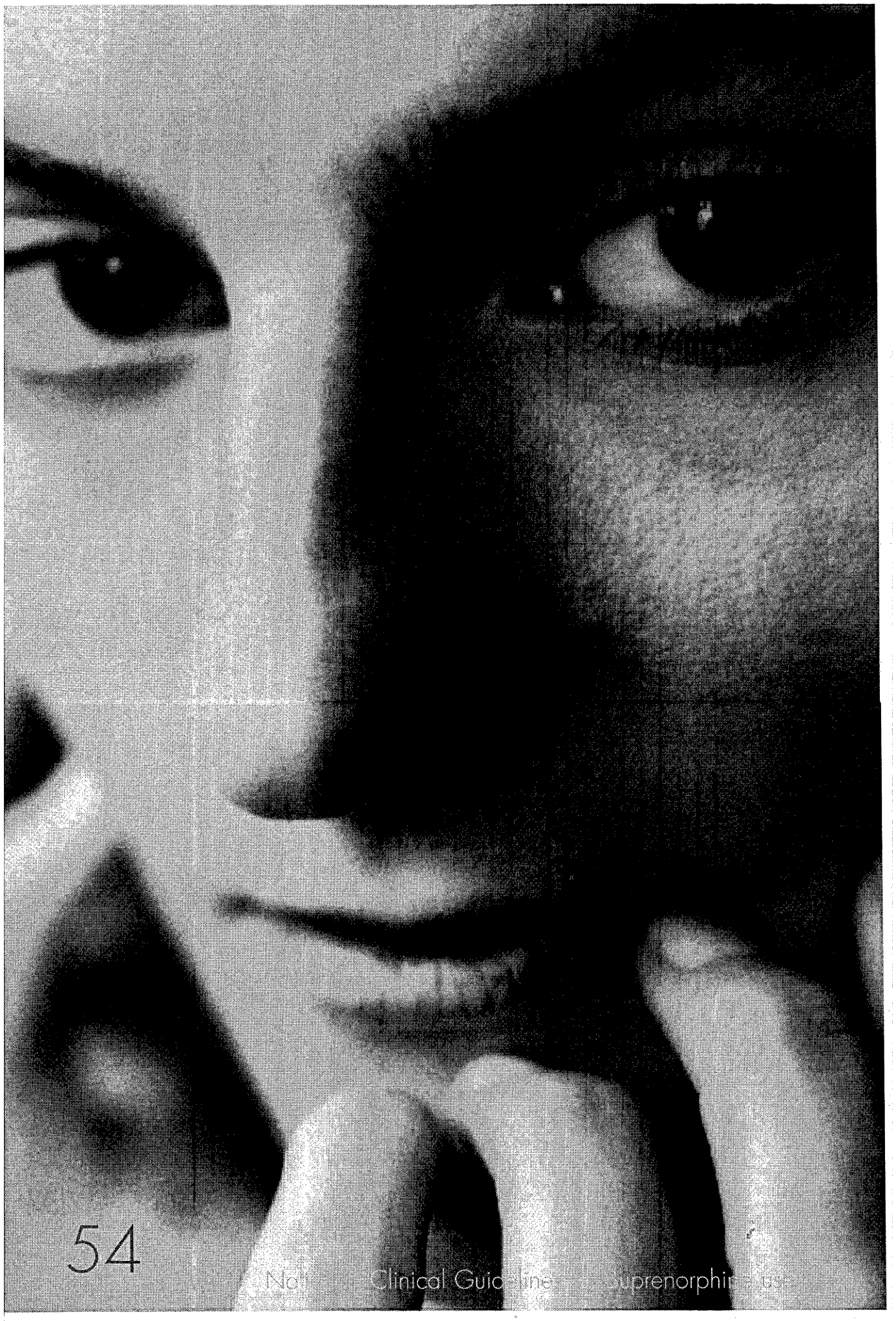
1. Count and check the buprenorphine tablets into a dry dosing cup. Double check number and strength.
2. For patients unfamiliar with buprenorphine dosing, issue the following instructions:
   - place the tablets under your tongue;



- do not chew the tablets;
- do not swallow saliva until tablets have dissolved (3 - 5 minutes on average);
- do not swallow the tablets (buprenorphine tablets have approximately half the bioavailability when taken orally compared to sublingually);
- once the tablets are given to you they are your responsibility and will not be replaced.

3. Give the cup to the patient and ask the patient to tip the contents under the tongue. Discourage patients from handling tablets.
4. Observe the patient until you are satisfied tablets are not divertable (usually > 2 minutes). Ask to see "how the tablets are dissolving" enough times for this to become an acceptable part of the patient's pick up routine.
5. Patients should sign that they have received their dose. Offer cordial or water to rinse taste out of mouth.
6. The prescriber should be notified if the pharmacist has concerns that patients may be attempting to divert their medication (see Section 5.5).





