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A comparison of methadone and slow-release oral morphine as maintenance pharmacotherapies for opioid dependence

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Declaration

I hereby declare that this thesis is my own work and contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution and to the best of my knowledge and belief contains no material that has been previously published or written by another person, except where due reference has been made in the text. Any contribution made to the research by others is explicitly acknowledged in the thesis.

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Tim Mitchell

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Abstract

Methadone is highly effective as a maintenance pharmacotherapy for opioid dependence but also exhibits several shortcomings. Of particular concern is the frequency with which patients report inadequate suppression of withdrawal symptoms or adverse effects despite seemingly adequate doses and the application of an individualised approach to dosing. The principal aim of this thesis was to evaluate slow-release oral morphine (SROM) as an alternative maintenance pharmacotherapy to methadone for the treatment of opioid dependence. Eighteen methadone maintenance patients reporting adequate (holders) or inadequate (non-holders) withdrawal suppression between doses were recruited to participate in an open-label, randomly-ordered crossover clinical trial of methadone and SROM. The study featured the concurrent measurement of plasma drug concentrations and both subjective and physiological indices of opioid effect throughout a 24-hour inter-dosing interval on one occasion for methadone and SROM after at least 4 weeks on a stable dose of each drug. Other foci included comparisons of clinical efficacy and acceptability and assessments of opioid withdrawal during the transition between medications. Compared to methadone, SROM was at least as effective overall in suppressing opioid withdrawal between doses and was associated with improved social functioning, fewer and less severe side effects, greater drug liking, reduced heroin cravings, and an enhanced sense of feeling 'normal', and yielded similar outcomes for measures of drug use, depression and health. The majority of patients stated a preference for SROM (78%) over methadone (22%), including 89% of the non-holders and 69% of the holders. The most frequently cited reasons for preferring SROM included fewer side effects, better withdrawal suppression, improved sleep, feeling more normal, improved health, and improved energy. Transfer from methadone to SROM was not associated with a prohibitive degree of opioid withdrawal, providing that an appropriate dose conversion ratio was applied. These findings suggest that SROM is a safe and efficacious maintenance pharmacotherapy for opioid dependence that may be particularly advantageous as an alternative for patients responding poorly to methadone. Further large-scale clinical

trials using double-blind methodologies and standard treatment outcome indicators are warranted.

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List of Abbreviations

6MAM	6-mono-acetylmorphine
AAG	Alpha-acid-glycoprotein
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
AUD	Australian dollar
BDI	Beck Depression Inventory
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
Css	Average steady-state plasma concentration
DAM	Diacetylmorphine
DASC	Drug and Alcohol Services Council
Df	Degrees of freedom
ECG	Electrocardiogram
EDDP	2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
Id. no.	Identification number
IMOR	Immediate-release oral morphine
LAAM	Levo-alpha-acetylmethadol
LSEQ	Leeds Sleep Evaluation Questionnaire
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MBG	Morphine Benzedrine Group scale
MG	Morphine Group scale
MSC	Methadone Symptoms Checklist
NAS	Neonatal abstinence syndrome
NMDA	N-methyl-D-aspartate
OTI	Opiate Treatment Index
P/T	Peak to trough plasma concentration ratio
POMS	Profile of Mood States
RAH	Royal Adelaide Hospital
RR	Relative risk ratio
SD	Standard deviation
SE	Standard error of the mean
SROM	Slow-release oral morphine
T>75%Cmax	Time plasma concentration exceeded 75% of Cmax
$T_{1/2}$	Half-life
Tmax	Time to reach maximum plasma concentration
TMD	Total mood disturbance
VAS	Visual analogue scale
Vd	Volume of distribution

Publications Related to This Thesis

Journal articles and reports

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1. INTRODUCTION

1.1. General introduction

Illicit opioid use and dependence are associated with significant adverse health, social and economic consequences in modern society. Since its introduction in the 1960s, methadone maintenance has expanded to become the most widely used pharmacological intervention for opioid dependence worldwide (Joseph, Stancliff, & Langrod, 2000). For the majority of patients, the provision of oral methadone on a once-daily basis is sufficient to suppress the manifestation of opioid withdrawal and facilitate abstinence from heroin and other drugs. Nonetheless, methadone has a number of shortcomings that limit its effectiveness in some cases. Up to a third of patients report the regular failure of their dose to 'hold' (i.e., suppress opioid withdrawal) for the duration of the standard 24-hour inter-dosing interval (Dyer and White, 1997). Many patients also report the occurrence of adverse effects attributable to methadone (e.g., constipation, sexual dysfunction) (Dyer & White, 1997; Goldstein & Judson, 1973; Judson & Goldstein, 1982; Kreek, 1973; Longwell, Kestler, & Cox, 1979). The limitations of methadone are further evidenced by the frequency with which the target population and health professionals involved in the delivery of methadone maintenance express ambivalent attitudes towards the treatment and by the number of patients who attempt to terminate treatment prematurely, despite recognition of the beneficial effects treatment has had on their lives and the high probability of relapse during detoxification (Lenne et al., 2001; Magura & Rosenblum, 2001; Stancliff, Myers, Steiner, & Drucker, 2002).

In response to the shortcomings associated with methadone maintenance, and the need to offer greater flexibility and choice to patients and treatment providers, a number of alternative pharmacotherapies have been evaluated in recent decades (Ling, Rawson, & Compton, 1994). Long-acting maintenance medications such as the partial agonist buprenorphine and the full agonist levo-alpha-acetylmethadol (LAAM) produce similar outcomes to methadone and have

the advantage of permitting less frequent dosing (Johnson et al., 2000). Nevetherless, like methadone, these alternative medications also have certain limitations. In particular, safety concerns regarding the use of LAAM mean that methadone is now the only long-acting full opioid agonist currently recommended for maintenance treatment in many countries (Clark et al., 2002a; Schwetz, 2001). Moreover, transfer from methadone to buprenorphine may have limited acceptability in some patients due to the possibility of precipitated opioid withdrawal (Ling et al., 1994). To this extent, there is a shortage of available options for patients who seeking to undergo maintenance treatment with an opioid agonist, but for whom methadone fails to suppress withdrawal or causes unacceptable adverse effects.

Slow-release oral morphine (SROM) formulations permissive of once-daily dosing schedules have recently been developed for use in the management of pain (Gourlay, 1998). To the extent that such formulations are efficacious in providing sustained opioid effects for 24 hours in the absence of significant adverse effects, they are likely to have clinical utility as an alternative to methadone for maintenance treatment of opioid dependence. There is currently a paucity of research evaluating the potential for SROM to be used for this purpose. Anecdotal reports and a small number of clinical trials have yielded promising preliminary results (Brewer, 1995; Eder et al., 2002; Fischer et al., 1996; Kraigher, Ortner, Eder, Schindler, & Fischer, 2002; Sherman, 1996), but a number of key questions remained unanswered. In particular, quantitative comparisons of methadone and SROM with respect to their pharmacokinetics, pharmacodynamics, clinical efficacy and patient acceptability are limited. Despite the fact that the most immediate clinical application of SROM maintenance would involve its selective use in patients responding poorly to methadone, there have also been no controlled evaluations of once-daily SROM in a methadone maintenance population.

The present research was undertaken to evaluate the potential clinical utility of SROM as a maintenance pharmacotherapy for opioid dependence by comparing outcomes for methadone

and SROM in an open-label crossover clinical trial. The study included subjects reporting adequate (holders) and inadequate (non-holders) withdrawal suppression whilst maintained on methadone and featured comparisons of the steady-state pharmacodynamics and pharmacokinetics, clinical outcomes and acceptability, and levels of opioid withdrawal associated with transfers between each drug. It was anticipated that the study would provide the basis for future large-scale comparisons of methadone and SROM maintenance using randomised controlled trials conducted under double-blind conditions.

1.2.Background

In evaluating prospective maintenance pharmacotherapies for opioid dependence, it is important to understand the nature of the problems that such interventions are intended to address. In modern society, illicit opioid use is associated with significant negative consequences for both users and the wider community. This section describes the patterns and consequences of illicit opioid use in modern society and highlights the importance of understanding the neurobiology of opioid dependence as a means of developing effective pharmacological interventions.

1.2.1. Origins and history of opioid use

The term opioid refers to a class of naturally occurring (e.g., morphine, codeine) and synthetically produced (e.g., methadone, buprenorphine) drugs derived from the opium poppy and its chemically related derivatives. Opioids produce a variety of pharmacological effects, the most notable being relief from pain, alterations in mood (e.g., euphoria), respiratory depression, sedation, miosis, decreased gastrointestinal motility (constipation), nausea, and vomiting (King & Miller, 1998). Medicinal use of opium, primarily as an analgesic and anti-diarrhoeal agent, has been documented for thousands of years, as has non-medicinal use of such drugs for their powerful euphoric properties (Brownstein, 1993; Gold & Johnson, 1998). The capacity of opioids to produce intense feelings of euphoria and well-being contributes to

the susceptibility of some individuals to engage in compulsive use of such drugs, often despite obvious harmful consequences (King & Miller, 1998; Koob, 2000).

Historically, use of opioids has mainly involved the smoking or eating of raw opium (Gold & Johnson, 1998). More recently, the era of patent medicines in the late 19th and early 20th centuries resulted in widespread abuse of tonics such as laudanum, which contained mixtures of opium and alcohol (Gold & Johnson, 1998). In response to public concerns regarding the prevalence of opium abuse in the early stages of the 20th century, the U.S. Congress introduced legislative acts designed to control medical- and prohibit non-medical use of opioids (Musto & Ramos, 1981); a measure that is now virtually universal among modern societies. Scientific advances during this same era drastically altered the magnitude of impact that opioids now have in modern society. These events include (1) the invention of the hypodermic syringe, (2) the isolation of the active compounds in opium (e.g., morphine), and (3) the synthesis of intensely potent opioids such as heroin from morphine (Gold & Johnson, 1998; Weddington, 1994). Collectively, these developments permitted the delivery of potent opioids into the central nervous system with unprecedented rapidity, thereby magnifying the euphoric effects and addictive liability previously associated with opioids. Another important historical factor in explaining the marked impact of opioids in modern society has been the increasing availability of such drugs, facilitated by advances in the manufacturing and distribution strategies utilised by illicit drug traders.

Ironically, diacetylmorphine, which was first synthesized in 1874 and subsequently marketed as a cough suppressant in 1898 by the Bayer company under the brand name "Heroin", was originally thought to be less addictive than morphine (Borg & Kreek, 1998; Sneader, 1998). Heroin is now used in common parlance to describe the impure street version of diacetylmorphine, which is currently the most frequently abused illicit opioid. Owing largely to its illicit status, heroin has rarely been the subject of sound research (Rentsch, Kullak-

Ublick, Reichel, Meier, & Fattinger, 2001). It crosses the blood-brain barrier more efficiently and elicits a more potent and rapid profile of euphoric effects compared to morphine when injected intravenously; factors that probably contribute to its popularity over other opioids (Quinn, Wodak, & Day, 1997). Although the prevalence of heroin smoking and sniffing is reported to be increasing, intravenous injection remains the predominant means of administration amongst users of heroin and other illicit opioids in most countries (Gold & Johnson, 1998).

1.2.2. Opioid tolerance and dependence

Repeated administration of opioids is associated with adaptations of the body to the continued presence of the drug. The most important of these adaptations include the development of: (1) tolerance, whereby increasing doses are required to produce the same degree of effect; (2) physical dependence, whereby abstinence is associated with the occurrence of unpleasant withdrawal symptoms; and (3) psychological dependence, whereby users experience strong cravings to engage in further opioid use, often in response to environmental cues associated with past drug use and despite awareness of the harmful consequences involved (Williams, Christie, & Mazoni, 2001). These adaptations contribute significantly to the problems associated with use of illicit opioids and the frequent need for pharmacological intervention.

The development of tolerance and both physical and psychological dependence to opioids requires recreational users of heroin and other opioids to obtain, finance, and use increasing amounts of the drug in order to maintain the same degree of desired effect, suppress the manifestation of opioid withdrawal, and satisfy cravings for the drug. Withdrawal from opioids is characterised by symptoms such as sweating, hypertension, nausea, increased heart and respiration rate, piloerection ("goose pimples"), dysphoria, yawning, anxiety, rhinorrhea and sleeping difficulties (Gold & Johnson, 1998; King & Miller, 1998). These symptoms usually appear within 12 hours of the last use of heroin, peak in intensity after two to four days, and eventually subside after seven to ten days. Compensatory opioid consumption

provides rapid amelioration of withdrawal symptoms and is thus negatively reinforcing, despite simultaneously contributing to a continuance of the dependent state (Koob, 2000). Over the long-term, neuronal adaptations induced by chronic opioid exposure, including repeated-pairings of drug effects and salient environmental stimuli, are thought to contribute to the manifestation of opioid cravings and to the frequency of relapse, which can occur many years after signs of opioid dependence and tolerance disappear (Koob, 2000).

Following several decades of research on the neurobiological substrates of opioid use and abuse (discussed in section 1.3.3), dependence on opioids is now viewed as a brain-related disorder exhibiting all the requisite characteristics of a medical illness (Kreek, 2000, 2001; Stimmel & Kreek, 2000). Nonetheless, diagnoses of opioid dependence are normally made in reference to behavioural patterns, including evidence of a "destructive pattern of opioid use leading to significant social, occupational, or medical impairment" (*Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)*, 1994). It is further evidenced by the individual having reported: greater opioid use than intended and over a greater period of time; unsuccessful attempts to cease or reduce levels of opioid use; a great amount of time spent seeking, using and recovering from opioid use; reductions in time devoted to social, recreational and occupational activities; and continued use of opioids despite awareness of serious adverse consequences. Opioid dependence is normally characterised by the presence of tolerance and physical dependence, but can occur in the absence of these factors.

1.2.3. Aetiology of opioid dependence

While there are published reports of medically induced or iatrogenic addiction (Portnow & Strassman, 1985; Walker, 1978), the people who represent the primary target population of modern pharmacotherapies, are those individuals who engage in recreational and often compulsive use of illicit opioids such as heroin. Although the reasons for initiating use of heroin and other drugs are often complex, it has been suggested that drug users can be broadly divided into two broad categories (Leshner, 1999). The first category includes novelty- or

sensation seekers, who engage in drug use to experience euphoric effects and other subjective changes, or to gain acceptance from peers. A second category use drugs as a means of coping with difficulties in life, including attempts to self-medicate for pre-existing mood conditions. Treatment of these groups can necessarily involve slightly different emphases; for example, the need to address underlying mental health issues amongst self-medicating drug users. Irrespective of the reasons for initiating opioid use, however, the development of opioid dependence and compulsive opioid seeking behaviour normally involve common neurobiological processes and thus require similar approaches to treatment.

The 2001 National Drug Strategy Household Survey (Australian Institute of Health and Welfare, 2002a) estimated the proportion of people in Australia aged 14 years older who have ever used heroin to be 1.6%. Of these individuals, 80% were no longer using heroin at the time of the survey, with only 0.2% of the sample reporting heroin use within the last 12 months. The relative infrequency of opioid dependence belies the degree of associated harm inflicted on users and the wider community.

1.2.4. Consequences of opioid use and dependence

Opioid dependence is associated with significant mortality and morbidity, and criminality, among other harms. Research indicates that among the opioid dependent population, untreated individuals die earlier than those in treatment and in comparison to the general population, with annual mortality rates estimated to be up to 20 times greater than would be expected among peers of the same age and gender (Darke, Ross, & Hall, 1996a; Joe, Lehman, & Simpson, 1982; Oppenheimer, Tobutt, Taylor, & Andrew, 1994; Vaillant, 1973). Deaths associated with opioid dependence have numerous causes, including drug-related accidents, suicide, violence, infectious diseases, and both drug-related and other illnesses (Rivara et al., 1997). The major contributing factor to premature death is fatal overdose (Ghodse, Sheehan, Stevens, Taylor, & Edwards, 1978; Powis et al., 1999), which normally results from respiratory depression, and frequently involves synergistic contributions from other sedatives

(e.g., benzodiazepines) (White & Irvine, 1999). Variability in the purity of illicitly traded opioids also contributes to the dangers of opioid overdose, particularly amongst users exhibiting low tolerance to the effects of the drug (Darke, Hall, Weatherburn, & Lind, 1999). Lack of knowledge and willingness to intervene amongst those who witness opioid overdoses similarly contribute to the magnitude of this problem (Best et al., 2002; Dettmer, Saunders, & Strang, 2001; Strang, Darke, Hall, Farrell, & Ali, 1996; Strang et al., 1999).

Other health and mortality risks relate to heroin users' predominant use of the intravenous administration route as a means of maximising the intensity and magnitude of euphoric effects and bypassing the inefficiency of oral drug delivery associated with first-pass metabolism in the liver. Intravenous injection is associated with an increased likelihood of opioid abuse (Quinn et al., 1997), complications at the injection site (e.g., soft tissue infections) (Harris & Young, 2002), and a greater risk of contracting infectious diseases such as hepatitis B and C and the human immunodeficiency virus (HIV) (Crofts et al., 1993; Des Jarlais et al., 1989; Piccolo et al., 2002). Injecting drug use has been estimated to be either directly or indirectly responsible for over a third of all cases of acquired immunodeficiency syndrome (AIDS) and directly responsible for more than 45% of the AIDS cases in New York (Stancliff et al., 2002).