APPENDIX 1

National Clinical Guidelines for Buprenorphine use

NATIONAL CLINICAL GUIDELINES FOR THE USE OF BUPRENORPHINE IN THE TREATMENT OF HEROIN DEPENDENCE

ABBREVIATED VERSION

CLINICAL GUIDELINES FOR THE USE OF BUPRENORPHINE IN THE TREATMENT OF HEROIN DEPENDENCE

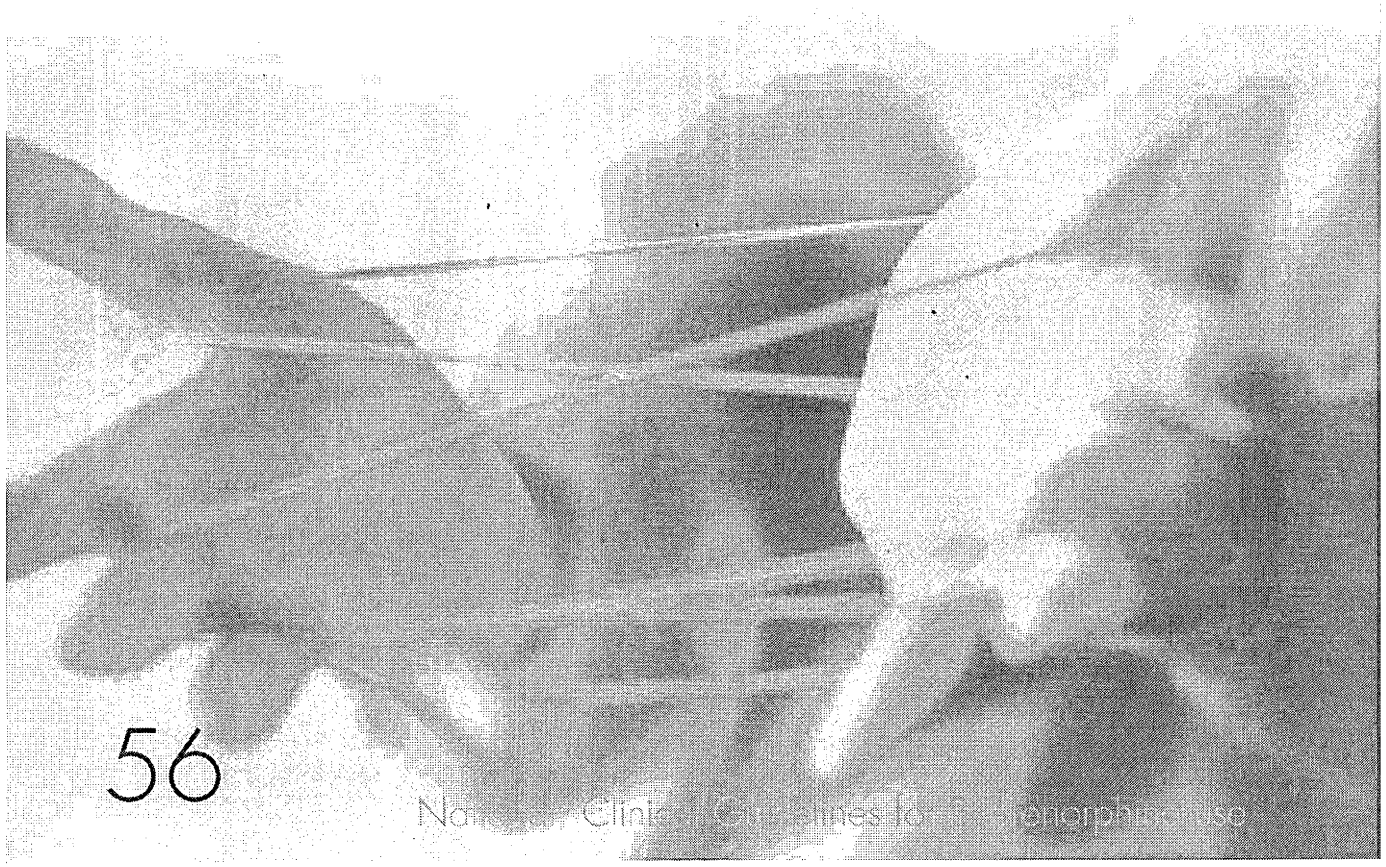
Abbreviated Version

These guidelines have been prepared to aid medical practitioners in the selection and management of patients seeking treatment with buprenorphine for heroin dependence.

These guidelines were prepared under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID) in collaboration with the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project, the Royal Australian College of General Practitioners (RACGP) and the Australian Professional Society on Alcohol and Other Drugs (APSAD), and are funded by the Commonwealth Department of Health and Aged Care.

These guidelines are based on international research literature and clinical experience with the use of buprenorphine in Australia. These guidelines have undergone a rigorous process of review and have been formally endorsed by the RACGP and APSAD.

The contribution of various individuals and organisations in the drafting and review process is gratefully acknowledged.



The sublingual buprenorphine preparation, Subutex®, is registered for treating heroin dependence in Australia. Subutex® contains buprenorphine hydrochloride, is available in 0.4, 2, and 8 mg strength tablets; and is registered for maintenance and withdrawal treatment.

1. Clinical Pharmacology

Buprenorphine is a synthetic opioid derived from the morphine alkaloid thebaine. It is a *partial* opioid agonist with low intrinsic activity and high affinity at μ opioid receptors.

It is effective in the treatment of heroin dependence because

- **it substitutes for heroin,** preventing the emergence of opioid withdrawal symptoms and reducing cravings;
- **it diminishes the effects of additional opioids** (e.g. heroin) due to a high affinity for m receptors;
- **it is long-acting,** allowing daily (or less than daily) dosing. The duration of action is related to the buprenorphine dose administered: low doses (e.g. 2 mg) exert effects for up to 12 hours; higher doses (eg 16 - 32 mg) exert effects for as long as 48 - 72 hours.

Other relevant properties:

- **Peak clinical effects** are achieved 1 - 4 hours after sublingual administration.
- **Elimination half-life** is between 24 and 37 hours.
- **Metabolised** principally in the liver by glucuronide conjugation and N-dealkylation.
- **Excreted** principally in the faeces and urine.

Withdrawal syndrome from buprenorphine.

Withdrawal on stopping treatment is milder than with other opioids (e.g. morphine). Typically, withdrawal from maintenance buprenorphine emerges 2 – 5 days after the last dose, with some features lasting up to several weeks.

Side effects:

- Similar to other opioids, the most common being constipation, disturbed sleep, drowsiness, sweating, headaches and nausea.
- Most prevalent in the initial treatment period.
- High doses well-tolerated - rarely induce clinically-significant respiratory depression, even in individuals with low tolerance to opioids.

Drug Interactions:

- **Other sedatives.** Buprenorphine in combination with other sedative drugs (e.g. alcohol, benzodiazepines) can result in respiratory sedation, coma and death.
- **Opioid antagonists.** Naltrexone can precipitate opioid withdrawal in patients on buprenorphine. Very high doses of naloxone (e.g. 10 - 35 mg) are required to reverse buprenorphine effects. As buprenorphine is not readily reversed by naloxone, in cases where buprenorphine is contributing to respiratory depression, ventilatory support will often be required.
- **Opioid agonists.** Buprenorphine exerts a degree of blockade on the effects of full agonist opioids, potentially complicating the use of opioids for analgesia. The initial dose of buprenorphine can precipitate opioid withdrawal in patients with high levels of opioid use (e.g. recent and heavy heroin use, methadone transfers).

2. Regulatory requirements

Buprenorphine is an S8 medication.

- **A medical practitioner must be authorised by the relevant jurisdictional body to prescribe it.**
- **A prescribing doctor must be authorised by the relevant jurisdictional health authority for each client being treated.**

See the national buprenorphine policy and your state policy for further information.

3. Indications, contra-indications, precautions

A comprehensive assessment by an authorised prescribing doctor is essential.

Indications: Buprenorphine treatment is indicated for individuals only when the following criteria have been established:

- opioid-dependent;
- 18 years of age or more. (a second or specialist opinion should be sought for individuals under 18);
- able to provide proof of identity (required for treatment with all S8 medications);
- able to give informed consent to treatment.

Precautions: Particular caution should be exercised in prescribing for clients in the following circumstances:

- in high-risk polydrug use;
- with chronic pain;
- with concomitant severe psychiatric condition;
- in methadone maintenance on high doses (>30 mg);
- with sensitivity to buprenorphine;
- with concomitant medical conditions.

(As with all opioids, caution should be used in the case of recent head injury; acute abdominal conditions and severe respiratory, hepatic or renal disease).

Contraindications:

Those who showed severe side-effects to buprenorphine from previous exposure;

Pregnant women and breast-feeding mothers.

Severe respiratory or hepatic insufficiency

4. Prescribing guidelines for maintenance treatment

Initial buprenorphine dose: inducting heroin users

The first dose of buprenorphine should be administered at least 6 hours after the last heroin use to reduce the risk of precipitated opioid withdrawal.

The initial dose should be between 2 and 8 mg.

The following must be taken into consideration when considering the initial dose:

- the degree of neuroadaptation (or tolerance) to opioids:
  - low or uncertain tolerance to opioids: 2 or 4 mg.
  - high levels of tolerance: 6 or 8 mg.
- extent of opioid withdrawal experienced by client at time of first buprenorphine dose:
  - moderate to severe opioid withdrawal: 6 to 8 mg.
  - little or no opioid withdrawal: 2 or 4 mg, or delay initial dose.
- perceived likelihood of continued alcohol, sedative drug (particularly benzodiazepines), or illicit heroin use warrants low initial buprenorphine doses, with frequent reviews.
- concurrent medical conditions may warrant the use of lower initial doses (see *Precautions*).

Initial buprenorphine dose: transferring from methadone maintenance treatment

Clients transferring from methadone programs may experience precipitated withdrawal on commencing buprenorphine, and a proportion will continue to describe mild withdrawal features or dysphoria for 1 - 2 weeks after the transition. The key factors impacting upon precipitated withdrawal are described below.

Factor	Discussion	Recommended strategy
Dose of methadone	Methadone doses higher than 30 mg are more often associated with precipitated withdrawal. In general the higher the methadone dose, the more severe the withdrawal experienced.	Attempt transfer from low dose of methadone (e.g. < 40 mg where possible). Clients on > 60 mg methadone should not attempt transfer
Time between last methadone dose and 1st dose buprenorphine	Buprenorphine should not be dispensed within 24 hrs of last methadone dose. Increasing the interval between last methadone and 1st buprenorphine dose reduces the incidence & severity of precipitated withdrawal	Cease methadone and delay first dose of buprenorphine until client experiencing features of methadone withdrawal

continued on page 60

continued from page 59

Dose of buprenorphine	Very low doses of buprenorphine (e.g. 2 mg) are generally inadequate to substitute for methadone (unless very low methadone dose). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal.	First dose of buprenorphine should generally be 4 mg; review client 2 - 4 hours later (or early the following day if evening dose)
Client expectancy	Clients who are not prepared for precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment drop-out, drug abuse).	Inform clients fully (and carers where relevant). Provide written information. Have contingency plan in place for severe symptoms.
Use of other medications	Symptomatic medication (e.g. clonidine) can be useful to relieve any precipitated withdrawal.	Prescribe and dispense in accordance to management plan

Transferring clients from low methadone doses (<40mg)

Methadone dose should be ceased abruptly, and the first buprenorphine dose given at least 24 hours after the last methadone dose. The following conversion rates should be used when converting from low-dose methadone to buprenorphine.

Last methadone dose (mg)	Initial buprenorphine dose (mg)	Day 2 buprenorphine dose (mg)
20 - 40 mg	4 mg	6 - 8 m
10 - 20 mg	4 mg	4 - 8 mg
1 - 10 mg	2 mg	4 mg

Transferring from medium dose methadone (40 - 60 mg) to buprenorphine

Clients who are unable to reduce their methadone dose to below 40 mg without becoming 'unstable' may attempt a transfer from methadone doses between 40 and 60 mg. The following procedures should be followed:

1. Prepare client, pharmacist and other staff. Provide information and organise supports.
2. Cease methadone dose and delay first buprenorphine dose until the client experiences significant withdrawal discomfort (generally 48 - 96 hours after last methadone dose). Symptomatic medication (limited amounts) may be required.
3. Give the first dose of 4 mg buprenorphine in the morning or early afternoon.
4. Review the client 2 - 4 hours after first buprenorphine dose. If client describes:
   - worsening of withdrawal following first buprenorphine dose - provide symptomatic medication for opioid withdrawal for remainder of the day.