In addition to the immediate dangers associated with overdose and needle use, repeated use of opioids is associated with a number of other behavioural patterns that impact adversely on users of illicit opioid users and the wider community. Of particular concern is the frequency with which heroin users engage in criminal behaviour as a means of financing their daily intake of heroin (Gossop, Marsden, Stewart, & Rolfe, 2000; Hall, Bell, & Carless, 1993). Other means through which illicit opioid use is commonly financed include prostitution, which exacerbates the risks associated with transmission of infectious diseases (Banks, Brown, & Ajuluchukwu, 1991; Gossop, Powis, Griffiths, & Strang, 1995), and public welfare

(Mark, Woody, Juday, & Kleber, 2001). Indeed, opioid users spent a great deal of their time obtaining and using drugs, often to the significant neglect of their health and social functioning and at significant cost to the wider community. The economic costs incurred by society as a result of opioid dependence, including those related to health care (e.g., treatment of hepatitis B and C, HIV), crime (e.g., judicial and law enforcement expenses), and unemployment (e.g., welfare benefits and lost-productivity), have been estimated to exceed US$20 billion per year in the United States alone (Mark et al., 2001). The total human costs are incalculable.

1.2.5. Summary

In summary, although opioids have been used medicinally and recreationally for thousands of years, relatively recent events have drastically increased the potential for use of opioids to result in harmful consequences. These events include the isolation of active alkaloids from opium, the synthesis of more potent drugs such as heroin, and widespread increases in both the availability of such drugs and use of the intravenous administration route. Collectively, these factors have increased the frequency and severity of opioid dependence during the same era that legislative prohibition of recreational opioid use became widespread. In addition to the immediate dangers associated with opioid overdose and needle use, the difficulties involved with finding, financing and using heroin with sufficient regularity to suppress withdrawal and satisfy opioid cravings are pronounced, particularly in an illicit market in which availability, purity and prices of opioids can fluctuate. These factors are associated with numerous maladaptive behavioural patterns, including a tendency for opioid dependent persons to engage in crime or prostitution and to become reliant on public welfare as means of financing their drug use. The health, social, and economic cost associated with opioid dependence is enormous and worthy of the considerable recent research investment aimed at understanding the causes and antecedents of these problems.

1.3.Neurobiology of opioid dependence

The development of repetitive and sometimes compulsive use of heroin and other opioids is often mediated by common mechanisms including the development of tolerance, physical dependence and long-lasting changes in brain function that predisposes the individual to relapse. An understanding of these mechanisms is vital in formulating effective pharmacological interventions for opioid dependence and has been the subject of intensive scientific enquiry in recent decades. The purpose of the present section is to highlight the cellular and synaptic events that contribute to the development of opioid tolerance and dependence and the tendency for compulsive opioid-seeking to develop following repeated use.

1.3.1. Opioid receptors and ligands

Opioids produce their effects by binding to specific protein receptors (opioid receptors) that are located on cell membranes throughout the central nervous system and peripheral tissues (Satoh & Minami, 1995). Drugs that interact with opioid receptors are classified as agonists, antagonists, or partial agonists, according to the pharmacological effects they produce (Zacny & Walker, 1998). Opioid agonists are drugs that produce maximal response upon binding to opioid receptors. Opioid antagonists bind to opioid receptors but produce very little or no response when administered alone. When present in combination with an opioid agonist, opioid antagonists can prevent the latter from binding to the opioid receptor and producing a pharmacological response. Partial agonists bind to opioid receptors but produce a less than maximal response (i.e., lower intrinsic efficacy compared to full agonists) (Zacny & Walker, 1998).

The existence of specific opioid binding sites in the brain was originally postulated because of the intensity and specificity of physiological and subjective changes associated with opioids such as morphine (Reisine, 1995). Multiple receptor types were predicted based on pharmacological evidence that opioid antagonists did not block the effects of all opioid

agonists to the same degree (Cox & Weinstock, 1964; Veatch, Adler, & Way, 1964). In the early 1970s, several groups of researchers independently succeeded in establishing the existence of endogenous opioid receptors in the brain and peripheral tissues (Chang & Cuatrecasas, 1979; Kosterlitz & Waterfield, 1975; Lord, Waterfield, Hughes, & Kosterlitz, 1977; Pert & Snyder, 1973). Based on the pharmacological actions of various opioids, three main types of opioid receptors were subsequently identified: mu (μ), kappa (κ), and delta (δ) (Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Alternative nomenclatures for the opioid receptor family have been proposed on two occasions by The International Union of Pharmacology, but have yet achieve uniform acceptance (for the mu, delta, and kappa opioid receptors, respectively: OP3, OP1, and OP2; and MOP, DOP, and KOP).

During the same period that these opioid receptors were being discovered, endorphins, enkaphlins and dynorphins were identified as endogenous opioid ligands for the mu, delta and kappa receptors, respectively (Simon, 1991). More recently, the molecular basis of opioid receptors has been established following successful cloning of the mu, delta and kappa receptors in a number of species including humans (Raynor et al., 1994; Reisine & Bell, 1993). Pharmacological evidence suggests there may be additional types and subtypes of opioid receptors, but these have not been established using cloning techniques. It is possible that these novel receptors and subtypes derive from post-translational processes and thus lack a genetic basis (Williams et al., 2001). In the aetiology and treatment of opioid dependence, the mu opioid receptor is considered the most important of the opioid receptor classes. Opioid agonists such as methadone, morphine and heroin all exhibit a high affinity for the mu opioid receptor.

1.3.2. Second messengers and effectors

The cellular processes influenced by an opioid ligand binding to an opioid receptor are achieved primarily via coupling to pertussis toxin-sensitive G-proteins (Harrison, Kastin, & Zadina, 1998). The three opioid receptor types exhibit a similar profile of coupling to the

various G-protein variations (e.g., G_i, G_o, and G_s), although subtle differences have been elucidated (Connor & Christie, 1999; Williams et al., 2001). These differences in G-protein interactions, in addition to the heterogenous distribution of the receptor types in the brain and within cells, may contribute to the different patterns of physiological and subjective effects associated with each receptor type (Terenius & Wahlstrom, 1973). Notably, the distribution of opioid receptors in the brain has revealed a general agreement between receptor densities and the functional importance of opioids in those regions (Mao, 1999). Although the primary effects of opioids are mediated by the central nervous system, opioid receptors exhibit a wider anatomical distribution throughout peripheral cells and tissues that give rise to numerous other effects (e.g., hormonal, immunological), whose importance and function are gradually being elucidated, but are currently incompletely understood (Williams et al., 2001).

By coupling to G-proteins, opioid ligand-receptor interactions influence the function of cells via numerous second-messenger effects. These most well-documented of these effects include inhibition of adenylate cyclase, opening of potassium channels, inhibition of voltage-gated calcium channels, and an inhibition of neurotransmitter release (Minami & Satoh, 1995; Satoh & Minami, 1995; Williams et al., 2001). The immediate net result of these second-messenger effectors is a reduction in the excitability of the cell due to hyperpolarisation and the inhibition of neurotransmitter release. Although the primary effects of opioids are therefore inhibitory, they can also exert excitatory effects on various neural pathways by preventing the release of inhibitory neurotransmitters (Williams et al., 2001). An example of this effect is the stimulation of dopamine release by opioids in cells located in the mesolimbic dopamine system, the neural system thought to mediate the rewarding effects of opioids and other drugs of abuse (Koob, 2000; Narita, Funada, & Suzuki, 2001; van Ree, Gerrits, & Vanderschuren, 1999).

1.3.3. Cellular and synaptic adaptations following chronic opioid use

Opioid dependence is associated with adaptations of the cells and neuronal circuits involved in opioid action following repeated opioid exposure. The predominant foci of studies aimed at understanding these adaptations have centred on those processes responsible for the manifestation of the core features of opioid dependence: namely, opioid tolerance, the withdrawal syndrome, and compulsive use of opioids in the face of known harm. A recent review by Williams et al. (2001) distinguished three types of mechanisms that contribute, often in overlap, to the development of these phenomena. Most of the available research relates to the mu opioid receptor; the contributions of delta and kappa opioid receptors to opioid dependence are less well characterised. A thorough review of these mechanisms is ancillary to the purposes of the present discussion and hence focus will be given to the most important and illustrative examples of each process.

The first category of mechanism implicated in the development of opioid dependence involves desensitisation, internalisation and down-regulation of opioid receptors (Williams et al., 2001). Desensitisation frequently involves phosphorylation of the receptor (i.e., the attachment of phosphate groups) following agonist binding; an effect that is mediated by G-protein activated kinases. This conformational change in the receptor gives it high affinity for the cytoplasmic protein arrestin that, in turn, prevents it from binding to inactive G-proteins and producing any effect. Other phosphorylation-independent mechanisms are thought to similarly reduce functional coupling of opioid receptors to G-proteins during repeated-opioid exposure. Following desensitisation by phosphorylation, the receptor may either be reactivated by phosphatases (which remove the phosphate groups from the receptor) or internalised within the cell (endocytosis). Internalisation of the receptor affects the capacity of agonists to produce an effect by removing opioid receptors from the surface of the cell membrane. Once internalised, opioid receptors are degraded and replaced by newly synthesised receptors. Several reports have suggested that the therapeutic efficacy of drugs such as methadone and buprenorphine in treating opioid dependence may be partially related

to their greater efficacy compared to morphine and heroin in promoting receptor internalisation (Blake, Bot, Freeman, & Reisine, 1997; Whistler, Chuang, Chu, Jan, & von Zastrow, 1999; Yu et al., 1997), but this possibility is yet to be adequately established. Although desensitisation and internalisation play a role in mediating short-term adaptations to opioids (e.g., acute tolerance), it is unclear if they contribute to longer-term changes involved in opioid dependence (e.g., compulsive drug use). Long-term adaptations may include down-regulation (i.e., reduced numbers) of opioid receptors. Early studies found no evidence of down-regulation of opioid receptors following chronic agonist treatment (Werling, McMahon, & Cox, 1989). More recent studies have observed down-regulation in brain tissue (Bernstein & Welch, 1998; Law & Loh, 1999; Tao et al., 1998), but it is unclear whether these findings reflect reduced receptor numbers on the cell surface or intracellular events involved in the coupling of G-proteins to opioid receptors.

Overall, the degree of adaptation (e.g., tolerance) seen at the cellular level following chronic exposure is small compared to the degree of tolerance seen in clinical settings, where the effective dose can increase more than a hundred-fold during chronic opioid dosing (Harrison et al., 1998; Williams et al., 2001). This reflects the contribution of other mechanisms operating downstream from the opioid receptor-ligand interaction. A second category of mechanism contributing to the core features of opioid dependence involves counter-adaptations that occur subsequent to receptor activation and act to restore normal functioning in the presence of the drug (Williams et al., 2001). To the extent that the presence of the drug is subsequently needed to maintain normal function, and must be exceeded to produce its normal pattern of effects, these compensatory changes equate to a form of tolerance. Moreover, the persistence of these changes following reductions or cessations in opioid exposure can produce a period during which over-compensation results in a pattern of effects often opposite to the effects of the opioid agonist (i.e., opioid withdrawal). In particular, rebound increases in adenylate cyclase in the locus coeruleus, a brain area dense in

noradrenergic neurons, are thought to be a major mediating factor in the expression of opioid withdrawal (Narita et al., 2001). This is supported by evidence showing that drugs which block certain adrenoreceptors (e.g., clonidine) are effective in suppressing or minimising the expression of opioid withdrawal (Gossop, 1988). Other similar compensatory changes occur at dopaminergic neurons located in the ventral tegmental area that project to the nucleus accumbens (mesolimbic dopamine pathway) and mediate drug reward. Reduced activation of these pathways following cessation of opioid intake is consistent with the dysphoria often associated with opioid withdrawal (Unnithan, Gossop, & Strang, 1992).

A third type of mechanism contributing to the core features of opioid dependence involves activity-dependent adaptations of the neural networks acted upon by opioids (Williams et al., 2001). The effects of opioid agonists on the excitability of cells that either express opioid receptors directly or are indirectly dependent on such cells (e.g., for neurotransmitter release) can lead to conformational changes in the interconnections between neurons in the central nervous system (known as synaptic plasticity). The processes mediating synaptic plasticity in this way include basic processes responsible for memory such as long-term potentiation and long-term depression. These processes are thought to play a primary role in the development of long-lasting brain changes that predispose chronic opioid users to cravings and relapse, often long after signs of opioid tolerance and dependence have dissipated. Indeed, synaptic plasticity is now considered an integral component of the neurobiological explanation for compulsive opioid use, and has replaced the focus on the opioid withdrawal syndrome as the key factor involved in maintaining patterns of repetitive opioid use, particularly over the longer-term (Koob, 2000). In particular, it has been suggested that the stimulatory effects of opioids on the mesolimbic dopamine system, which is involved in attaching motivational importance to internally rewarding and aversive events, may be the central area through which compulsive opioid seeking and using behaviours are maintained (Koob, 2000). Notably, all drugs of abuse so far tested share with opioids the capacity to produce rewarding

states via this neural pathway, although the rewarding effects of opioids are also thought to involve dopamine-independent mechanisms (Koob, 2000). Despite many important advances, a lot remains to be understood regarding the neural processes responsible for the often life-long, chronic, relapsing nature of opioid dependence.

1.3.4. Cross-tolerance and -dependence

Since the cellular and synaptic adaptations responsible for opioid tolerance and dependence occur downstream from the opioid receptor, consequent alterations in the dosage of drug required to produce normal effect or restore normal function will also apply to other ligands binding at the same receptor site. This means that withdrawal symptoms associated with physical dependence on heroin can be ameliorated by the administration of another opioid agonist whose effects are similarly mediated through the mu opioid receptor, such as methadone (Dole & Nyswander, 1965; Dole & Nyswander, 1967). Similarly, individuals repeatedly exposed to one particular opioid agonist will also show tolerance to other opioid agonists that produce their effects through the same opioid receptor (Houtsmuller et al., 1998; Schuh, Walsh, Bigelow, Preston, & Stitzer, 1996; Volavka, Verebey, Resnick, & Mule, 1978). These phenomena, known as cross-tolerance and dependence, are important in understanding the treatment of opioid dependence using the maintenance pharmacotherapy approach.

1.3.5. Neurobiological basis of maintenance pharmacotherapies

The neurobiological changes associated with repeated-exposure to short-acting opioids such as heroin form the rationale for maintenance pharmacotherapies, which have been defined as "the administration of a long-acting opioid drug to an opioid dependent person, usually by a non-parenteral route of administration, for the therapeutic purposes of preventing or substantially reducing injection of illicit opioids" (Ward, Mattick, & Hall, 1998d). This approach to treatment normally involves two main mechanisms of action: (1) cross-tolerance, whereby the maintenance opioid is administered to prevent opioid withdrawal; and (2)

competition for opioid receptor binding sites, whereby the maintenance drug blocks the effects of other opioids (Fiellin & O'Connor, 2002). Thus, maintenance pharmacotherapies aim to facilitate abstinence from illicit opioids by suppressing opioid withdrawal and cravings, blocking the euphoric effect of exogenously administered opioids, or some combination of these effects (Ward et al., 1998d). Opioids permissive of infrequent (e.g., once-daily) dosing by a non-parenteral route are favoured as these minimise the inconvenience and costs associated with treatment and avoid the hazards and complications of needle use.

1.3.6. Summary

In summary, repeated exposure to short-acting opioids is associated with neurobiological changes in cellular and synaptic systems that mediate the effects of opioids. These adaptations include those that function to produce normal physiological function in the presence of the drug (opioid tolerance), abnormal physiological function in the absence of the drug (opioid withdrawal), and a long-lasting predisposition towards compulsive use of the drug in the face of obvious harm (cravings). Maintenance pharmacotherapies seek to facilitate abstinence from illicit opioids by stabilising the perturbations in brain neurochemistry associated with repeated cycles of opioid use and abstinence. This typically involves the administration of a long-acting opioid that is effective in suppressing opioid withdrawal and cravings, blocking the euphoric effects of heroin, or some combination of these effects.

1.4. Methadone maintenance treatment

Methadone is an opioid that is used almost universally in maintenance programs for opioid dependence worldwide and is the gold standard against which prospective pharmacotherapies are compared. The following discussion reviews the origins, history, pharmacology and effectiveness of methadone maintenance as an exemplar of the maintenance pharmacotherapy approach and highlights the need for alternative pharmacotherapies to be identified.

1.4.1. Origins and history of methadone maintenance

During the past century, the means by which society has sought to resolve problems arising from opioid dependence have undergone considerable change. In recent decades, scientific advances have helped to reveal the neurobiological substrates of opioid dependence and have guided a general paradigm shift in the ways in which problems associated with use of heroin and other illicit opioids are approached. In particular, there is growing recognition that, irrespective of the reasons why people initiate opioid use, dependence on opioids is essentially a brain-related medical condition for which pharmacological intervention is often necessary (McLellan, Lewis, O'Brien, & Kleber, 2000). Awareness of these issues has supported the development and expansion of the maintenance pharmacotherapy approach, which is now the predominant form of pharmacological intervention for opioid dependence worldwide.

In the early 20th century, it was not uncommon for physicians in the United States to treat opioid dependence by the prescription of opioids such as morphine as a means of relieving the symptoms of opioid withdrawal (Musto & Ramos, 1981). Although this practice was not forbidden by legislation introduced to curb illicit opioid dependence (Harrison Act), it was considered problematic amongst the authorities responsible for enforcing those laws. Following indictments and prosecutions of individual practitioners, and their subsequent cessation of the practice, morphine-dispensing clinics were eventually established to cope with the need for treatment of opioid dependence. These clinics closed in 1920 by decree of American Medical Association, which believed prescription of opioids to dependent users was not an acceptable medical practice.