- no worsening of withdrawal, or an improvement in withdrawal symptoms following the first buprenorphine dose - a further 2 to 4 mg of buprenorphine can be dispensed that afternoon / evening.

5. Review the client prior to dosing the following day. Titrate the dose to between 6 -10 mg, according to the response on the previous day. Continue frequent reviews and dose titration.

Stabilisation

The key principles to stabilising clients are:

- frequent review of the client by the prescribing doctor and other members of the treatment team;
- increases in buprenorphine dose only after review by the prescribing doctor;
- titration of the buprenorphine dose according to:
  - features of intoxication, withdrawal and cravings over preceding 24 hours;
  - additional drug-use (eg heroin), including the reason stated by the client for using;
  - side-effects or other adverse events (including intoxicated presentations, overdoses);
  - adherence to dosing regime (attendance for dosing, route of administration);
  - client satisfaction with buprenorphine dose.
- dose changes:
  - increases should be by increments of 2 - 4 mg at a time;
  - allow at least 2 - 3 days between dose increases, although daily increases are possible.

Clients should generally be able to achieve maintenance buprenorphine dose levels within 1 to 2 weeks of commencing buprenorphine. Daily dosing is recommended during the stabilisation period.

Alternative regime for rapid induction onto buprenorphine

- a faster rate of induction may be safely undertaken and may reduce the risk of early drop out from the program.
- achieves maintenance doses within 2-3 days
- dose increments:
  - Day 1 8 mg
  - Day 2 16 mg
  - Day 3 24 mg
- Prescribers who undertake this regime should review clients daily, looking particularly for signs and symptoms of toxicity (especially nausea and dizziness).
- If there is evidence of toxicity dose increases should be slowed.

Maintenance treatment

Evidence suggests that most people achieve optimal outcomes on daily doses of 12 - 24 mg. The maximum recommended dose of buprenorphine is 32 mg daily.

Frequency of dosing

Most clients can be maintained on doses of buprenorphine administered every 2 or 3 days. The following conversion is recommended:

2-day buprenorphine dose = 2 x daily dose of buprenorphine (to a maximum of 32 mg)

3-day buprenorphine dose = 3 x daily dose of buprenorphine (to a maximum of 32 mg)

This conversion serves as a guide only, and the dose should be titrated according to clinical response. A proportion of clients (10-20%) do not tolerate alternate or three-day dosing.

Ancillary services / interventions

Psychosocial services:

All clients should be encouraged to join a comprehensive treatment program that includes psychosocial services such as counselling. However, attending counselling should be voluntary.

Take-away doses:

The take-away policy for buprenorphine is determined by each Australian jurisdiction. There are both benefits and problems associated with take-aways, and particular care should be exercised by prescribers in authorising them.

Urine-testing:

Buprenorphine is not detected in routine urine tests for opioids.

Addressing continued high-risk drug use:

Attempts should be made to stabilise clients who continue high-risk heroin or other drug-use (as evidenced by frequent intoxicated presentations, overdoses, chaotic drug-related behaviours, or drug-related deterioration of medical or mental health).

This requires a review of:

(a) psychosocial interventions and supports;

(b) precipitants to continued drug use; *and*

(c) medication regimes.

Ensure an adequate dose of buprenorphine is prescribed and that the client is taking it as prescribed (which may require stopping take-away doses, supervising consumption, and imposing daily dosing regimes).

Clients who cannot stabilise on buprenorphine should consider transferring to an alternative pharmacotherapy (e.g. methadone); or consider non-pharmacological treatment options (e.g. therapeutic communities, counselling and support) and withdrawal from substitution maintenance treatment.

Cessation of buprenorphine maintenance treatment

Withdrawal from buprenorphine treatment

Most clients do not experience significant withdrawal discomfort until they reduce to low doses of buprenorphine, or even until after doses have stopped (see pharmacology for description). A gradual dose reduction is proposed at the following rate:

Daily buprenorphine dose	Reduction rate
Above 16 mg	4 mg every 1 – 2 weeks
8 - 16 mg	2 to 4 mg every 1 – 2 weeks
Below 8 mg	2 mg per week or fortnight

Some clients will request doses of less than 2 mg. An increase in heroin or other drug-use, or a worsening of the client's physical, psychological or social well-being, may warrant a temporary cessation or slowing-down of the reduction rate.

Induction on to naltrexone

Some clients may wish to commence naltrexone as a relapse-prevention agent following buprenorphine maintenance treatment. Induction on to naltrexone at least 5 - 7 days after the last buprenorphine dose is generally possible with minimal discomfort. Naltrexone can be commenced more quickly (within several days of ceasing buprenorphine), but this has attendant risks, and the reader is referred to the more comprehensive guidelines for recommendations.

Transfer to methadone maintenance treatment

Clients should be stabilised on daily doses of buprenorphine prior to transferring to methadone. *Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of up to 40mg.* Clients transferring from low doses of buprenorphine (eg 4 mg or less) should be commenced on lower methadone doses (e.g. <20 mg). The client should be reviewed frequently, and the methadone dose titrated accordingly.

5. Guidelines for the management of heroin withdrawal

The non-pharmacological management of heroin withdrawal should include:

- *Assessment and treatment selection;*
- *Environment and support management:* involving family, friends, alcohol & drug workers, self-help and peer groups;
- *Supportive care* (including provision of information and supportive counselling);
- *Monitoring* (use of withdrawal scales and daily review is recommended);
- *links to post withdrawal services.*

Prescribing and administering buprenorphine for withdrawal

- Delay first dose until at least 6 hours after last heroin use, and preferably until the client is experiencing early features of opioid withdrawal.
- Dispense daily, with daily clinical review.
- Titrate doses against the client's experience of withdrawal severity, cravings, side-effects and other drug use.

Outpatient withdrawal regimes

The following 4 - 8 day dosing regime is proposed for outpatient withdrawal services:

Day	Proposed regime	Recommended upper and lower limits
Day 1	6 mg	4 – 8 mg
Day 2	8 mg	4 – 12 mg
Day 3	10 mg	4 – 16 mg
Day 4	8 mg	2 – 12 mg
Day 5	4 mg	0 – 8 mg
Day 6	-	0 – 4 mg
Day 7	-	0 – 2 mg
Day 8	-	0 – 1 mg

Clients who do not stop their heroin use during their outpatient withdrawal episode may benefit from:

(i) an extension of the outpatient buprenorphine withdrawal regime over several weeks;

(ii) transfer to inpatient withdrawal services; or

(iii) transfer to longer-term maintenance programs.

Inpatient withdrawal regimes

Modify inpatient regimes according to:

- the duration of the withdrawal episode, and
- degree of monitoring and supervision available.

Regime proposed for a 7 - 8 day admission.

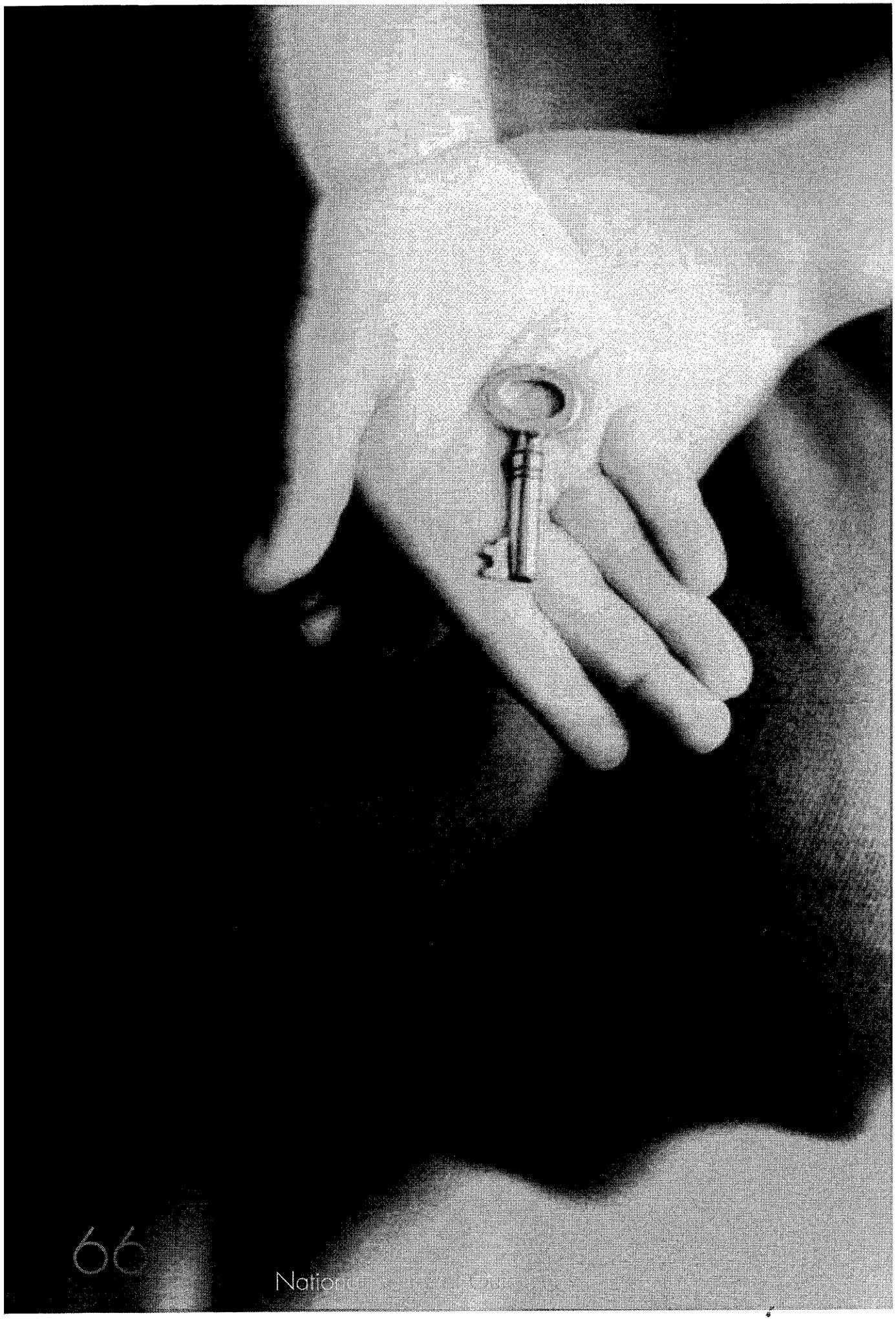
Day	Proposed regime	Total daily dose
Day 1	4 mg at onset of withdrawal, & additional 2 to 4 mg evening dose prn	4 - 8 mg
Day 2	4 mg mane, with additional 2 to 4 mg evening dose prn	4 - 8 mg
Day 3	4 mg mane, with additional 2 mg evening dose prn	4 - 6 mg
Day 4	2 mg mane prn; 2 mg evening prn	0 - 4 mg
Day 5	2 mg prn	0 - 2 mg
Day 6	no dose	
Day 7	no dose	
		Total proposed dose = 12 - 28 mg

Ancillary medications: Because buprenorphine is effective in reducing most withdrawal symptoms, other withdrawal medications are not routinely required. Some clients may complain of sleep disturbance, but only limited amounts of benzodiazepines should be prescribed (e.g. temazepam 10 - 20 mg nocte for two nights), with supervised dispensing. The use of high doses of benzodiazepines in combination with buprenorphine can result in overdose.