Following the legislative banning of non-medical opioid use, and prior to the contemporary understanding of opioid dependence as a brain-related medical illness, dependence on opioids and other narcotics has been commonly conceived as a "self-inflicted disease of the will or moral flaw" (National Institutes of Health, 1997). Under this approach, the criminal judiciary

system has been the primary means through which problems arising from opioid dependence were addressed, namely by arresting those who manufactured, distributed and used illicit opioids. Notwithstanding the sophistication of modern drug-importation interception methods, investigations of their effectiveness suggest that even large heroin seizures have no measurable impact on the availability of heroin or rates of overdose and HIV infection (Weatherburn & Lind, 1997; Wood et al., 2003).

In the 1960s, researchers in New York re-instigated the practice of administering controlled doses of opioids to dependent persons four decades after the first maintenance clinics were closed. Dole and Nyswander (1967) conceptualised heroin dependence as a permanent metabolic deficiency that needs to be restored in order to achieve normal functioning. Their approach differed from earlier attempts at maintenance treatment in that they used once-daily oral methadone instead of morphine (which requires several doses per day in standard formulations) as the maintenance agent and also provided a comprehensive range of social support services (e.g., assistance in obtaining jobs, housing and education). Results indicated that methadone was useful in reducing "narcotic hunger" and in inducing high levels of tolerance sufficient to block the euphoric effects of subsequently used heroin. The original group of 22 patients showed marked improvement on measures of social functioning (Dole & Nyswander, 1965). Few complications, other than frequent reports of constipation and the need to carefully individualise treatment, particularly during methadone dose titration, were reported in the conduct of these early investigations.

Since first being evaluated in New York nearly four decades ago, methadone maintenance treatment has become the predominant pharmacological intervention for opioid dependence worldwide. There are over 500,000 patients currently in substitution treatment around the world, most of whom receive methadone maintenance (European Monitoring Centre for Drugs and Addiction, 2000). Methadone was first used for substitution treatment in Australia

in 1969 (Ali & Quigley, 1999). In 2001, it was estimated that there were approximately 32,000 methadone maintenance patients in Australia (Australian Institute of Health and Welfare, 2002b). This number increases by approximately 15% per annum (Ali & Quigley, 1999).

The practice of prescribing opioids to dependent persons has attracted controversy throughout its history, with some critics questioning the ethical validity of a treatment that maintains dependence on opioids (Ward et al., 1998d). Nonetheless, the goal of a drug-free life may be unattainable or unsustainable for a significant proportion of opioid dependent persons. By comparison, research shows treatment goals including reductions in drug use and criminal behaviour and improvements in health and social functioning are readily achievable for many patients who are prescribed opioids using a maintenance approach (Ward, Mattick, & Hall, 1994). Increasing acceptance of 'harm-minimisation' as the principal goal of drug abuse interventions has led to the implementation of several initiatives designed to improve access to methadone maintenance, including general practitioner-based prescribing and pharmacy-based dispensing of methadone, although adoption of these methods has only recently or partially occurred in some countries.

1.4.2. Pharmacology of methadone

Methadone was originally synthesised in Germany for use as an analgesic on the battlefields of World War Two. It is normally delivered as a racemic mixture of two enantiomers, (R)- and (S)- methadone. Although the primary opioid effects of methadone appear to be mediated almost entirely by the (R)-methadone enantiomer (Scott, Robbins, & Chen, 1948), the racemic mixture is less expensive to produce and thought to be as effective as (R)-methadone alone in treating opioid dependence (Eap, Buclin, & Baumann, 2002). As a full opioid agonist that is selective for the mu opioid receptor (Codd, Shank, Schupsky, & Raffa, 1995), methadone produces a similar profile of pharmacological effects to heroin and its active metabolite morphine (Jasinski & Preston, 1986). However, methadone differs from morphine

by showing a much longer half-life (2 h vs. >24 h) and higher oral bioavailability (30% vs. 80-90%) (Gourlay, Cherry, & Cousins, 1986). These characteristics normally permit sustained suppression of opioid withdrawal and cravings using once-daily oral dosing regimens, thereby minimising the inconveniences associated with the usual requirement for supervised dosing (a measure designed to reduce inappropriate use of the maintenance medication) and avoiding the hazards and problems associated with intravenous injection. In addition to these pharmacokinetic differences, *in vitro* animal studies suggest that methadone further differs from morphine by showing greater selectivity (Ki values for (R)-methadone and morphine) for mu (0.9 and 1.24 nM/L) over delta (371 and 145 nM/L) and kappa (1860 and 23.4 nM/L) opioid receptors (Codd et al., 1995) and greater intrinsic efficacy at the mu opioid receptor (Adams, Paronis, & Holtzman, 1990). In addition to their different opioid properties, methadone differs from morphine by also showing (Ki values for (R)- and (S)-methadone, respectively), N-methyl-D-aspartate (NMDA) receptor antagonist characteristics (3.4 and 7.4 μM/L) (Ebert, Thorkildsen, Andersen, Christrup, & Hjeds, 1998; Gorman, Elliott, & Inturrisi, 1997) and the capacity to inhibit neuronal re-uptake of both noradrenaline (0.702 and 12.7 μM/L) and serotonin (0.014 and 0.992 μM/L) (Codd et al., 1995). The clinical significance of these differences is presently unclear.

1.4.3. Effectiveness of treatment

Overwhelming evidence of the effectiveness of methadone maintenance in reducing the mortality, morbidity and criminality associated with opioid dependence has accumulated since its introduction (Strain & Stitzer, 1999). In addition to this evidence base, other contextual factors, including an improved neurobiological understanding of opioid dependence and increased public awareness regarding the HIV epidemic in the 1980s, have similarly contributed to the proliferation and acceptance of methadone maintenance programmes around the world. The present section summarises the research literature pertaining to its effectiveness as a maintenance treatment for opioid dependence.

In controlled clinical trials, methadone maintenance has been shown to be more effective in reducing illicit opioid use than no treatment (Dole et al., 1969; Yancovitz et al., 1991), drug-free treatments (Gunne & Gronbladh, 1981), placebo medications (Newman & Whitehill, 1979; Strain, Stitzer, Liebson, & Bigelow, 1993), and detoxification (Vanichseni, Wongsuwan, Choopanya, & Wongpanich, 1991). These studies were recently the subject of a meta-analysis, which indicated statistically significant advantages for methadone over 'no replacement therapy' (expressed in terms of relative risk: RR) in retaining patients in treatment (RR = 3.05, 3 studies, n = 505) and the frequency of morphine-positive urine samples (RR = -0.32, 2 studies, n = 409), although trends towards less criminal activity (RR = 0.39, 3 studies, n = 363) and prevention of deaths (RR = 0.49, 3 studies, n = 435) were not statistically significant (Mattick, Breen, Kimber, & Davoli, 2002). It should be noted that criminal activity is sometimes more difficult to measure compared to health and drug use indicators, given the reluctance of patients to divulge information of an incriminating nature.

In addition to studies involving controlled research methodologies, observational and longitudinal studies attest to the many benefits associated with retention in a methadone maintenance program, including improvements in health and social functioning and reduced mortality due to overdose and HIV (Ball, Lange, Myers, & Friedman, 1988; Des Jarlais et al., 1989; Hall, Ward, & Mattick, 1998; Ryan & White, 1996; Schoenbaum et al., 1989). The body of evidence supporting the effectiveness of methadone maintenance is strengthened by the diversity of cultures and research groups from which it has emanated. Importantly, the benefits associated with methadone maintenance have also been shown to outweigh the costs of providing treatment (Barnett, 1999; Barnett & Hui, 2000).

The manner in which methadone maintenance treatment is delivered is known to vary considerably between different clinics, with resultant variation in the quality of treatment outcomes (D'Aunno, Folz-Murphy, & Lin, 1999; D'Aunno & Pollack, 2002; D'Aunno &

Vaughn, 1992). Clinic characteristics associated with poorer outcomes in terms of treatment recruitment, retention and outcomes include inadequate dosing (Caplehorn & Bell, 1991; Saxon, Wells, Fleming, Jackson, & Calsyn, 1996), restrictive entry criteria (Uchtenhagen, 1990), rigid goals and requirements of patients (Bell, Chan, & Kuk, 1995; Caplehorn, Irwig, & Saunders, 1996; Szapocznik & Ladner, 1977), inadequate provision of counselling services (McLellan, Woody, Luborsky, & Goehl, 1988), an orientation towards abstinence rather than maintenance (Bell et al., 1995; Caplehorn, McNeil, & Kleinbaum, 1993), lack of patient involvement in dose determination (Condelli, 1993; Maddux, Vogtsberger, Desmond, & Esquivel, 1993; Magura et al., 1988), and poor accessibility of treatment (Gaughwin, Solomon, & Ali, 1998). The effectiveness of methadone maintenance is also dependent on the availability of treatment. In New York, it has been estimated that less than 20% of heroin users have access to methadone maintenance (Stancliff et al., 2002). Other studies similarly report long-waiting lists for treatment entry (Dore, Walker, Paice, & Clarkson, 1999).

1.4.4. Shortcomings of methadone maintenance

Although methadone has proven to confer enormous benefits to treatment recipients and the wider community, it is not without shortcomings (Ling et al., 1994). Some of these limitations relate to the pharmacological characteristics of methadone itself; others simply reflect the need to enhance patient choice and clinician flexibility by offering a greater range of alternatives pharmacotherapies. The complexity of opioid dependence requires a diversity of therapeutic approaches and thus no single therapeutic strategy (i.e., once-daily oral methadone dosing) is likely to be effective in all cases. The purpose of the following discussion is to highlight some of the major factors limiting the effectiveness, attractiveness and safety of methadone as a maintenance pharmacotherapy for opioid dependence.

1.4.4.1. Mechanism of intervention

At a fundamental level, methadone maintenance has been criticised because it involves continued exposure to an opioid agonist and thus continued dependence on opioids (Ausubel,

1983; Bell & Zador, 2000; Ward et al., 1998d). Proponents of this argument can be divided into two broad categories. The first category includes those whose primary objection to the use of methadone is of a moral nature, often involving the belief that it is either immoral or unethical to maintain a person indefinitely on opioids. In response to this argument, the many differences between dependence on methadone in the context of a therapeutic setting (e.g., controlled oral doses, provision of ancillary support) and dependence on illicit heroin (e.g., intravenous needle use, unreliable availability and purity, exposure to criminal underworld, high costs) need to be considered. Moreover, evidence indicating that methadone maintenance is the most effective known intervention for reducing the mortality, morbidity and criminality associated with illicit opioids similarly provides a strong ethical justification for treatment (Bell & Zador, 2000).

A second category of objections to the continuance of opioid dependence inherent in methadone maintenance can be made from a medical viewpoint. As detailed earlier, numerous cellular and synaptic adaptations occur following prolonged exposure to opioid agonists such as methadone and morphine. Although methadone maintenance is therapeutically effective in restoring the compensatory adaptations that require the presence of opioids to attain normal function (i.e., suppressing opioid withdrawal), the treatment is less effective in attenuating other core features of opioid dependence including tolerance, psychological dependence (i.e., cravings) and other adaptations (e.g., immunosuppression, sexual dysfunction, affective changes) that may also have significant ramifications regarding predisposition to relapse and long-term health. Nevertheless, these problems may be less deleterious to the health of methadone maintenance patients than continued dependence on illicit opioids such as heroin.

1.4.4.2. Methadone-related deaths

Of considerable concern is the frequency with which methadone is associated with premature deaths during treatment; in particular, deaths caused by accidental drug toxicity during the induction and dose finding phase following commencement of treatment. Although

methadone maintenance reduces the mortality rate associated with heroin use by a factor of four overall, the risk of fatal accidental drug toxicity during the first two weeks of methadone maintenance treatment has been estimated to be nearly seven times greater compared to heroin users not in treatment (Caplehorn & Drummer, 1999, 2002a, 2002b). A review of 238 deaths among methadone maintenance patients in New South Wales between 1990 and 1995 indicated that over 20% had died during the first week of treatment (Zador & Sunjic, 2000). Lack of methadone tolerance, poly drug use (e.g., methadone in addition to alcohol, benzodiazepines and other opioids) and inappropriate methadone prescribing (e.g., initial doses too high or increased too rapidly) have been implicated as the most important factors in explaining cases of toxicity early in treatment (Caplehorn & Drummer, 2002a; Drummer, Opeskin, Syrjanen, & Cordner, 1992; Williamson, Foreman, White, & Anderson, 1997; Zador & Sunjic, 2000; Zador, Sunjic, & Darke, 1996; Zador & Sunjic, 2002). Methadone-prescribing clinicians must achieve a careful balance between the risks associated with over-prescribing (e.g., delayed methadone toxicity) and under-prescribing (e.g., supplementary use of other sedatives to combat withdrawal) methadone during the induction period. Surprisingly little is known about the causes of methadone-related deaths that occur during the later maintenance phase of treatment.

A second category of deaths related to methadone maintenance occur as a result of inappropriately used or diverted methadone. Studies indicate that between one-third and two-thirds of all methadone-related deaths occur in persons not currently registered in a methadone maintenance program (Sunjic & Zador, 1999). The source of methadone in such cases is presumed to be "take-away" methadone doses (Bell & Zador, 2000; Cairns, Roberts, & Benbow, 1996), diversion of which for intravenous injection or sale appears to be common (Darke, Ross, & Hall, 1996b). Contrary to the interpretation that methadone maintenance and, in particular, take-away doses are placing opioid naïve persons at risk of accidental methadone toxicity, consumers of diverted methadone are often observed to be similar to

regular heroin users and thus already at an increased risk of mortality (Zador & Sunjic, 2000; Zador et al., 1996; Zador & Sunjic, 2002). It has even been speculated that diverted methadone may serve a protective mechanism against opioid overdose among heroin users (Hall, Lynskey, & Degenhardt, 2000). Nonetheless, it is evident that methadone does have abuse liability. To this extent, it is liable to be used inappropriately by both methadone maintenance patients and recipients of diverted methadone and may contribute to methadone-related fatalities.

1.4.4.3. Individual variability in response to methadone

Individuals vary considerably in their response to methadone. This includes variability in the concentration of methadone in plasma achieved by a single-oral dose and in the magnitude of opioid effect associated with a given plasma methadone concentration (Eap et al., 2002; Garrido & Troconiz, 1999). Individual variability in methadone disposition and effects has two major clinical consequences. Firstly, an individualised approach to dosing must be utilised in order to achieve an optimal balance between the therapeutic (i.e., suppression of opioid withdrawal and cravings) and adverse (e.g., constipation, sedation, respiratory depression) effects produced by the maintenance dose. This may have negative consequences regarding the costs and availability of treatment, given the finite resources available to operators of methadone maintenance clinics. Second, in instances where an individualised approach to dosing fails to yield an acceptable balance between therapeutic and adverse effects, alternative treatment strategies may be indicated (Dyer & White, 1997). These problems are outlined below.

1.4.4.3.1. Therapeutic effects: the problem of 'not holding'

Even when an individualised approach to dosing is implemented, up to a third of methadone maintenance patients report the regular failure of their methadone dose to adequately hold (i.e., suppress opioid withdrawal) for the full 24-hour inter-dosing interval (Dyer & White, 1997). Although higher methadone doses and plasma concentrations are associated with a

reduced likelihood of illicit drug use (Gossop, Strang, & Connell, 1982; Ling, Blakis, Holmes, Klett, & Carter, 1980; Strain, Stitzer, Liebson, & Bigelow, 1994), the relationship between methadone dose and plasma concentration and the severity of subjective opioid withdrawal is not strong (Horns, Rado, & Goldstein, 1975; Tennant, Rawson, Cohen, Tarver, & Clabough, 1984). Withdrawal is highly likely if plasma methadone concentrations fall below 50 ng/mL (Bell, Seres, Bowron, Lewis, & Batey, 1988; Wolff, Sanderson, Hay, & Raistrick, 1991), but some patients require very high doses (e.g., 350 mg) to achieve adequate withdrawal suppression (Byrne, 1996). Given the increased likelihood that non-holders will use illicit drugs, be unsatisfied with treatment and leave treatment prematurely (Hiltunen et al., 1999; Holmstrand et al., 1978), it is important that the causes of withdrawal complaints be identified.

Two previous studies have investigated differences in the pharmacokinetics of methadone between patients reporting inadequate withdrawal suppression (non-holders) and those reporting no such problem (holders). Nilsson et al. (1983) compared the pharmacokinetics of methadone in a group of non-holders (n = 8) and a group of unselected controls (n = 12). Although both groups showed similar overall plasma methadone concentrations, the non-holders exhibited significantly smaller volumes of distribution (Vd) compared to the holders (e.g., Vd at steady-state: 2.7 L/kg vs. 4.2 L/kg). The authors hypothesised that this would result in more rapid changes in methadone concentrations during the inter-dosing interval. This would include a more rapid decline between peak and trough, resulting in an unacceptable degree of pharmacodynamic change, and reports of the dose not holding. Consistent with this hypothesis, Dyer et al. (1999) compared the steady-state pharmacokinetics of racemic methadone in holders (n = 9) and non-holders (n = 9) and found no significant differences in means between the two groups for trough plasma methadone concentrations (249 ng/mL vs. 257 ng/mL) or area under the plasma methadone concentration-time curve (AUC 0-23 h, 7.4 mg·h/L vs. 8.2 mg·h/L). Rather, the non-holders

differed from the holders by showing a greater maximal rate of decline in plasma methadone concentrations in the period from peak to trough (42 ng/mL/h vs.75 ng/mL/h), although this difference only reached statistical significance when 2 subjects whose urinalyses were positive for opioids were excluded. The authors of each of these studies concluded that once-daily methadone dosing is an inappropriate treatment strategy for some patients.