Post-withdrawal treatment options: Withdrawal alone has limited long-term benefits, and all clients attempting withdrawal should be encouraged to pursue ongoing drug treatment.

Options open to them include:

- counselling services,
- substitution maintenance treatment (with methadone or buprenorphine),
- naltrexone treatment,
- self-help groups (e.g. Narcotics Anonymous), or
- residential rehabilitation programs.



THE SUBJECTIVE OPIOID WITHDRAWAL SCALE (SOWS)

Date .....
Time .....

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)

Two New Rating Scales for Opiate Withdrawal, American Journal of Alcohol Abuse, 13, 293-308.

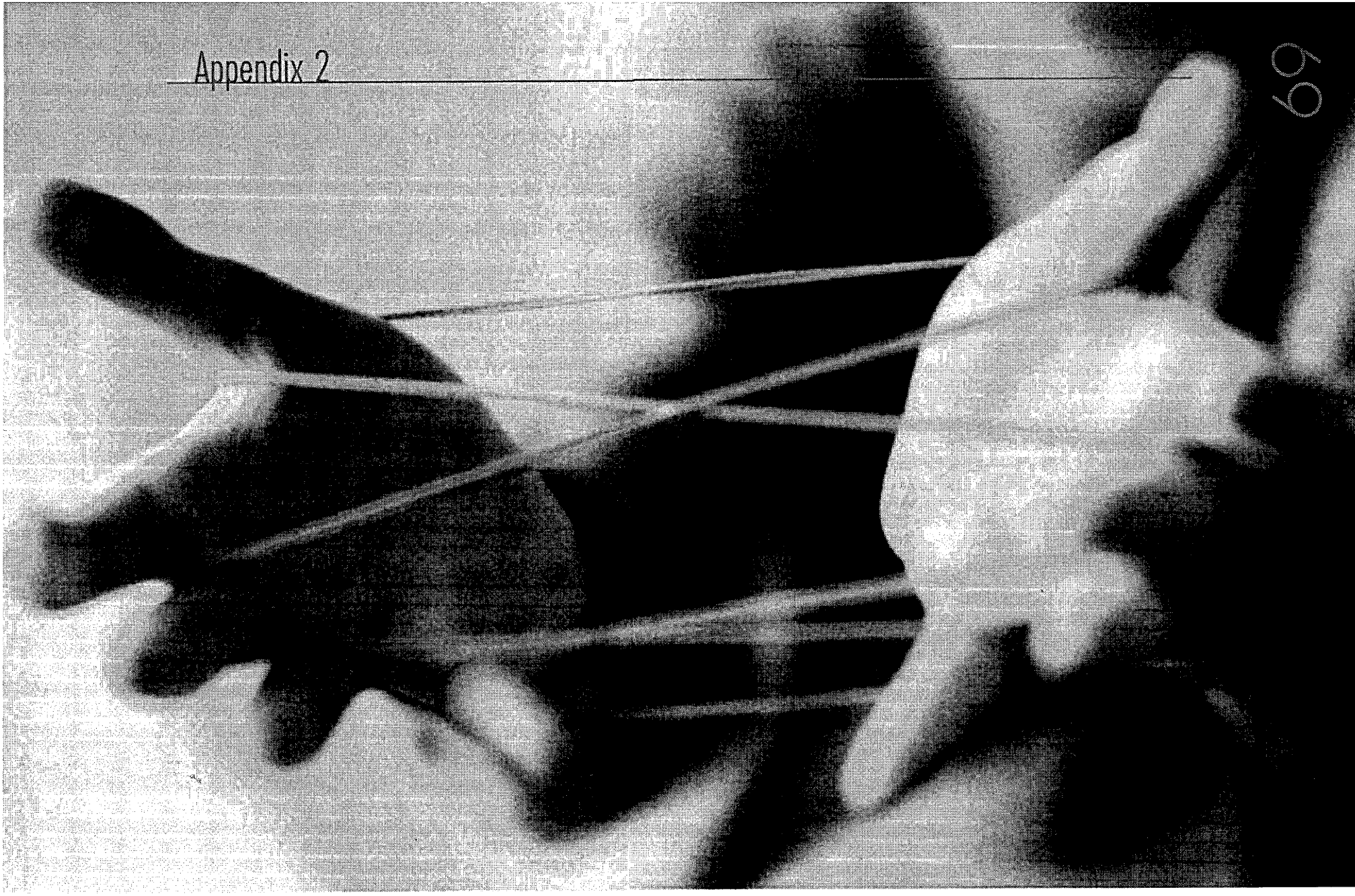
THE OBJECTIVE OPIOID WITHDRAWAL SCALE (OOWS)

Date .....
Time .....