The frequency with which methadone patients report non-holding is of particular concern given the limitations associated with current strategies for addressing the problem. The standard clinical response of increasing the daily methadone dose is likely to be effective in some patients, particularly if the dose is significantly below putative thresholds for effective treatment, but also has a number of major drawbacks. Firstly, many patients may be reluctant to undergo dose increases for fear of adverse effects or prolonging eventual withdrawal from treatment (Bell et al., 1995). Second, the studies reviewed above indicate that increasing the methadone dose in some patients may exacerbate the degree of pharmacodynamic change that occurs during the inter-dosing interval, including an increased likelihood of adverse effects (e.g., respiratory depression, sedation and intoxication) at times of peak plasma methadone concentrations and possibly continued withdrawal complaints at times of trough plasma methadone concentrations (Dyer et al., 1999; Nilsson et al., 1983). The strategy of shortening the dose interval (e.g., twice-daily dosing) to minimise such fluctuations in plasma methadone concentrations is also problematic. Patients may find such dosing schedules impractical and inconvenient, particularly given the common requirement that doses be consumed under supervision. The provision of take-away doses to enhance patient acceptability of frequent dosing schedules entails risks associated with methadone diversion, as outlined earlier. Finally, there are also certain limitations associated with the option of transferring patients from methadone to other currently available long-acting maintenance medications such as buprenorphine and LAAM (described in section 1.5).

1.4.4.3.2. Adverse effects

Even when adequate withdrawal suppression is achieved, many methadone maintenance patients report significance adverse effects attributable to their maintenance dose. Among those symptom complaints most commonly reported by methadone maintenance patients are constipation, sweating, painful joints and bones, insomnia, general malaise, sexual dysfunction (e.g., reduced libido), and menstrual irregularities, each of which have been reported to occur in excess of 50% of patients (Dyer & White, 1997; Goldstein & Judson, 1973; Judson & Goldstein, 1982; Kreek, 1973; Longwell et al., 1979). Other chronic adverse effects sometimes associated with methadone include depression, weight gain and appetite changes (Dyer & White, 1997; Sherman, 1996). Sedation, intoxication, cognitive impairment (Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001) and electrocardiogram (ECG) abnormalities (e.g., QT prolongation) (Deamer, Wilson, Clark, & Prichard, 2001; Katchman et al., 2002) have also been associated with methadone, particularly at times of peak plasma methadone concentrations. These symptom complaints include direct pharmacological effects of methadone to which tolerance has not fully developed and may never fully-develop (Dyer & White, 1997). In one study, for example, sweating and constipation were reported by 48% and 17%, respectively, of high-dose methadone maintenance patients after three or more years of treatment (Kreek, 1973). Adverse effects impact negatively on treatment recruitment, retention and outcomes and are thus a major concern.

1.4.4.4. Affective responses

Normalisation of mood states is a particularly important objective during maintenance treatment for opioid dependence, given evidence that negative or unstable mood patterns can make patients more vulnerable to relapse to illicit heroin use and less amenable to psychosocial interventions (Calsyn, Wells, Fleming, & Saxon, 2000; Kanof, Aronson, & Ness, 1993; Powell, Bradley, & Gray, 1992; Unnithan et al., 1992). Recent studies have highlighted two major ways in which methadone maintenance sometimes fails to normalise mood states. Firstly, many patients experience significant changes in mood during the inter-

dosing interval in response to fluctuations in plasma methadone concentrations (Dyer et al., 2001; Hiltunen et al., 1999). These mood fluctuations are particularly pronounced in patients reporting the failure of their dose to hold for 24 hours (Dyer et al., 2001; Hiltunen et al., 1999). Second, methadone maintenance patients generally show a greater overall degree of mood disturbance (i.e., negative mood states) (Dyer et al., 2001) and are up to 10 times more likely to be diagnosed with psychiatric disorders, particularly depression and anxiety disorders, compared to normal populations (Callaly, Trauer, Munro, & Whelan, 2001; Ward, Mattick, & Hall, 1998b).

It is possible that the high levels of dysphoria and depression associated with methadone maintenance are partially related to the effects of chronic exposure to methadone and other opioids, although environmental (e.g., lifestyle) and genetic factors are also implicated. Cellular and synaptic adaptations accompanying repeated opioid exposure sometimes result in dysfunction of the endogenous opioid system (Williams et al., 2001), which is involved in the regulation of mood. Numerous reports and observations suggest that repeated exposure to opioids leads to the development of a generalised dysphoric state, in contrast to the acute mood effects that are often euphoric (Fraser, Jones, Rosenberg, & Thompson, 1963; Griffith, Fann, & Tapp, 1968; Martin & Jasinski, 1970; Martin et al., 1973; McNamee, Mirin, Kuehnle, & Meyer, 1976; Mirin, Meyer, & McNamee, 1976a; Mirin, Meyer, McNamee, & McDougle, 1976b; Wikler, 1952). Additionally, it should be noted that, unlike heroin and morphine, methadone inhibits the reuptake of noradrenaline and serotonin (Codd et al., 1995), and acts as a non-competitive antagonist at NMDA receptors (Ebert et al., 1998; Gorman et al., 1997). Whereas serotonin and noradrenaline uptake inhibition is associated with anti-depressant effects (Ressler & Nemeroff, 2000), NMDA antagonists have been associated with severe mood disturbances (Abi-Saab, D'Souza, Moghaddam, & Krystal, 1998; Adler et al., 1999; Curran & Monaghan, 2001; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996). In this regard, methadone might cause mood changes that are distinct from those

associated with other opioids. Affective responses during maintenance treatment for opioid dependence are addressed in greater detail in Chapter 5.

1.4.4.5. Hyperalgesia

Clinical and empirical evidence indicates that chronic opioid exposure is associated with the development of a heightened sensitivity to pain, or hyperalgesia (Compton, Charuvastra, Kintaudi, & Ling, 2000; Compton, Charuvastra, & Ling, 2001; Doverty et al., 2001a; Doverty et al., 2001b). In the context of maintenance treatment for opioid dependence, hyperalgesia is problematic for two main reasons. Firstly, persistent pain is associated with secondary symptoms including anxiety and depression (Hunt & Mantyh, 2001) that may promote compensatory opioid use and hence compromise treatment outcomes. Secondly, hyperalgesia is likely to further complicate the difficulties associated with management of pain in opioid dependent populations (Compton & McCaffery, 2001). These difficulties include misguided beliefs and suspicions amongst medical practitioners who may believe the maintenance dose is sufficient to provide analgesia or who may be resistant to provide normal opioid doses to persons with a history of substance abuse (Cleeland, 1987). This is problematic because methadone maintenance patients are, if anything, more likely than the rest of the population to require pain management at some point in their lives (Cameron, 1964; Sapira, 1968), yet show virtually no analgesic response to morphine for pain induced by the cold pressor method, even at concentrations well above those associated with post-operative pain relief (e.g., > 200 ng/mL) (Athanasos et al., 2002).

1.4.4.6. Methadone during pregnancy

Opioid dependent pregnant women are often exposed to the normal range of health (e.g., infectious disease, poor nutrition, inadequate rest), social (e.g., homelessness, poverty, legal crises) and psychological (e.g., depression, anxiety) problems associated with an opioid dependent lifestyle, in addition to many pregnancy-specific risks (e.g., premature labour, abruption of the placenta) that can jeopardise the health of both the woman and foetus

(Finnegan, 1991; Ward, Mattick, & Hall, 1998a). Although opioids have no known teratogenic effects themselves, exposure to the contaminants found in illicit heroin have the capacity to cause morphological changes in the developing foetus (Hoegerman, Wilson, Thurmond, & Schnoll, 1990; Ward et al., 1998a). Unfortunately, early signs of pregnancy in opioid dependent women are sometimes misinterpreted either as opioid withdrawal or because of the high incidence of menstrual irregularities (e.g., amenorrhea) known to occur in this population (Hoegerman et al., 1990; Ward et al., 1998a). In addition to fears of prejudice and stigma (e.g., loss of child to welfare agencies), these factors can contribute to undesirable delays in the time taken to present for care during pregnancy (Ward et al., 1998a). Neonatal abstinence syndrome (NAS) occurs commonly among infants born to opioid dependent mothers and includes symptoms of neurological excitability, gastrointestinal dysfunction, vomiting, dehydration, poor weight gain and seizures (Osborn, Cole, & Jeffery, 2002; Ward et al., 1998a). Studies further suggest that infants born to mothers using opioids or other illicit drugs exhibit greater risks of neonatal mortality (Hulse, Milne, English, & Holman, 1998), sudden infant death syndrome (Kandall, Gaines, Habel, Davidson, & Jessop, 1993) and abnormal neurodevelopment outcomes (Ornoy, Michailevskaya, Lukashov, Bar-Hamburger, & Harel, 1996).

Methadone maintenance is associated with better outcomes during pregnancy compared to no treatment (Ward et al., 1998a). This is consistent with the knowledge that methadone reduces the frequency of withdrawal cycles, exposure to heroin contaminants, and the likelihood of the mother engaging in numerous behaviours associated with illicit opioid use that are likely to deleteriously impact on the child or foetus (e.g., crime, prostitution, needle sharing). The treatment setting also provides a contact point for the provision of antenatal support and care. Despite these advantages over no treatment, methadone maintenance during pregnancy presents several challenges. In particular, infants born to methadone maintained mothers are still likely to experience withdrawal, which is often more prolonged and delayed than for

heroin (Doberczak, Kandall, & Wilets, 1991; Kandall & Gartner, 1974). There is also evidence that seizures associated with NAS may be more common for methadone than for heroin (Herzlinger, Kandall, & Vaughan, 1977). Although clinically significant withdrawal is uncommon when the methadone dose is below 20 mg per day, this is well below the normal dose range (>50 mg/day) (Ward et al., 1994). Opioid withdrawal during pregnancy is considered more dangerous to the child than NAS (Ward et al., 1998a). Thus, methadone maintenance provides a sub-optimal environment for foetal development and is likely to have negative consequences for neonatal well-being.

1.4.4.7. Methadone withdrawal syndrome

There are many instances in which methadone maintenance patients may undergo a reduction in maintenance dose, either to obtain a lower dosage level or to terminate treatment and attempt to achieve a completely opioid-free life (Magura & Rosenblum, 2001). Example scenarios include patients wishing to lower their dose to enable maintenance with an antagonist or partial agonist (e.g., naltrexone, buprenorphine), to reduce the likelihood of neonatal abstinence syndrome during pregnancy, or to achieve complete abstinence from methadone following successful rehabilitation or because of poor treatment outcomes (e.g., inadequate withdrawal suppression, adverse effects). Withdrawal from methadone is considered milder but more prolonged compared to shorter-acting opioids such as heroin and morphine (Jaffe, 1990; King & Miller, 1998). Whereas heroin withdrawal generally peaks in two to four days and subsides within ten days, methadone withdrawal may reach maximal intensity in three days and not begin to subside until the third week, with complete dissipation of symptoms taking months to occur (Jaffe, 1990).

The protracted nature of methadone withdrawal limits the effectiveness of the treatment in a number of ways. Although abstinence and not detoxification is usually the goal of treatment, many individuals may resist entering treatment or increasing the daily dose once enrolled in treatment to avoid prolonging eventual withdrawal from methadone or for fear of side effects

(Bell et al., 1995; Rosenblum, Magura, & Joseph, 1991). Patients maintained on inadequate doses or who are attempting to reduce their daily dose are likely to experience greater withdrawal and cravings and are thus more likely to engage in illicit drug use (Magura & Rosenblum, 2001). The difficulties associated with methadone withdrawal are exacerbated by the anxieties many patients have regarding detoxification attempts, which are sometimes disproportionate to the amount of distress likely to be involved (Hall, 1979).

1.4.4.8. The process of treatment delivery

Methadone maintenance is a highly regulated treatment subject to numerous controls and restrictions of both medical and socio-political origin. Despite extensive research validation of the benefits and cost-effectiveness of treatment, and decades of subsequent expansion, numerous factors continue to impede the scale on which methadone maintenance can be delivered (e.g., financial resources, public acceptance of methadone programs) (Hall, 1979). As mentioned previously, the current availability of methadone maintenance slots in New York allows less than 20% of regular heroin users access to the best treatment (Stancliff et al., 2002). Even when supply is sufficient, demand for treatment may be adversely affected by perceptions of the treatment process as overly restrictive and intrusive (Uchtenhagen, 1990). Concerns regarding the ease of access to treatment, the stigma associated with often highly-visible public clinics, negative staff attitudes, the effects of methadone on health, and the restrictions associated with daily supervised dosing all contribute to the ambivalence of many prospective patients towards entering or re-entering treatment (Bell et al., 1995; Stancliff et al., 2002; Uchtenhagen, 1990). The provision of take-away doses can lessen the burden of daily supervised dosing, but these and other forms of treatment privileges are often contingent upon the patient's compliance with treatment (e.g., opiate-free urinalyses, attendance at clinic). Although the hazards associated with take-away methadone necessitates certain precautionary measures, these procedures can be viewed as punitive by patients and obstruct a sense of validation and affirmation (i.e., transition from 'drug addict' to patient) that would otherwise facilitate achievement of treatment objectives (Bell, 1998). On a practical level, the

requirement for frequent supervised dosing can directly impede achievement of treatment goals by impeding social integration; for example, by making it difficult to attend employment, avoid contact with other drug users and dealers, and travel (Ling et al., 1994).

Of further concern is the extent to which external, non-medical factors can infiltrate the treatment delivery process. Some treatment providers continue to promote abstinence from opioids as the primary goal of treatment (Caplehorn, Lumley, Irwig, & Saunders, 1998b) despite overwhelming evidence of the poor prognosis for success in most cases (Magura & Rosenblum, 2001). Moreover, the frequency with which methadone maintenance is presented as primarily being a public health measure (e.g., for reducing crime and the spread of HIV), rather than as a medical treatment for individuals, is also alarming (Bell, 1998).

1.4.4.9. Attitudes of intended recipients, patients and providers of treatment

Although methadone maintenance is considered the most effective known treatment for opioid dependence worldwide, it is often held in low regard by its target population and sometimes even the health professionals involved in its delivery (Caplehorn et al., 1996; Caplehorn, Lumley, & Irwig, 1998a; Stancliff et al., 2002; Zule & Desmond, 1998). While surveys have found that a large percentage of methadone maintenance patients believe the treatment has had a positive impact on their life, similarly large proportions express the belief that discontinuing treatment is an important goal, despite evidence of the poor prognosis for success, and are unsure or certain that methadone has a bad effect on one's health (Stancliff et al., 2002). Indeed, beliefs about the deleterious effects of methadone, though sometimes based on misinformation, contribute to the ambivalence shown by many prospective recipients of treatment (Hunt, Lipton, Goldsmith, Strug, & Spunt, 1985b). Moreover, providers of methadone maintenance treatment sometimes show negative attitudes towards the treatment and its recipients and a tendency to favour abstinence from all drugs as a more desirable goal than indefinite maintenance on methadone (Caplehorn et al., 1996; Caplehorn et al., 1998a;

Caplehorn et al., 1993). More broadly, stigma and prejudice towards drug users and methadone maintenance programs are likely to impact adversely on many individuals' willingness to enter and remain in treatment, particularly in the context of highly visible public clinics (Zule & Desmond, 1998). The persistence of negative attitudes towards methadone maintenance amongst each of the above-mentioned groups is a major threat to the effectiveness of the treatment.

1.4.5. Summary

In summary, the effectiveness of methadone maintenance is limited by a number of factors including the risks of accidental drug toxicity (particularly during treatment induction), individual variability in response to methadone (e.g., the problem of 'non-holding', adverse effects), mood abnormalities, altered responses to pain, difficulties in managing pregnancy, the protracted nature of methadone withdrawal, restrictive aspects of treatment delivery, and the attitudes towards methadone of those directly involved in the treatment and in the wider community. These problems need to be considered in view of the enormous benefits conferred by methadone maintenance to innumerable recipients of the treatment and the likelihood that no single medication is likely to present a panacea for the problems of opioid dependence. As a strategy for treating opioid dependence, the maintenance pharmacotherapy approach is limited primarily by the need to offer a greater selection of treatment options for both recipients and providers of treatment. The supplementation of methadone maintenance with additional treatment options is likely to impact positively on treatment recruitment, retention and outcomes in maintenance programs for opioid dependence.

1.5. Alternative maintenance pharmacotherapies for opioid dependence

In response to the shortcomings of methadone maintenance, a number of alternative maintenance pharmacotherapies for opioid dependence have been evaluated in recent decades. Many of these medications retain many of the desirable characteristics of methadone (e.g., infrequent, oral dosing) but exhibit a unique pharmacological profile than in some cases

proves more acceptable to the patient (Ling et al., 1994). The present section provides an overview of the most commonly used alternatives to methadone in maintenance programs and highlights the respective advantages and disadvantages associated with each option.

1.5.1. LAAM

One of the most promising alternatives to methadone maintenance to emerge in recent decades is LAAM. Like methadone, LAAM is a synthetic full opioid agonist primarily selective for the mu opioid receptor and is well absorbed from the gastrointestinal tract (Borg & Kreek, 1998). Unlike methadone, LAAM undergoes hepatic metabolism by N-demethylation to form two active metabolites, nor-LAAM and dinor-LAAM, which are both more potent opioid agonists than the parent drug. LAAM, nor-LAAM and dinor-LAAM show extended half-lives of approximately 2.6, 2 and 4 days, respectively, and are thus permissive of bi-daily and in some cases thrice-weekly oral dosing schedules (Borg & Kreek, 1998). Plasma concentrations of LAAM can vary considerably over time, but are much more stable for nor- and dinor-LAAM (Borg & Kreek, 1998).