OBSERVE THE PATIENT DURING A 5 MINUTE OBSERVATION PERIOD
THEN INDICATE A SCORE FOR EACH OF THE OPIOID WITHDRAWAL SIGNS LISTED BELOW (ITEMS 1-13). ADD THE SCORES FOR EACH ITEM TO OBTAIN THE TOTAL SCORE

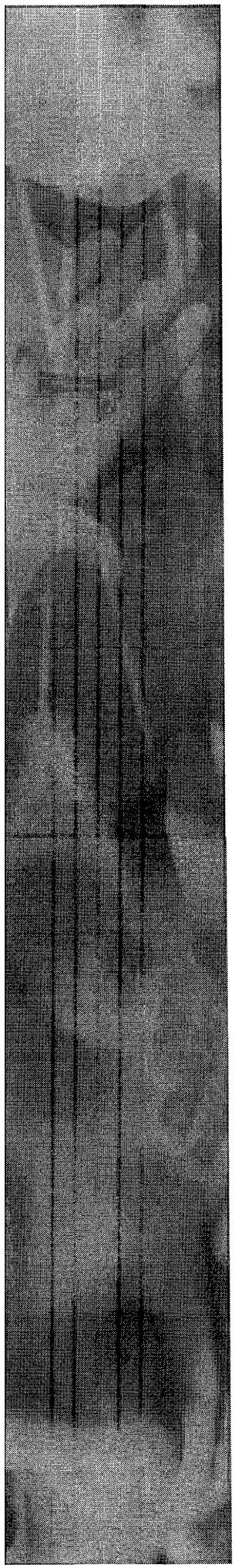
	SIGN	MEASURES		SCORE
1	Yawning	0 = no yawns	1 = ≥ 1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 = ≥ 3 mm	
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			

Range 0-13 Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, American Journal of Alcohol Abuse, 13, 293-308.



APPENDIX 3

National Clinical Guidelines for Buprenorphine use



CONSULTANCY AND SUPPORT MECHANISMS

AUSTRALIAN CAPITAL TERRITORY

ACT Department of Health, Housing and Community Care

GPO Box 825

Canberra ACT 2601

Alcohol and Drug Program

Acting Director

Management & Administration

Telephone: (02) 6205 0947

Facsimile: (02) 6205 1180

ACT Community Care Alcohol and Drug Program

Senior Medical Officer

Telephone: (02) 6205 4545

Facsimile: (02) 6205 0951

Chief Health Officer

Telephone: (02) 6205 0883

Facsimile: (02) 6205 1884

Chief Pharmacists

Telephone: (02) 6205 9061

Facscimile: (02) 6205 0997

Policy Information

Manager

Alcohol and Drug Priorities

Telephone: (02) 6205 0909

Facsimile: (02) 6205 2037

APPENDIX 3

NEW SOUTH WALES

Alcohol and Drug Information Service

Telephone: (02) 9361 2111

Toll Free: 1800 023 599

NSW Drug and Alcohol Specialist Advisory Service

Telephone: (02) 9557 2905

Toll Free: 1800 023 687

NSW Health Drug Programs Bureau

Telephone: (02) 9391 9244

NORTHERN TERRITORY

Alcohol and Other Drug Services

PO Box 40596

CASUARINA NT 0811

Building 9 North, Royal Darwin Hospital Campus

Rocklands Drive, TIWI, NT

Telephone: (08) 8922 8399

Facsimile: (08) 8922 8403

QUEENSLAND

Alcohol, Tobacco and Other Drug Services

Medical Advisor

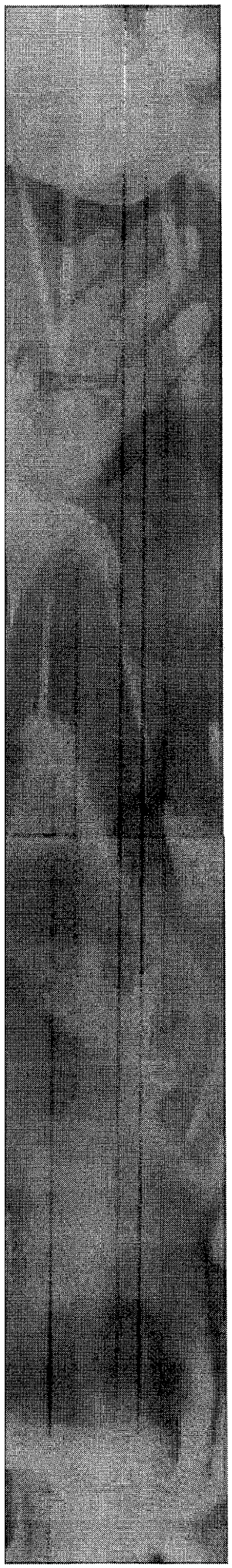
Telephone: (07) 389 63900

Policy and Specific State Information

Senior Advisor

Alcohol, Tobacco and Other Drug Services

Telephone: (07) 3234 1700



TASMANIA

Alcohol and Drug Service State Office

State Manager

Telephone: (03) 6233 3860

Coordinator Illicit Drugs

Telephone: (03) 6233 2269

Deputy Chief Pharmacist

Telephone: (03) 6233 3906

Alcohol and Drug Service

Southern Regional Office

Manager

Telephone: (03) 6222 7511

Opiate Treatment Medical Officer

Telephone: (03) 6222 7511

Pharmacist

Telephone: (03) 6233 3906

Alcohol and Drug Service

North/North West Regional Office

Manager

Telephone: (03) 6336 5577

Opiate Treatment Medical Officer

Telephone: (03) 6233 5577

SOUTH AUSTRALIA

ADIS (Alcohol and Drug Information Service)

Toll Free: 1300 13 13 40

Drug & Alcohol Clinical Advisory Service

Toll Free: 1300 13 13 40

Warinilla Clinic

92 Osmond Terrace

Norwood SA 5067

Telephone: (08) 8130 7500

Northern Methadone Service

22 Langford Drive

Elizabeth SA 5112

Telephone: (08) 8252 4040

Southern Clinic

82 Beach Road

Christies Beach SA 5165

Telephone: (08) 8326 6644

VICTORIA

Victorian Drug and Alcohol Clinical Advisory Service

Exclusively for health and welfare professionals. Provides advice and information on clinical management of patients with drug and or alcohol problems, including:

- advice on recognition and management of withdrawal syndromes
- drug use complications
- drug information
- prescribing information
- assistance with cases of acute intoxication

Metropolitan: (03) 9416 3611

country areas (toll free): 1800 81 2804

Drugs and Poisons Unit, Department of Human Services

The Unit issues permits for approved practitioners to prescribe methadone. It also approves individual medical practitioners and pharmacists to respectively prescribe or dispense methadone.