The main advantages associated with LAAM relate to the slow onset and long duration of its opioid action. These characteristics reduce the frequency and expense of supervised dosing, the need for take-away medications, and congregation at dispensing sites (which improves public acceptance of clinics), and provide longer-lasting withdrawal suppression in patients reporting the failure of their methadone dose to hold for 24 hours (Ling et al., 1994). A recent meta-analysis of 18 studies comparing methadone and LAAM as maintenance pharmacotherapies found that LAAM was associated with lower retention in treatment but greater reductions in heroin use compared to methadone (Clark et al., 2002a). Conclusions from this review are complicated by variations in the methodological features of each study (e.g., requirement of daily attendance during LAAM maintenance in order to provide effective blinding, use of variable dosing protocols). A recent controlled clinical trial showed comparable treatment outcomes for methadone and LAAM (Johnson et al., 2000). LAAM

appears most beneficial in patients for whom reduced clinic attendance is likely to be beneficial and less effective in patients requiring intensive support (e.g., early in treatment) (Savage, Karp, Curran, Hanlon, & McCabe, 1976).

LAAM was approved by the U.S. Food and Drug Administration for use as a maintenance medication in 1993, approximately two decades after it was first evaluated for the treatment of opioid dependence and three decades following the implementation of methadone maintenance (Borg & Kreek, 1998). Despite the apparent advantages of using LAAM as a supplementary option to methadone in maintenance programs, regulatory authorities in the U.S. and Europe have recently discouraged its use following associations with cardiac abnormalities including QT prolongation and severe arrhythmias (Clark et al., 2002a; Schwetz, 2001). It is unclear whether further research will identify any mechanism by which these risks can be satisfactorily minimised and thus enable further implementation of LAAM maintenance. Like methadone, LAAM is associated with a risk of delayed toxicity due to its prolonged duration of action (Borg & Kreek, 1998). It also shows a prolonged withdrawal syndrome that may deter some patients for whom ease of eventual exit from treatment is a priority (Borg & Kreek, 1998).

1.5.2. Buprenorphine

Buprenorphine possesses a unique pharmacological profile that makes it particularly amenable for use as a maintenance pharmacotherapy for opioid dependence. It is a partial agonist exhibiting high affinity for both the mu and kappa opioid receptors and is approximately 25-40 times as potent as morphine when used as an analgesic (Cowan, Lewis, & Macfarlane, 1977). Consistent with the classification of buprenorphine as a partial agonist, a study comparing the effects of buprenorphine and methadone in ascending doses in human volunteers found that the subjective and respiratory-depressant effects of buprenorphine reached a plateau level (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine produces no serious adverse effects and only marginal effects on respiratory depression at

doses for which equi-analgesic doses of morphine or methadone would be fatal (Walsh et al., 1994). The halve-lives of buprenorphine and its active metabolite norbuprenorphine have been estimated at 42 and 57 hours, respectively (Kuhlman, Levine, Johnson, Fudala, & Cone, 1998). Buprenorphine also disassociates very slowly upon binding to mu opioid receptors (Hambrook & Rance, 1976). These factors result in a prolonged duration of action permissive of bi-daily dosing in maintenance patients (Lewis, 1985). The slow disassociation of buprenorphine from opioid receptors is also postulated to account for its apparent safety (i.e., minimal respiratory effects) (Lewis, 1985). In one case report, a heroin user who had consumed 11 × 8 mg diverted buprenorphine tablets did not show significant respiratory depression, but rather experienced a severe withdrawal phase of 4 days duration (Clark, Lintzeris, & Muhleisen, 2002b).

Buprenorphine possesses many of the advantages over methadone discussed above with regard to LAAM (e.g., reduced clinic attendance, reduced provision of take-away doses, improved cost-effectiveness) (Ling et al., 1994). In addition, the partial agonist characteristics of buprenorphine make it safer than full-agonists such as methadone with respect to the dangers of respiratory depression, reduce the likelihood of dose diversion, and provide a greater blockade of the effects of heroin and other opioid agonists (Mattick et al., 1998). Other advantages associated with buprenorphine are that it appears to produce less physical dependence and thus a less severe withdrawal syndrome than the long-acting, full-agonists such as methadone and LAAM (Ling et al., 1994). A recent meta-analysis of controlled trials comparing buprenorphine to methadone and placebo treatments concluded that it "is an effective intervention for use in the maintenance treatment of opioid dependence, but is not more effective than methadone in adequate doses" (Mattick, Kimber, Breen, & Davoli, 2002). Nonetheless, in practice, many patients are unwilling to enter the high-dose methadone range (Bell et al., 1995) and may find buprenorphine a preferable treatment option.

Despite the numerous benefits associated with buprenorphine, it not a viable or preferable treatment option for all opioid dependent or methadone-maintained individuals. Its partial agonist characteristics may elicit problematic withdrawal in methadone maintenance patients with a daily methadone dose exceeding 40 mg per day (Ling et al., 1994), which is below the standard dose range (>50 mg/day) (Ward et al., 1994), and may also elicit withdrawal in heroin dependent individuals (Clark et al., 2002b). These characteristics can make it difficult for patients experiencing inadequate withdrawal suppression or troublesome adverse effects whilst maintained on higher doses of methadone to transfer to buprenorphine (Bouchez, Beauverie, & Touzeau, 1998). Another complicating factor associated with the use of buprenorphine is its poor oral bioavailability, due to extensive first-pass metabolism (Ling et al., 1994). Although it has moderate bioavavailability via the sublingual route, which is normally used, this can be difficult for patients maintained on higher doses and may entail greater risks of diversion than methadone syrup (i.e., easier to retain dose without swallowing). To reduce the abuse potential of buprenorphine, it is now available in combination with naloxone which has low oral bioavailability and thus in appropriate buprenorphine:naloxone ratios will not antagonise the effects of buprenorphine unless the dose is injected (Stoller, Bigelow, Walsh, & Strain, 2001). Nevertheless, buprenorphine/naloxone does show abuse liability in studies of non-opioid dependent volunteers (Comer & Collins, 2002; Strain, Stoller, Walsh, & Bigelow, 2000).

1.5.3. Opioid antagonists: naloxone and naltrexone

The alternative maintenance pharmacotherapies reviewed thus far are characterised by the use of substitute opioids with some degree of agonist activity at the mu opioid receptor, whereby the aim is to reduce heroin use by suppressing opioid withdrawal and cravings and providing partial cross-tolerance to the effects of heroin. An alternative strategy is to administer opioid antagonists that competitively displace or prevent binding of opioid agonists at mu opioid receptor sites and therefore block the reinforcing effects of heroin. In theory, reductions in the rewarding effects of heroin will decrease the incentive to seek and use the drug. Naloxone is

one antagonist that has been tried as a maintenance pharmacotherapy for opioid dependence. Although naloxone adequately blocks the effects of opioids, oral doses of 2-3 g are required to provide adequate blockade for 24 hours, making it costly to administer (Mattick, Oliphant, Ward, & Hall, 1998). Naltrexone, which is much more long-acting (up to 72 h), in part because of its active metabolite 6β-naltrexol (Verebey, 1981; Verebey & Mule, 1975), and has only minor side effects, represents a more suitable antagonist for use in this manner. Maintenance with naltrexone is normally only attempted following either gradual or rapid detoxification from opioids, since its antagonist properties are likely to produce severe withdrawal in opioid dependent individuals. Reviews of the effectiveness of naltrexone have generally concluded that this treatment is of limited value due to the very high rates of relapse observed in the months following commencement of treatment (Kirchmayer, Davoli, & Verster, 2002). However, it does appear to have distinct advantages in certain target populations, including highly motivated patients with adequate social support, and provides a pharmacological alternative for patients in whom abstinence from opioids is the immediate and preferred goal of treatment (Mattick et al., 1998).

1.5.4. Short-acting and injectable opioids

The use of short-acting opioids such as heroin and morphine as alternative maintenance pharmacotherapies to methadone has also received research attention in the past few decades (Metrebian, Carnwath, Stimson, & Storz, 2002; Perneger, Giner, del Rio, & Mino, 1998). Investigation of these possibilities is based on the premise that, although the use of long-acting oral medications may be preferable in many respects (e.g., less frequent dosing, increased cost-effectiveness, risks associated with needle use), the existing range of treatment options is unlikely to fully cater for the needs of all opioid dependent persons seeking help (Mattick et al., 1998). This includes those who respond poorly to the available range of medications and those who find such options unattractive due to either the effects of the opioid or the route of administration (Perneger et al., 1998). Injecting drug use sometimes continues unabated during oral maintenance treatment and it has been argued that the

provision of injectable maintenance with either long- or short-acting opioids may facilitate better outcomes in a proportion of cases and is thus justifiable from a harm-minimisation perspective. In attracting such people into treatment settings, stabilisation on short-acting or injectable opioids could be used as a precursor to subsequent stabilisation on longer-acting opioids such as methadone or LAAM and avoids many of the problems associated with illicit opioids (e.g., variable prices, purity and availability) (Battersby, Farrel, Gossop, Robson, & strang, 1992). The medications most frequently evaluated within the framework of maintenance with short-acting or injectable opioids are heroin and morphine.

1.5.4.1. Heroin

Heroin (diacetylmorphine) undergoes biotransformation into active metabolites including 6-mono-acetylmorphine, morphine, and morphine-6-glucuronide that are thought to mediate its primary opioid effects via the mu opioid receptor (Borg & Kreek, 1998). Its has a very short plasma half-life (<0.25 h) and correspondingly short duration of action (4-5 h) that necessitates frequent administration in order to provide sustained suppression of opioid withdrawal (Borg & Kreek, 1998). Owing largely to its illicit status and political obstructions to its evaluation as a maintenance agent in some countries (e.g., Australia), heroin maintenance has rarely been the subject of sound scientific investigation. Contrary to assertions that adequate stabilisation on short acting opioids such as heroin or morphine is not possible (Dole, 1972, 1988; Fink, 1972), the available studies suggest that opioid dependent patients can be adequately stabilised on heroin and that injectable heroin maintenance may be advantageous in respect to treatment retention for some patients in comparison to oral methadone maintenance (Battersby et al., 1992; Hartnoll et al., 1980; Perneger et al., 1998; Rehm et al., 2001; Sell, Farrell, & Robson, 1997; Strang & Sheridan, 1997; Uchtenhagen, Dobler-Mikola, & Gutzwiller, 1996). Heroin maintenance is several times more expensive than oral methadone maintenance and is unlikely to represent a mainstream treatment option, but, rather, may yield distinct advantages when used as a supplementary option to methadone (Bammer, 1997).

1.5.4.2. Morphine

Morphine is an opioid agonist primarily selective for the mu opioid receptor (Ki values of 1.24, 145, and 23.4 nM/L for the mu, delta, and kappa opioid receptors, respectively) (Codd et al., 1995) Its low oral bioavailability (approximately 30%) and short duration of action (4 h) (Borg & Kreek, 1998) have traditionally limited its value as an alternative maintenance pharmacotherapy to methadone for treatment of opioid dependence. Nonetheless, use of morphine to stabilise opioid dependence has been reported in numerous studies. Since morphine is the agent under evaluation in the present research, albeit in the context of slow-release formulations, these earlier reports are of considerable relevance to the current discussion and will thus be reviewed in detail.

Experience with morphine maintenance dates back to the 1920s, when morphine prescribing as a treatment for opioid dependence was practised in several clinics throughout the United States. Although these early experiments with morphine maintenance were not systematically analysed at the time, they have been subjected to historical review. Waldorf, Orlick and Reinarman (1974) conducted a historical analysis of one clinic in Shreveport, Louisiana, where morphine prescribing was practised between 1919 and 1923. Their analysis involved tracking down the clinic's former director and the records of 762 patients (62% of total) who attended the clinic during its short-lived operations. All patients were mono-drug users (only opiates), with more than half reporting an addiction period of at least six years, and a quarter reporting addiction periods in excess of 11 years. In contrast to modern patient populations, the majority of patients (nearly 90%) cited medical reasons as the origin of their dependence. Waldorf et al.'s ability to evaluate the Shreveport clinic was severely inhibited as the medical records only contained information about patients at entry to treatment. However, alternative information sources (e.g., criminal records) enabled Waldorf et al. to conclude that the Shreveport clinic produced "favourable if not praising reports" (p. 41) and that the experience "supports the use of morphine" as a maintenance drug. The clinic's director, Dr Butler,

further recalled that "maintenance patients could be stabilised on a steady dose when 'drug balance' was reached" (p. 45). A less comprehensive historical evaluation of a second morphine maintenance clinic in New Haven, Connecticut, which operated between 1918 and 1920, is provided by Musto and Ramos (Musto & Ramos, 1981). These authors managed to trace the histories of some of the clinic's patients following its enforced closure in 1920 using police records and death certificates, but this report contains little valuable information with regard to the effectiveness of morphine as a maintenance pharmacotherapy.

More recently, injectable morphine was prescribed as a treatment for opioid dependence in Italy, following a ministerial decree in 1980 legalising the use of morphine for this purpose. Like the earlier experience in the United States, however, the Italian experience with morphine maintenance was not the subject of sound scientific investigation. The only available data regarding the Italian experience with morphine maintenance pertains to the effects of the treatment on reducing the transmission rate of HIV. Sagliocca et al. (1997) retrospectively compared the prevalence of HIV amongst injecting drug users receiving either injectable morphine or oral methadone maintenance to see whether the availability of morphine maintenance in Naples could explain that city's relatively low HIV prevalence amongst injecting drug users (5%) relative to other cities (e.g., Rome 30%, Milan 50%). The authors postulated no difference between methadone and morphine, but suggested higher rates of HIV might be observed in morphine-maintained individuals due to their continued injection practices. However, results indicated that HIV infection was less likely amongst those prescribed morphine compared with methadone-maintained patients, although the difference was only marginally significant. Interpreting these findings, Sagliocca et al. noted that methadone was often given at low insufficient doses that may have led to the continued injection of illicit opioids, whereas morphine-maintained patients frequented pharmacies on a daily basis where they were also able to purchase sterile injecting equipment. Although lacking the scientific rigour of a randomised controlled trial, this report nonetheless raises the

possibility that the availability of injectable morphine attracted new users into treatment and facilitated protection against HIV.

Further reports concerning the effectiveness of morphine maintenance come from the Netherlands, where the treatment was trialed in Amsterdam in the early 1980s. Derks (1990a; 1990b) described the treatment of 37 extremely problematic opioid users, with extensive histories of drug abuse and failed treatment attempts, with methadone, injectable morphine or a combination of the two treatments. Unfortunately, just two of these patients were maintained solely on injectable morphine at the end of the two-year evaluation period, thereby preventing strong conclusions about the effectiveness of morphine maintenance. Nineteen patients were receiving a combination of oral methadone and injectable morphine, thirteen received solely methadone, and the remaining three patients had died, become abstinent from all opioids, and ceased treatment, respectively. Derks (1990b) concluded that the goals of the morphine dispensing program were achieved to a satisfactory degree, adding that "neither the high hopes nor the frightful expectations of the morphine dispensing program became a reality" (p. 105). Although severely limited scientifically, Derk's evaluation seems to suggest that injectable morphine was an acceptable treatment for patients seeking stabilisation on a licit supply of opioids. However, the fact that it took 18 months to enroll the 37 trial participants and that just two chose to be maintained solely on injectable morphine suggests that injectable morphine may have very low patient acceptability.

Indeed, this hypothesis is supported by reports from Switzerland following investigations of injectable morphine, heroin and methadone in the 1990s (Moldavanyi, Ladewig, Affentranger, Natsch, & Stohler, 1996; Uchtenhagen et al., 1996). A high-drop out rate was observed for patients stabilised onto morphine maintenance. In one study, seven of sixteen patients entering morphine maintenance dropped out, mostly due to dissatisfaction and all within the first ten days of treatment (Moldavanyi et al., 1996). Although this was partly

attributable to a high occurrence of side effects (e.g., swollen arms, severe headaches), other factors may have contributed to the treatment's low popularity, including (1) the concurrent availability of heroin maintenance and (2) the strict treatment setting, featuring three supervised injections per day. The remaining patients, whilst stating a preference for heroin maintenance, preferred injectable morphine to injectable methadone, leading Moldovanyi et al. (1996) to conclude that "morphine is a possible substitute for opioid-dependent patients and viable alternative to methadone substitution" (p. 208).

Whitten et al. (1996) report a case study of a 35 year old opioid dependent male with a long history of alcohol and drug use. The patient had developed severe skin complications due to intravenous drug use and showed progressive pain, weakness and numbness in both arms following recurrent forearm ulcerations, multiple skin grafts, and other medical interventions. He had also sustained fractured vertebrae in a truck accident in his 20s and later a head injury from a motorbike accident that resulted in frontal lobe damage. The patient reported use of heroin and other opioid analgesics and had been to a number of detoxification and rehabilitation programs for his drug problems, but had found his needs for analgesia not met. Attempts at methadone maintenance were similarly found to be unsatisfactory; the patient reporting that once-daily dosing was inadequate for his needs. The authors report that in the preceding two years the patient had been successfully stabilised on oral morphine mixture (20 mg, five times per day) and had shown great improvement in the way he interacted with medical staff at the outpatient clinic. They concluded that although longer-acting maintenance agents are preferable, it is possible to stabilise opioid dependent patients on short-acting opioids such as morphine for extended periods, particularly in the context of a good doctor-patient relationship.

Comer et al. (1999) report the use of immediate-release morphine to stabilise opioid dependence in the context of a study that compared the pharmacodynamics and

pharmacokinetics of intravenous and intranasal heroin in 8 heroin-dependent individuals. To minimise the effects of opioid withdrawal on pharmacodynamic assessments of heroin during experimental sessions, subjects were maintained on oral morphine for the duration of the trial. Subjects received either 20 mg (n = 3) or 30 mg (n = 5) oral morphine four times daily for the duration of the 2.5 week inpatient study, although these doses were reduced on testing days (total of 10) depending on the amount of heroin that had been previously administered. Although the study was not designed to assess the efficacy of morphine maintenance, the authors state that their attempts to control for withdrawal using morphine were successful and that the morphine produced minimal subjective effects in their heroin-dependent subjects.

The above studies suggest that morphine in its immediate-release preparation is pharmacologically effective in suppressing the opioid withdrawal syndrome. Patient acceptability of morphine maintenance appears reduced in the context of intravenous injection, due to the occurrence of adverse effects (e.g., histamine reactions), and may also suffer in the context of regular supervised dosing (i.e., multiple doses per day) that is normally mandatory in modern maintenance programs. These problems may be overcome with the use of slow-release oral morphine formulations, which are discussed below.

1.5.5. Summary

In summary, a number of efficacious alternatives to methadone have been evaluated and implemented as maintenance pharmacotherapies for opioid dependence. These additional treatment options have significantly enhanced the degree of choice and flexibility available to both patients and clinicians and, more generally, have reaffirmed the value of the maintenance pharmacotherapy approach as an intervention for opioid dependence. Although none of the available alternatives has proven to confer substantially more benefits to either patients or the wider community than methadone overall, it must be emphasised that opioid dependence is a complex condition requiring a diversity of approaches and an effort to individualise treatment delivery. Whilst the evaluation of maintenance pharmacotherapies normally occurs at a group

level, involving comparisons of average responses to treatment, the targets of such treatment are individuals who can vary considerably in their response to any given medication. Alternatives to methadone must therefore be judged in terms of the extent to which they complement the overall range of available treatments.

In evaluating the overall adequacy of the available treatment options for opioid dependence, one particular problem is readily discernible. Due to restrictions regarding the use of LAAM, methadone is the sole long-acting opioid agonist currently recommended for use in maintenance programs in most countries. For reasons outlined above, the use of short-acting opioids is not considered an optimal treatment strategy owing to the increased costs and inconvenience associated with frequent dosing and, when used, the intravenous administration route. These treatment options are also not feasible on the large-scale that is possible with long-acting oral maintenance. Many patients report inadequate withdrawal suppression (i.e., dose 'not holding) and troublesome adverse effects whilst maintained on methadone. Transfer to buprenorphine may yield improved outcomes in some such cases, but this treatment strategy is also associated with a risk of precipitated withdrawal, particularly amongst patients maintained on methadone doses of 40 mg per day or more, and may not be acceptable to all patients (Bouchez et al., 1998; Ling et al., 1994). Therefore, it is desirable that opioid agonists capable of providing long-lasting withdrawal suppression using infrequent oral dosing schedules are identified, particularly as an option for patients responding poorly to methadone maintenance treatment.

1.6. Slow-release oral morphine (SROM): a new alternative to methadone

The potential for short-acting opioids (e.g., heroin and morphine) to be used as alternative maintenance pharmacotherapies to methadone for treatment of opioid dependence has been greatly enhanced with the advent of slow-release drug preparations in recent decades; in particular, slow-release oral morphine (SROM). SROM formulations were first introduced about two decades ago and are now widely used in the management of chronic pain (Gourlay,

1998). They entail less frequent dosing intervals in comparison to immediate-release morphine solution and are thus advantageous in minimising inconvenience to patients (e.g., sleep disturbances), reducing delivery costs in hospice settings, improving compliance in outpatient settings (i.e., simpler dosing regimen) and limiting the adverse effects associated with regular peaks and troughs in plasma morphine concentrations (Thirlwell et al., 1989). SROM is mainly used for chronic morphine treatment of moderate to severe pain (e.g., cancer-related), but has also been used to provide long-lasting acute pain relief during and after surgical procedures (Derbyshire, Bell, Parry, & Smith, 1985; Simpson, Dearden, Ellis, & Jack, 1988; Slowey, Reynolds, Mapleson, & Vickers, 1985).

To date, SROM has rarely been used in the treatment of opioid dependence, primarily because most SROM formulations require dosing intervals of 12 hours or less. More recently developed SROM formulations have been shown to provide sustained analgesia using once-daily dosing intervals (Gourlay et al., 1997). To the extent that such formulations are also capable of providing sustained withdrawal suppression in the absence of significant adverse effects using once-daily dosing schedules, they may also have clinical utility in maintenance programs for opioid dependence. The purpose of the present section is to review existing evidence regarding the use of SROM for maintenance treatment of opioid dependence and the safety and efficacy of Kapanol™ (GlaxoSmithKline; also marketed as Kadian™); the only once-daily SROM product that was available in Australia at the commencement of the present research and hence the subject of this evaluation.

1.6.1. SROM for maintenance treatment of opioid dependence

Despite the potential for SROM to be used as a maintenance pharmacotherapy for opioid dependence, there have been few scientifically-controlled evaluations of its clinical utility for this purpose. Previous case studies and clinical trials of SROM maintenance, which are reviewed in this section, have generally yielded promising preliminary appraisals of its effectiveness and acceptability, but a number of important questions are yet to be adequately

addressed. Specifically, whereas a key objective of the present study is to investigate once-daily SROM as an alternative for patients responding poorly to methadone, controlled-evaluations of once-daily SROM have previously only been conducted in heroin users entering treatment.

1.6.1.1. Anecdotal reports and case studies

Regarding the clinical utility of Kapanol™, there is just one published single case study documenting its use as an alternative to methadone. Sherman (1996) describes the successful transfer of a methadone-intolerant male who developed "bilateral carpal tunnel syndrome secondary to fluid retention within weeks of commencement" onto a once daily Kapanol™ dose of 140 mg (methadone dose not specified). Following this change in maintenance drug, the patient reported feeling more "normal" and energetic, without the side effects that had accompanied methadone maintenance (e.g., sweating, depression, and insomnia). It is further stated that the patient presented opiate-free (diacetylmorphine and 6-mono-acetylmorphine) urines on weekly or bi-weekly assessment, and that the SROM dose was sufficient to suppress the patients' heroin cravings and withdrawal symptoms. Brewer (1995) describes a similarly successful conversion of a methadone-intolerant male from 115 mg of methadone once-daily to 240 mg of SROM twice-daily. The patient described himself as "well-satisfied" following the switch, despite the fact that SROM cost the individual over three times as much as methadone.

1.6.1.2. Clinical trials

In addition to these anecdotal reports, there have been several larger-scale clinical evaluations of SROM maintenance. All of these studies have taken place in Austria, where SROM has been used for treatment of opioid dependence since 1990, and have predominantly been carried out by Fischer and colleagues (Eder et al., 2002; Fischer, Bitschnau, Peternell, Eder, & Topitz, 1999a; Fischer et al., 1998; Fischer et al., 1999b; Fischer et al., 1996). Several of these investigations have evaluated SROM as an alternative to methadone for pregnant opioid

dependent women. Studies pertaining to the non-pregnant opioid dependent population are more relevant to the purposes of the present research and will be reviewed first.

In the earliest available account of SROM maintenance, Schneider (1995) described the utilisation of SROM maintenance in Austria as an alternative treatment option for patients responding poorly to methadone maintenance. It was noted that a number of patients experienced considerable adverse effects during methadone maintenance, including depression, dysphoric mood, apathy, vegetative dysfunction, weight gain (up to 20 kg per person), and sleep disturbances accompanied by nightmares. At the time of the report, a total of 37 (28 male, 9 female) patients had been switched from methadone to oral morphine sulphate following the occurrence of such adverse effects. The mean daily dose and duration of morphine sulphate treatment among these patients were 584 mg (120-1200 mg) and 11 months (1-29 months), respectively. Although the morphine formulation used in these patients is not specified, subsequent and related reports indicate it was likely to be a SROM formulation requiring multiple doses per day (Fischer, 1996), since once-daily SROM preparations were not available until 1996. Following the transition from methadone to SROM, patients displayed improved concentration abilities, increased drive, and a dissipation of all methadone-related side effects, including a return to normal weight within 14 days. It is further stated that psychophysiological examinations evaluating differences in central nervous system activation for methadone and morphine had been performed and supported the observed clinical results, although these data were not reported.

In a subsequent report, Fischer et al. (1996) similarly reported positive patient outcomes following the transfer of 16 methadone maintenance patients (11 males, 5 females) from once-daily methadone to thrice-daily dosing with the SROM product, Mundidol Retard™ (morphine sulphate; mean dose 564 mg, range 120-1200 mg), for a mean period of 14 months (range 1 – 47 months). Whilst maintained on methadone, these individuals had experienced

numerous adverse effects, including weight gain (up to 20 kg per person), low drive, depressed mood, anxiety, avoidance behaviour, and nightmares. The authors report that transfer to SROM was associated with an amelioration of these psychopathological features within 14 days and a return to normal weight within one month. It was also observed that patients experienced improved concentration abilities whilst maintained on SROM.

Unfortunately, no quantitative assessments of outcomes during methadone or SROM maintenance are presented in support of the results specified by Fischer et al. (1996) and Schneider (1995). These studies also used SROM formulation requiring three doses per day, which in clinical practice may result in reduced patient acceptance and increased costs of the treatment, particularly in situations where supervised dosing is normally required. More recently, three controlled evaluations of SROM maintenance using once-daily formulations have been conducted.

The first of these, reported by Eder et al. (2002), featured a crossover comparison of SROM and racemic methadone under double-blind, double-dummy conditions in a sample of 64 heroin dependent individuals entering treatment. After a one-week dose-titration period at commencement of each treatment phase, subjects were maintained on a stable dose for a further 6 weeks, before switching to the other treatment. Doses ranged from 55 to 100 mg for methadone and from 200 to 800 mg for SROM, although mean doses are not provided. The trade name of the SROM formulation used, which is referred to simply as "morphine sulphate capsules", is also not stated. Retention rates for the study evaluation periods were high and did not differ for methadone and morphine (>84% overall). Significant differences were found in favour of SROM over methadone for measures of patient well-being and craving for nicotine and heroin over the last two weeks of treatment. The authors concluded that both methadone and SROM were effective and safe for the treatment of opioid dependence, with no adverse effects being reported in either case. However, interpretation of these findings is

complicated by the use of dextromethorphan (an NMDA antagonist) as a 'placebo' to mask the taste of each maintenance medication, since NMDA antagonists themselves have purported therapeutic benefit in the treatment of opioid dependence (Bisaga & Popik, 2000). Moreover, the study sampled heroin users entering treatment. Initial use of SROM in Australia and other countries is more likely to involve its use as alternative for patients responding poorly to methadone maintenance.

Kraigher et al. (2002) reported a second evaluation of once-daily SROM for maintenance treatment of opioid dependence. Their study comprised a three-week longitudinal evaluation of SROM maintenance in 67 ambulatory heroin dependent patients entering treatment. Patients were commenced on the SROM product, Vendal Retard™ (morphine hydrochloride), and doses increased in increments of 100 mg up to a maximum of 800 mg daily until adequate stabilisation was achieved. The mean stabilised doses were 591mg (range 200-800 mg) and 595 mg (range 200-800 mg) for the female and male patients, respectively. SROM was associated with a 95% retention rate over the three-week evaluation period, during which significant reductions were observed in the number of methadone and benzodiazepine positive urinalyses, ratings of the severity of opioid dependence, the strength of cravings for heroin and cocaine, and depressive symptoms (Beck Depression Inventory). Although these results imply good efficacy and patient acceptability for once-daily SROM maintenance, they are limited by the absence of a comparison group (e.g., no-treatment or methadone maintenance). For reasons outlined above, the use of heroin users entering treatment is also less informative with respect to the clinical utility of SROM for patients responding poorly to methadone.

Giacomuzzi et al. (2001) reported a third and final evaluation of once-daily SROM maintenance carried out to date. Their study comprised a cross-sectional survey of 60 heroin dependent individuals randomised to receive either methadone (n = 30) or SROM (n = 30)

maintenance. The two groups were compared in terms of urinary indices of drug use and questionnaire assessments of their quality of life and subjective well-being (e.g., somatic characteristics). The authors state that both Kapanol™ and Substitol™ are used for once-daily SROM dosing in maintenance programs in Austria, but do not specify the proportion of their SROM maintenance sample who were maintained on each product. Results indicated that SROM was associated with lower quality of life, a greater frequency of psychological and physical problems, and a higher consumption of other drugs of abuse (e.g., hashish, cocaine). On the basis of these results, the authors conclude that no advantages could be determined for using SROM instead of methadone and that with use of the former 'an increased consumption of other drugs must be accepted' (English translation).

The Giacomuzzi et al. (2001) study produced results that are inconsistent with other evaluations of SROM maintenance and thus warrant some attention. On inspection of the methodology and results, a number of possible reasons for these inconsistencies are readily discernible. Firstly, despite efforts to randomly allocate patients to each treatment, there were important differences in the two groups that may have influenced the variables under consideration, including the disproportionately high number of HIV-positive patients in the SROM (33%) compared to methadone (7%) groups. Second, many of the quality of life indices, which may be influenced by HIV status, were also unlikely to demonstrate significant change in the relatively short time frame of the study (e.g., proportion of subjects participating in sport, receiving social service benefits, living alone or being visited by relatives more than once a week). The presence of significant differences between the two groups on these measures, mainly favouring methadone, may therefore constitute additional evidence that differences between the groups (e.g., HIV status, quality of life) were present at baseline and thus not attributable to the treatment conditions. Third, descriptions of the doses of each maintenance drug used, the frequency and timing of subject assessments, the presence of co-medications (e.g., for HIV) and what happened to the SROM group at the end of the

study are not explicitly stated. Given the above limitations, it is possible that the results of this investigation are attributable to pre-existing differences between the subject groups and variability in delivery of the two treatments (e.g., doses of methadone and morphine).

A number of reports have investigated or proposed the use of SROM as an alternative to methadone for maintenance treatment in opioid dependent pregnant women (Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Schneider et al., 1996). In the most informative of these studies, Fischer et al. (1999b) randomly allocated 48 opioid dependent pregnant women to receive one of two forms of maintenance treatment involving once-daily methadone (n = 24, mean dose 53 mg, range 13-120 mg) or twice-daily SROM (mean total dose 300 mg, 60-660 mg). Notably, the SROM group showed significantly fewer injection sites (21% vs. 50%) and less use of benzodiazepines compared to the methadone group. There were no differences between the two groups on measures of neonatal outcomes. Other studies have evaluated SROM, methadone and buprenorphine as alternative maintenance pharmacotherapies for opioid dependent, pregnant women, but have not focused on comparisons of each treatment (Fischer et al., 1999a; Fischer et al., 1998; Schneider et al., 1996). The relevance of these studies to the present research is reduced due to the special nature of the population under investigation, including possible differences between pregnant and non-pregnant maintenance patients in the level of additional psychosocial support sought and provided, motivation to achieve better health, and metabolism of opioids such as methadone and morphine. Nonetheless, these studies are informative in that they provide further evidence of the apparent efficacy, safety and patient acceptability of SROM as an alternative maintenance option to methadone.

1.6.1.3. Summary

In summary, the available evidence suggests that SROM may have clinical utility as an alternative maintenance pharmacotherapy to methadone for the treatment of opioid dependence. However, many of these studies used shorter-acting SROM products requiring

multiple doses per day or failed to provide sufficient quantitative data for strong conclusions to be made. There have been just three controlled evaluations of once-daily SROM maintenance. Each of these studies had at least one major methodological limitation (e.g., use of dextromethorphan as a placebo, absence of a control group, use of apparently non-comparable groups in a cross-sectional design) and were conducted in heroin dependent users entering treatment. Given the abundance of research supporting methadone maintenance as the first choice opioid agonist for maintenance treatment of opioid dependence, initial use of SROM in countries such as Australia is likely to involve its selective use in patients failing to respond to conventional treatments. Hence, it is vital that further studies evaluate the outcomes of SROM in methadone maintenance patients and characterise the optimal means of switching patients between these medications. Specifically, such studies should target the individuals most likely to benefit from the availability of an alternative opioid agonist maintenance agent (e.g., patients reporting 'non-holding' on methadone).

1.6.2. Safety and efficacy of Kapanol™

The clinical utility of Kapanol™ as an alternative maintenance pharmacotherapy to methadone is likely to be highly dependent on its ability to provide adequate withdrawal suppression in the absence of adverse effects throughout the 24-hour inter-dosing interval. This, in turn, is likely to be related to the extent to which Kapanol™ maintains plasma morphine concentrations at a relatively stable level between doses (Dyer et al., 1999). Pharmacokinetic and pharmacodynamic evaluations of Kapanol™ have not been previously conducted in a methadone maintenance population, but have been conducted in pre-clinical studies in volunteers and clinical evaluations of Kapanol™ for the management of pain. These studies are likely to be highly informative regarding the safety, efficacy and patient acceptability of Kapanol™ in a methadone maintenance population and will be reviewed in some detail.