Address: PO Box 1670N, Melbourne, 3001

Telephone: 1300 364 545

Fax: 1300 360 830

Direct Line

For the general public and health and welfare professionals. Provides counselling, information and referral, including:

- needle syringe exchange and bin location
- drug and alcohol agencies and drug withdrawal beds
- methadone program contact details
- HIV/AIDS information and referral
- drink/drive education and assessment referral

Metropolitan: (03) 9416 1818

Country areas: (toll free):1800 13 6385

Youth Substance Abuse Service

YSAS provides information, outreach and residential services for young people aged between 12 and 21 experiencing significant problems related to their use of drugs and/or alcohol.

14-18 Brunswick Street Fitzroy 3065

Telephone: (03) 9415 8881

Fax: (03) 9415 8882

Website: http://www.ysas.org.au

YSASLine

YSASline provides 24 hour access to information, telephone counseling, and referral to YSAS outreach teams. The service is open to young people, their families, health and welfare workers, police and ambulance officers. Call YSASline to contact an outreach team. Access to the YSAS residential service is made by contacting your local outreach team via YSASline.

Metro: (03) 9244 2450

Country freecall: 1800 014 446

VIVAIDS: the Victorian Users Group

VIVAIDS provides information on anything and everything to do with drugs. They also provide peer support, peer education, referrals, needle exchange and advocacy to drug users, while promoting harm reduction to users and the community.

765a Nicholson Street

North Carlton 3054

Telephone: (03) 9381 2211

Specialist Methadone Services

Specialist Methadone Services provide a consultative service to methadone prescribers seeking expert opinion about the management of patients with special problems, such as psychiatric, social, medical or treatment problems. Patients may be referred by arrangement, or advice sought by contacting the service.

Turning Point Drug and Alcohol Centre

54 Gertrude St., FITZROY 3065

Administration

Telephone: (03) 9254 8061

Fax: (03) 9416 342

Clinical Services

Telephone: (03) 9254 8050

Fax: (03) 9486 9766

South Eastern Methadone Consultancy Clinic

61-69 Brighton Rd., ELWOOD 3184

Telephone: (03) 9525 7399

Fax: (03) 9525 7369

Western Hospital Drug and Alcohol Service

Gordon St., FOOTSCRAY 3011

Telephone: (03) 9317 2217

Fax: (03) 9319 6027

Austin and Repatriation Medical Centre Specialist Methadone Service

Studley Rd., HEIDELBERG 3084

Administration

Telephone: (03) 9496 5000

Pharmacy

Telephone: (03) 9496 4999

Fax: (03) 9459 4546

Eastern Region Specialist Methadone Service

Whithorse Community Health Service

65Carrington Street, BOX HILL, 3128

Telephone: (03) 9890 2220

Royal Women's Hospital Chemical Dependency Unit

For women who are pregnant and use drugs. The unit provides a direct service for women who live within a 25 km radius, and secondary consultation for other women. Midwives and social workers are available for consultation.

264 Cardigan Street Carlton 3053

Telephone: (03) 9344 2363

Health Insurance Commission.

The HIC provides information about medical consultations and pharmaceutical benefits obtained through its Doctor Shopper Hotline. It is also able to provide this information if the patient signs a privacy release form authorising the HIC to provide this information. Forms and explanatory letters are available from the HIC.

Health Insurance Commission

134 Reed Street Tuggeranong ACT 2900

Doctor shopper hotline (free call): phone 1800 631 181

Hepatitis C information

Hepatitis C Support Line
Hepatitis C Council

The Hepatitis C Council has produced a booklet "Hepatitis C Contact" which provides information, and answers frequently asked questions.

Carlow House

Level 9

289 Flinders Lane

Melbourne 3000

Telephone: (03) 9639 3200

Country Calls: 1800 703 003

Hepatitis C Helpline

Telephone: (03) 9349 1111

Country Calls: 1800 800 241

TTY: 1800 032 665

Vietnamese Line: 1800 456 007

Department of Human Services.

DHS pamphlet ***"Hepatitis: the Facts"*** available from the Department of Human Services, or on the internet at: http://www.dhs.vic.gov.au/phd/9904043/index.htm

The Department of Human Services has produced a booklet ***"Management, Control and Prevention of Hepatitis C: Guidelines for Medical Practitioners"***. It is available from the Department.

Health care providers can obtain information and assistance with counselling from the Hepatitis C Educator (03 9288 4127). Advice on notification of hepatitis C can be obtained from the Infectious Diseases Unit.

AIDS information

AIDSLINE

Telephone: (03) 9347 6099

Country Calls: 1800 133 392

TTY: 1800 032 665

Melbourne Sexual Health Centre

580 Swanston Street

Carlton 3053

Telephone: (03) 9347 0244

Country Calls: 1800 032 017

Needle and Syringe Exchange Programs (NSEPs).

Contact details of Victorian NSEPs is available:

On the internet at: http://hna.ffh.vic.gov.au/phb/9808109/index.htm

or by calling Direct Line (see above).

WESTERN AUSTRALIA

Alcohol and Drug Information Service

Telephone: (08) 9442 5000

Country Calls: 1800 198 024

Clinical Advisory Service

Next Step

32 Moore Street

EAST PERTH WA 6004

Phone: (08) 9442 5042

Country Calls: 1800 688 847

Pharmaceutical Services (Doctors and Pharmacists)

Health Department of Western Australia

Telephone: (08) 9388 4985