1.6.2.1. Pre-clinical studies

Five pre-clinical evaluations of Kapanol™ have been reported. In the first of these, Jones et al. (1996) report two *in vitro* experiments in which the effect of alternative administration methods on the morphine-release rate of Kapanol™ was investigated. These studies assessed whether the morphine-release profile of Kapanol™ was altered when the polymer-coated pellets were poured onto foodstuffs (including jam, yoghurt, apple sauce and ice-cream) and liquids (orange juice, milk, water), or administered via gastrostomy tubes. Results indicated that the morphine-release profile of Kapanol™ was not altered by these alternative administration methods. The principal motivation for conducting these studies was to find alternate methods of administering morphine to cancer pain patients who often have difficulty swallowing tablets or capsules. However, the results are also of relevance to the current investigation in which Kapanol™ was administered to patients in orange juice and drunk through a straw in an effort to reduce the chances of patients diverting or chewing their dose. Specifically, it is notable that the morphine-release rate was not significantly altered when the Kapanol™ pellets were poured into orange juice, even when the exposure time was 60 minutes.

Maccarone et al. (1994) report three single-dose, open-label crossover studies in health male volunteers (n = 24 to 30) comparing the pharmacokinetic profiles, dose-proportionality and influence of food on morphine administered as Kapanol™, MST-Continus™ (a 12-hourly SROM formulation) or oral morphine solution. Doses were administered seven days apart following either a standard high-fat meal or a 12 hour fasting period. Blood samples collected for up to 48 hours post-dose were analysed by high performance liquid chromatography. Kapanol™'s pharmacokinetic profile was found to be characteristic of a slow-release formulation. The peak plasma morphine concentration (Cmax) for Kapanol™ was approximately one-fifth the level of an equivalent dose of oral morphine solution. Furthermore, the time to reach maximum plasma morphine concentration (Tmax) exceeded 8

hours, compared with approximately 1 hour for the oral morphine solution. The time during which the plasma morphine concentration of morphine exceeded 75% of the Cmax (T>75%Cmax; used to quantify the degree of control a slow-release formulation has over the morphine release rate) (Gourlay, 1998) was also longer for Kapanol™ (approximately 7-8 h) compared to the oral morphine solution (approximately 1 h). Estimations of morphine's terminal half-life following Kapanol™ administration yielded values approximating 17-18 hours. The only significant effect of food on the pharmacokinetics of Kapanol™ was a small but statistically significant increase in Tmax from 8.5 to 10.1 hours.

Broomhead et al. (1997b) compared the pharmacokinetic profiles of Kapanol™ and an alternative once-daily SROM formulation, MXL™, in 24 healthy male and female volunteers using a randomised, single-dose, open-label, crossover research design. A 60 mg dose of each formulation was administered seven days apart following either a standard high-fat meal or a fasting period of 10 hours. Blood samples taken for 48 hours post-dose were analysed by high performance liquid chromatography using electrochemical detection. Consistent with the findings of Maccarone et al. (1994), food significantly prolonged the Tmax for Kapanol™, but had no effect on the extent of absorption or the Cmax. Estimations of morphine's terminal half-life following the administration of Kapanol™ yielded values approximating 15 hours. The authors concluded that because Kapanol™'s bioavailability was unaffected by food, it can be taken without regard to meals.

Subsequently, Broomhead et al. (1997c) examined whether Kapanol™ capsules swallowed whole were bioequivalent to Kapanol™ pellets sprinkled on apple sauce in both the fasted and fed states in 25 healthy male and female volunteers in a randomised, single-dose, open-label, 4-way crossover study. A 50 mg Kapanol™ dose was administered seven days apart following either a standard high-fat meal or a 10 hour fast. Based on 90% confidence interval and mean ratio analysis, the authors concluded that Kapanol™ administered as a whole

capsule or via the sprinkling of pellets on apple sauce were bioequivalent under both the fasted and fed states. Consistent with the earlier-reported studies, food was found to lengthen the Tmax. The respective Tmax values of Kapanol™ capsules (swallowed whole) and pellets (sprinkled on apple sauce) approximated 7-8 hours in the fasted state and 11-12 hours in the fed state, respectively. Estimations of morphine's terminal half-life following the administration of Kapanol™ yielded values in the range of 15-17 hours.

Bochner et al. (1999) compared the single-dose pharmacokinetics of Kapanol™, Reliadol™ (a once-daily morphine preparation currently unavailable in Australia) and an immediate release morphine tablet (Morfin™ 'DAK') in 24 healthy volunteers using a three-way, randomised, crossover design. Results indicated that a mean Tmax of approximately 8 hours was achieved following Kapanol™ administration. Consistent with Maccarone et al.'s (1994) findings, the Cmax was significantly lower for Kapanol™ than for immediate-release morphine. Of additional interest is Bochner et al.'s finding that Reliadol™ and Kapanol™ exhibited similar sustained-release pharmacokinetic profiles. Specifically, the only difference between these two once-daily SROM formulations was that the Tmax occurred about 4 hours earlier on average for Reliadol™ compared to Kapanol™. This finding highlights the fact that there are alternative once-daily SROM formulations that, like Kapanol™, may have potential for use as maintenance pharmacotherapies for opioid dependence.

The pre-clinical investigations reviewed above produced consistent appraisals of the slow-release profile of Kapanol™. Relative to immediate-release oral morphine solution and shorter-acting slow-release preparations, the pharmacokinetic profile of Kapanol™ was characterised by equivalent bioavailability, a lower Cmax, and a greater Tmax. Furthermore, estimations of the terminal half-life and the time during which plasma morphine concentrations exceeded 75% of maximum concentrations yielded values in the range of 15-18 hours and 5-8 hours, respectively. The only effect of food on the above pharmacokinetic

parameters appeared to be a moderate increase in Tmax. Because food did not impair the overall bioavailability of Kapanol™, however, it was concluded that the drug could be taken without regard to meals. Collectively, these findings suggest that Kapanol™ would represent a safe and efficacious means of morphine delivery, with several notable advantages over shorter-acting SROM formulations, including reductions in the (1) frequency of dosing and (2) fluctuations in plasma morphine concentrations throughout the 24-hour period. These characteristics are likely to translate into a more convenient and clinically comfortable inter-dosing period for patients. In the next section, evidence pertaining to this hypothesis is reviewed.

1.6.2.2. Clinical studies

There are five published studies investigating the clinical safety and efficacy of Kapanol™, all of which were conducted with patients requiring morphine as a treatment for chronic pain (predominantly cancer-related). In the first of these, Broomhead et al. (1997a) reported a randomised, double-blinded study comparing the safety and efficacy of Kapanol™ (administered either 12-hourly or 24-hourly) and MS Contin™ (administered 12-hourly) in providing analgesia to 152 patients with cancer-related pain. Patients underwent dose titration during a 3-14 day lead-in period, before being randomly allocated to one of the above 3 conditions for a period of 7 ± 1 days. Final day outcome measures for safety and efficacy included time to first re-medication, total rescue medication, pain scores, global assessments, and incidences of morphine-related adverse effects. Analyses revealed that the percentages of patients requiring rescue medication in the Kapanol™ 24-hour, Kapanol™ 12-hour and MS Contin™ 12-hour conditions were 46%, 51% and 55%, respectively. The mean time to first re-medication was significantly longer in the Kapanol™ 24-hour condition (16 h) than the two 12-hour conditions (9.1 h for Kapanol™, 8.7 h for MS Contin™). The total amount of re-medication was less in the two Kapanol™ conditions than the MS Contin™ condition, but these differences were not statistically significant. Patient assessments of pain control in the

Kapanol™ 24-hour and 12-hour conditions were better than in the MS Contin™ 12-hour condition, although these difference were not statistically significant in the latter case. Furthermore, there were no statistically significant differences between any of the three groups in terms of side-effects when adjusted for baseline. These findings suggest that Kapanol™ administered once-daily provides equivalent if not superior pain management to twice-daily morphine dosing schedules with reduced levels of inconvenience to the patient.

Gourlay et al. (1997) similarly compared once-daily Kapanol™ and twice-daily MS Contin™ in the management of severe cancer pain using a randomised double-blind, double-dummy, crossover design. These authors extended the work of Broomhead et al. (1997a) by including a full pharmacokinetic evaluation in their methodology. Twenty-four patients with cancer pain had their doses optimised during the lead-in to the study, before being randomly allocated to one of the two treatments for 7 ± 1 days. Morphine pharmacodynamics and pharmacokinetics were assessed on the final day (blood samples and assessments of pain and adverse effects were taken for 24 h), following which patients entered the second treatment phase. Comparisons of mean pharmacokinetic parameters (normalised to a 100 mg morphine dose) showed that relative to MS Contin™, Kapanol™ exhibited: (1) a higher Cmin (7.6 ng/mL vs. 9.9 ng/mL); (2) an equivalent Cmax (37 ng/mL vs. 37 ng/mL); (3) equivalent bioavailability, as measured by the AUC (457 ng.h/mL vs. 501 ng.h/mL); (4) less fluctuation in plasma morphine concentrations throughout the inter-dosing interval (1.6 vs. 1.4: calculated as the ratio of Cmax-Cmin to Css, where Css is the average steady-state plasma concentration, AUC / 24 h); (5) a longer Tmax (10.3 h vs. 4.4 h); and (6) a greater T>75%Cmax (6.0 h vs. 4.8 h). There were no statistically significant differences between the two treatments with respect to any of the pharmacodynamic efficacy measures, including the incidence of morphine-related adverse effects, the proportion of patients requiring rescue medication, patients' treatment preference, patient and investigator assessments of global effectiveness, and visual analogue scale indices of pain severity. Based on these results, the

authors concluded that, in the management of cancer-related pain, once-daily Kapanol™ has a superior pharmacokinetic profile and an equivalent pharmacodynamic profile compared to twice-daily MS Contin™.

A third study comparing the effectiveness of Kapanol™ and MS Contin™ was reported by Floter et al. (1997). However, these authors administered both formulations on a twice-daily basis. Consequently, this study is of reduced importance to the present investigation, which seeks to evaluate once-daily Kapanol™ as a means of providing withdrawal suppression in opioid dependent patients. In their study, Floter et al. randomly allocated 165 patients with severe chronic pain (of malignant and non-malignant origins) to receive either Kapanol™ or MS-Contin for an evaluation period of two weeks, following dose-optimisation. The proportion of patients who did not complete the study was 24% for the Kapanol™ condition and 42% in the MS-Contin condition. The authors concluded that Kapanol™ was superior to MS Contin™ based on significantly better final physician assessments, assessments of each formulation's effect on sleep and mood, and an equivalent degree of observed morphine-related side-effects between the two formulations.

Leelanuntakit (1999) compared the safety and efficacy of Kapanol™ administered every 12 hours to every 24 hours in randomised, open-label, parallel group study. Thirty patients with moderate to severe cancer-related pain were commenced on Kapanol™ for a dose-finding period of 3 to 14 days, following which they were randomised to receive Kapanol™ either 12-hourly or 24-hourly for an evaluation period of 7 days. Visual analogue scale assessments of pain control did not differ, with more than 80% of patients in each group reporting good to very good pain relief. There were also no differences between the two groups in terms of rescue medication (immediate release morphine) requirements, adverse effects (none were reported) and measures of quality of life. Although no differences were reported in preference for either dosing regimen, the author concluded that the 24-hour dosing regimen "seemed to

be more advantageous". This study is significant in demonstrating that Kapanol™ is equally safe and effective administered once-daily compared to twice-daily.

Kerr and Tester (2000) used a randomised, open-label, multi-centre, crossover design to compare the clinical efficacy and acceptability of once-daily Kapanol™ versus twice-daily MS Contin™ in 178 patients requiring morphine for the management of cancer-related pain. Following a 3-14 day dose-optimisation period, patients were randomised to receive either of these two SROM formulations for an evaluation period of 10 ± 1 days, following which they received the alternative formulation. No significant differences were found between Kapanol™ and MS Contin™ with respect to patients' pain assessments, rescue medication usage, investigators' global assessments, health-related quality of life measurements, morphine-related adverse effects or drop-out rates. When asked to state a preference for either formulation, 55% of patients chose once-daily Kapanol™, 33% chose twice-daily MS Contin™, and 12% had no preference. The authors attributed this statistically significant difference to the reduced level of disruption (e.g., to patients' sleep) and inconvenience that the once-daily dosing schedule of Kapanol™ entails.

The five clinical evaluations of Kapanol™ reviewed above are consistent with evidence presented in pre-clinical studies in suggesting that Kapanol™ represents a safe and effective means of morphine delivery. Moreover, Kapanol™ appears to provide an equivalent degree of analgesia to alternative SROM formulations, but has the added benefit of offering less-frequent dosing. This translates into a more clinically comfortable inter-dosing interval for patients, as evidenced by patients' preference for Kapanol™ in the Kerr and Tester (2000) study.

1.6.2.3. Summary

In summary, pre-clinical and clinical evaluations of Kapanol™ indicate that it has a number

of characteristics that are likely to make it amenable for use as a maintenance pharmacotherapy for opioid dependence. Using a once-daily dosing schedule, Kapanol™ provides sustained opioid effects in the absence of significant adverse effects and is well-tolerated by patients. Plasma concentrations are generally stable throughout the inter-dosing interval and are relatively unaffected by food intake or the mode of administration (i.e., in food, liquid, or swallowed whole). The achievement of stable plasma morphine concentrations is particularly relevant given previous indications that methadone non-holders differ from holders by showing a more rapid decline in plasma methadone concentrations towards the end of the inter-dosing interval (Dyer et al., 1999). To the extent that pharmacokinetics are important in determining treatment response, it is also notable that methadone and morphine are metabolised by different mechanisms (Borg & Kreek, 1998). This means that patients showing rapid metabolism of methadone are not necessarily any more likely to experience the same problem whilst maintained on SROM.

1.7. Overview of the present research

Methadone maintenance is highly effective in reducing the harms associated with use of illicit opioids such as heroin, but also has a number of shortcomings (Ling et al., 1994). Many patients report the failure of their dose to suppress opioid withdrawal for the full 24-hour inter-dosing interval and adverse effects attributable to methadone (Dyer & White, 1997; Judson & Goldstein, 1982; Kreek, 1973, 1991). The deficiencies of methadone are further evidenced by the frequency with which complete opioid abstinence is pursued as the primary treatment goal (Lenne et al., 2001), despite overwhelming evidence of the poor prognosis for success (Magura & Rosenblum, 2001), and by the ambivalent attitudes that the target population and providers of methadone maintenance often express towards the treatment (Bell et al., 1995; Stancliff et al., 2002; Zule & Desmond, 1998).

In response to these shortcomings, a number of alternative maintenance medications such as buprenorphine and LAAM have been introduced to offer greater flexibility and choice for

both patients and treatment providers (Ling et al., 1994). Unfortunately, these too have a number of limitations. In particular, concerns regarding the safety of LAAM (Clark et al., 2002a; Schwetz, 2001) mean that there is currently no long-acting full agonist alternative to methadone currently recommended for maintenance treatment in many countries. Furthermore, transfer to buprenorphine is not always a feasible or acceptable option for patients responding poorly to methadone maintenance, particularly given the likelihood of withdrawal precipitation in patients whose daily methadone dose exceeds 40 mg (Bouchez et al., 1998; Ling et al., 1994).

Although preliminary reports indicate that SROM may have clinical utility as an alternative to methadone in maintenance programs for opioid dependence, a number of important questions have yet to be adequately addressed. Most of these earlier investigations of SROM maintenance comprised anecdotal or case study reports (Brewer, 1995; Roberts & Crofts, 2000; Sherman, 1996), used short-acting SROM formulations requiring multiple doses per day (Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Fischer et al., 1996; Schneider, 1995; Schneider et al., 1996), or involved the use of SROM for maintenance of opioid dependent pregnant women (Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Schneider et al., 1996). There have been just three controlled evaluations of once-daily SROM products, all of which sampled heroin users entering treatment and exhibited at least one significant methodological limitation, including the use of dextromethorphan as a placebo medication (Eder et al., 2002), the failure to include a control group (Kraigher et al., 2002), and the use of a cross-sectional comparison of seemingly non-comparable groups (Giacomuzzi et al., 2001).

Since methadone is well-supported as the first-choice agonist option for maintenance of opioid dependence, the potential value of SROM is most likely to involve its use as an alternative for patients responding poorly to methadone. In particular, SROM may have

particular clinical utility as an alternative treatment option for patients reporting inadequate withdrawal suppression or adverse effects whilst maintained on methadone and in whom current treatment options are likely to be ineffective, unsafe, or unacceptable to the patient. To this extent, it is important to demonstrate that the duration of morphine action following SROM administration is sufficient to allow once-daily dosing in methadone maintenance patients. However, studies of morphine disposition and effects following once-daily SROM dosing have not previously been conducted in a methadone maintenance population. Similarly, further evaluation and clinical implementation of SROM is significantly impeded by a lack of knowledge regarding the most appropriate way to transfer patients between methadone and SROM and the extent to which treatment outcome indicators (e.g., drug use, health, satisfaction with treatment) may change following such transfers.

The present research investigated the potential for once-daily SROM (administered as Kapanol™) to be used as a maintenance pharmacotherapy for opioid dependence by comparing outcomes for methadone and SROM in a crossover clinical trial. Subjects were methadone maintenance patients reporting either adequate (holders) or inadequate (non-holders) withdrawal suppression between doses. The study design featured the concurrent measurement of plasma concentrations for (R)- and (S)-methadone and morphine and both subjective and physiological indices of opioid effect and treatment safety across a 24-hour inter-dosing interval on one occasion for methadone and SROM after at least 4 weeks on a stable dose of each drug. Clinical outcomes in the month prior to these assessments and patient outcomes during transfers between maintenance medications were also assessed. A detailed description of the study methodology and research participants is presented in Chapter 2.

1.7.1. Aims

The primary aims of the present study were to compare methadone and SROM as maintenance pharmacotherapies for opioid dependence with respect to the following areas:

- Pharmacokinetics (Chapter 3) and pharmacodynamics (Chapters 4 to 6).
- Clinical efficacy and acceptability (Chapter 7).
- Opioid withdrawal during the transition between medications (Chapter 8).

1.7.2. Expected outcomes

It was anticipated that the present study would inform the treatment community regarding the potential for SROM to be used as an alternative to methadone for maintenance treatment of opioid dependence by providing a detailed quantitative comparison of the effects of each drug (e.g., withdrawal suppression, adverse effects, drug use, health and depression) in relation to their pharmacological characteristics (e.g., pharmacokinetics). By using an experimentally powerful crossover methodology, and sampling from a target population likely to benefit from an alternative opioid agonist option to methadone (i.e., methadone non-holders), it was expected that this research would also provide a basis for further large-scale double-blind, randomised, controlled trials of SROM maintenance whilst maintaining the ethical integrity of the study; specifically, by minimising the numbers of patients in whom outcomes may have been jeopardised by transferring to a novel treatment strategy with a limited evidence base. To the extent that preliminary evaluations of SROM have yielded promising results regarding its efficacy and safety in patients responding poorly to methadone, and has yielded similarly satisfactory results when used once-daily for the management of pain, it was anticipated that results would support further evaluation of SROM as an alternative to methadone for maintenance treatment of opioid dependence.

2. OVERVIEW OF RESEARCH METHODOLOGY AND PARTICIPANTS

2.1. Introduction

The present study involved a crossover clinical trial of methadone and SROM as maintenance pharmacotherapies for opioid dependence. In Chapters 3 to 8, results pertaining to six distinct areas of investigation included in the research design will be presented. Methodological details specific to each of these areas of investigation will also be presented in the relevant later chapters. The purpose of the present chapter is to provide a synopsis of the research methodology and participants, with an emphasis on those elements of the study that are common to all subsequent chapters. This methodological overview will serve as the basis for a discussion of the ethical and scientific integrity of the study in relation to its objectives.

2.2.General methods

2.2.1. Subjects

Ethical approval for the present research was obtained from the Royal Adelaide Hospital Research Ethics Committee (No. 991217). Subjects were opioid dependent individuals undergoing methadone maintenance treatment and included patients reporting both adequate (holders) and inadequate (non-holders) withdrawal suppression between doses. To ensure equivalent statistical power for analyses according to methadone holding status, equal numbers of holders and non-holders were intentionally recruited. The holding status of patients was determined by self-report during the pre-study screening interview (described below). Approval was obtained to recruit a maximum of 30 participants, based on the expectation (from previous studies in this population) that as many as 10 subjects could drop-out of the study prior to completion, yielding a sample size of approximately 20.

Participation in the study was on a voluntary basis. All subjects provided written informed consent prior to commencement of the study and were encouraged to discuss their participation with family and friends prior to giving consent. They were informed that all information collected during the trial would be confidential, that they were free to drop-out of the study at any time, and that their participation in the trial would not impact on their regular treatment outside the confines of the study in any way. Subjects were financially remunerated for their participation, with a maximum payment of AUD$250, subject to satisfactory completion of all study requirements.

Eligibility for the study was subject to several restrictions. Subjects were required to have been maintained on methadone for more than 6 weeks without a dose change in the preceding 4 weeks. Patients were also required to be aged between 18 and 65 years and were excluded if they were taking part in any other research project, considered unwilling to comply with the study protocol, had poor venous access, exhibited significant medical (including positive HIV

serology) or psychiatric problems, showed severe liver impairment (serum aspartate aminotransferase and alanine aminotransferase concentrations greater than 3 times the upper limit of normal range; albumin <33g/l) or haemoglobin outside the normal range, were pregnant, breastfeeding, taking medications known to interfere with methadone or morphine pharmacokinetics (e.g., enzyme inducers, enzyme inhibitors, monoamine oxidase inhibitors), or demonstrating excessive levels of benzodiazepine use considered potentially hazardous by clinic medical officers.

Subjects were recruited from public methadone clinics (Warinilla and Northern clinics) associated with the Drug and Alcohol Services Council (DASC) of South Australia and private medical practitioners registered as methadone prescribers during 2000 and 2001. Prospective participants were provided with an information sheet describing the nature and purpose of the study during appointments with duty counsellors and medical officers (e.g., for review of methadone prescription) or upon direct approach of the researcher. Information sheets and a cover letter explaining the purpose of the study were sent to approximately 30 private methadone prescribers.

2.2.2. Study design

An open-label, randomly-ordered, crossover design was used to compare racemic methadone hydrochloride oral solution (5 mg/mL: GlaxoSmithKline Australia, Boronia, Victoria, Australia) and once-daily morphine sulphate as Kapanol™ (GlaxoSmithKline Australia, Boronia, Victoria, Australia) capsules. Subjects were transferred from methadone to SROM for an evaluation period of approximately 6 weeks. Since SROM is currently not an approved maintenance medication for opioid dependence in Australia, all subjects were required to resume methadone maintenance upon completion of the study. Primary outcome measures for methadone and SROM were assessed for each drug after at least 4 weeks on a stable dose. Outcome assessments for SROM occurred at the end of the SROM maintenance evaluation

period for all subjects. In order to control for the possibility of transfer effects, outcome assessments for methadone maintenance were randomised (using SPSS™ for Windows, SPSS Inc, Chicago, Illinois, USA) to occur either immediately before transfer to SROM, or several weeks following resumption of methadone maintenance at the end of the SROM maintenance phase (i.e., at least 4 weeks after dose stabilisation). Equal numbers of subjects were randomised to each of these assessment order conditions.

2.2.3. Clinical procedures

All clinical procedures relating to treatment delivery for methadone and SROM maintenance were managed by the Maintenance Pharmacotherapy Unit at Warinilla Clinic, Adelaide, South Australia. Doses of methadone and SROM were determined on an individual basis by clinic medical officers such that opioid withdrawal and adverse effects were minimised. For both drugs doses were administered once-daily under supervision of the pharmacist (or the principal investigator during testing sessions). Granulated Kapanol™ doses were administered by emptying the pellets from capsules into a liquid (orange juice or water) that subjects consumed through a drinking straw. This method was used to reduce the likelihood that doses would be chewed (which compromises the slow-release characteristics of Kapanol™) or diverted for inappropriate use. Take-away doses were provided according to normal clinic policies.

At the commencement of the SROM maintenance phase, temporary authority to prescribe morphine as a maintenance treatment for opioid dependence as part of a clinical trial was obtained for each participant from the South Australia Health Commission. Transfer from methadone to SROM occurred 24 hours after the last methadone dose using an initial morphine:methadone dose ratio of approximately 3.5:1, based on previous experience suggesting an oral equivalence of 4:1 (Sherman, 1996). As Kapanol™ is available in 10 mg increments only, SROM doses were rounded up or down to the nearest 10 mg where

appropriate. SROM doses were initially increased by 10-30 mg daily as required to minimise withdrawal up to an initial maximum SROM:methadone dose ratio of 4.5. Increases in dose outside these guidelines were permitted following consultation with the attending medical officer. Following completion of the SROM maintenance phase, methadone was recommenced at the same dose used prior to commencing SROM maintenance unless there was a specific reason for doing otherwise. Whilst mild transient withdrawal was considered possible prior to methadone plasma concentrations reaching steady-state, significant methadone dose adjustments were not anticipated. In subjects for whom methadone dose changes were necessary, incremental changes of 5-10 mg daily were used.

2.2.4. Research procedures and measures

The study featured three phases of data collection, as follows: (1) pre-study interview and eligibility assessment initial eligibility assessment featuring the collection of basic demographic and treatment details; (2) the assessment of opioid withdrawal during the first 5 days following the transfer from methadone to SROM, and vice versa; (3) 2 × 24 hour inter-dosing interval assessments featuring the collecting of pharmacodynamic, pharmacokinetic, clinical efficacy and patient acceptability data for methadone and SROM. Specific measures taken during each of these stages of data collection are listed below and are described in more detail in the relevant later chapters.

2.2.4.1. Pre-study interview and eligibility assessment

Following expressions of interest in the trial, prospective participants were screened for eligibility (according to the criteria described above) either by the medical staff at DASC clinics or the researcher. Eligible participants were subsequently engaged in a pre-study interview with the researcher during which they were informed about the requirements of the trial. Once written consent was obtained, a semi-structured interview was conducted to collect standard information regarding subjects' demographic details, medical history, drug use and treatment history, and criminal and legal history. Subjects also completed a questionnaire

regarding their attitudes towards methadone maintenance comprising 30 statements about the treatment for each of which subjects rated their degree of agreement or disagreement (from 1 = strongly agree to 5 = strongly disagree; see section 2.3.1.6). This questionnaire was developed from a review of the research literature aimed at identifying common favourable or negative attitudes expressed by opioid users in and out of treatment towards methadone maintenance (Atlas, 1982; Brown, Bass, Gauvey, & Kozel, 1972; Brown, Benn, & Jansen, 1975; Caplehorn, Hartel, & Irwig, 1997; Heiman, 1979; Hunt, Lipton, Goldsmith, Strug, & Spunt, 1985a; Sutker, Allain, Smith, & Cohen, 1978). An assessment of patient attitudes was considered important in interpreting the data collected during the study. For patients referred by private prescribers, arrangements were made at the end of the interview to transfer the responsibility of care for that patient from the private prescriber to Warinilla clinic for the duration of the trial. According to the randomisation procedure described above (section 2.2.2), arrangements were also made for all subjects to either undergo the 24-hour inter-dosing assessment for methadone maintenance or to be transferred from methadone to SROM maintenance. Data collected during the pre-study interview and eligibility assessment are presented later in the present chapter (section 2.3).

2.2.4.2. Transfer between medications

Two types of data were used to assess patient outcomes during the transfer from methadone to SROM, and vice versa. Firstly, for the first five days following a change of maintenance medication, subjects completed the Methadone Symptoms Checklist (MSC) (Dyer & White, 1997) prior to dosing and at 3, 6 and 12 hours following dosing. Secondly, data were collected on the daily maintenance dose for the first ten days following changes of the maintenance medication and upon stabilisation (if greater than 10 days), the number of days taken until doses had stabilised (i.e., no further dose change required), and the total number of dose changes required until a stable dose was reached. Data collected during the transfers between medications are presented in Chapter 8.

2.2.4.3. 24-hour inter-dosing interval study

The primary data collection phase consisted of two 24-hour assessments during which the steady-state pharmacokinetics and pharmacodynamics of each medication were assessed and clinical efficacy and acceptability data were collected. These procedures were carried out under controlled conditions at the Royal Adelaide Hospital (RAH), Adelaide, South Australia. Data collection occurred between the hours of 9am-10pm on the first day of testing and 9am-10:30am the following morning. Participants spent the intervening night in the inpatient unit at Warinilla clinic, to ensure consistency in the treatment of subjects and to preclude use of additional drugs during the assessment period. Participants were provided with all meals and permitted to smoke tobacco and consume caffeinated beverages during the study and were asked to refrain from using psychoactive drugs (e.g., opioids, cannabis) in the period leading up to the commencement of data collection (i.e., for at least 12 h). Transport of subjects to and from home and between the RAH and Warinilla clinic (approximately 3km; accompanied by researcher) was achieved by taxi.

2.2.4.3.1. Pharmacodynamics and pharmacokinetics

The following procedures were used to investigate the pharmacokinetics and temporal change in opioid effects during the inter-dosing interval for both methadone and SROM, based upon the original methods of Dyer and colleagues (Dyer et al., 1999; Dyer & White, 1997). At the commencement of testing, an 18-22 gauge Insyte™ intravenous catheter (Becton Dickinson, Sandy, Utah, USA) was inserted into a suitable forearm vein by the RAH duty anaesthetist. Prior to the administration of the maintenance drug, blood and urine samples were obtained for detection of additional drug consumption. All testing was performed with the subject seated in a comfortable armchair. A sample (7mL) of venous blood was taken immediately before dosing and at the following times after dosing with either methadone or SROM: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 11, and 23 hours.

Following centrifugation, plasma samples were separated stored at -20^0C until later analysis by high performance liquid chromatography (HPLC). Plasma concentrations of (R)- and (S)-methadone and morphine during the inter-dosing interval for methadone and SROM were determined using methods previously described in detail by Foster et al. (2000) and Doverty et al. (2001a), respectively. The lower limits of quantification for these assays were 0.5ng/mL for morphine and 15ng/mL for both (R)- and (S)-methadone. Precision and inaccuracies, as assessed by coefficients of variation, were less than 10% for all quality control samples (high, medium, and low) for all assays. These assays were conducted by Andrew Menelaou and Ingvild Quinn (Department of Clinical and Experimental Pharmacology, University of Adelaide, South Australia). Pharmacokinetic data for methadone and SROM are presented in Chapter 3.

To detect additional heroin use prior to each testing session, baseline plasma samples for methadone and SROM were assayed for morphine (applicable to methadone session only) and the specific heroin metabolite 6-mon-acetylmorphine (using the same assay procedure as for morphine). These samples were also analysed for plasma concentrations of benzodiazepines (diazepam, clobazam, clonazepam, desmethyldiazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam and temazepam). Benzodiazepine assays had a limit of quantification of 1μM/L and were conducted by the Department of Chemical Pathology, Women's and Children's Hospital (Adelaide, South Australia). Baseline urine samples were immunoassayed for the presence of (cut-offs to denote positive results in parentheses) opiates (morphine) (300ug/L), methadone metabolite (2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine, EDDP) (100ug/L), benzodiazepines (200ug/L), sympathomimetic amines (including amphetamines) (300ug/L), cannabinoids (50ug/L), cocaine (300ug/L) and barbiturates (200ug/L) by the Institute of Medical and Veterinary Science (Adelaide, South Australia). Data regarding the frequency of additional drug use prior to the 24-hour inter-

dosing interval assessments for methadone and SROM, as detected using the above methods, are presented later in the present chapter (section 2.3.2.3).

Pharmacodynamic responses were recorded at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11 and 23 hours following dosing. At each of these times, a range of measures were taken. Firstly, subjects completed three questionnaires measuring withdrawal severity (Methadone Symptoms Checklist) (Dyer & White, 1997), mood states (Profile of Mood States) (McNair, Lorr, & Droppleman, 1971), and euphoric drug effects (Morphine Benzedrine Group and Morphine Group scales of the Addiction Research Centre Inventory) (Haertzen & Hickey, 1987). Second, physiological measures were recorded including pupil diameter, heart rate, respiratory rate, and blood pressure. Third, subjects' response to pain induced by electrical stimulation of the ear lobe was measured. Finally, subjects' tolerance of pain induced by the cold pressor test was assessed on one occasion during the 24-hour inpatient assessment for each drug, after the completion of all other procedures and immediately prior to administration of the next maintenance dose. Pharmacodynamic data collected during the 24-hour inter-dosing interval assessments for methadone and SROM are analysed in Chapters 4 to 6.

2.2.4.3.2. Clinical efficacy and acceptability

The 24-hour inter-dosing interval study was also used to collect data on clinical outcomes based on patients' experiences in the preceding 4 weeks. Between the period of 7 and 11 hours following dosing, the following procedures were carried out. Firstly, a sample of hair (1cm of most recent growth) was obtained for later analysis of heroin, 6-mono-acetylmorphine and morphine concentrations. Second, subjects were engaged in a structured interview with the researcher regarding their employment, welfare benefits, drug use, criminal behaviour, legal pressures, contact with medical specialists, illnesses and medication usage in the previous 4 weeks. Third, subjects completed questionnaires including visual analogue scale (VAS) assessments of their maintenance drug (White et al., 2002), the SF-36 health

survey (Ware, Snow, Kosisnki, & Gandek, 1993), the Beck Depression Inventory (BDI-II revised) (Beck, Steer, & Brown, 1996), sleep patterns (Parrott & Hindmarch, 1980), social functioning (Opiate Treatment Index) (Darke, Hall, Wodak, Heather, & Ward, 1992), self-esteem (Bachman & O'Malley, 1977), and qualitative response items regarding their perceptions of each maintenance drug. Finally, during the second 24-hour assessment, subjects were asked to state a preference for methadone or SROM, indicate the strength of that preference on a 0-100 mm VAS, and specify the reasons for their choice. Clinical efficacy and acceptability data collected during the 24-hour inter-dosing interval assessments for methadone and SROM are presented in Chapter 7.

2.3.Research participants

This section presents a description of the research participants recruited in the present study based on data collected during the pre-study interview and eligibility assessment and the subsequent progress of each subject through trial protocol. Data are presented as mean ± standard deviation (SD) (range) unless otherwise indicated. All tests of statistical significance (specified in the text) were two-tailed and used an alpha level of 0.05.

2.3.1. Subject details

Twenty five (18 male, 7 female) methadone maintenance patients expressed an interest in taking part in the study. Following preliminary assessments, seven were excluded from participating for reasons relating to excessive benzodiazepine use (n = 2), intake of medications that interfere with methadone and morphine pharmacokinetics (n = 1), being either pregnant (n = 1) or breastfeeding (n=1), and failing to attend following the initial screening interview (n = 2). The remaining 18 patients were recruited to participate. This included 10 from Warinilla, 3 from the Northern Clinic and 5 from private methadone prescribers. Patients recruited from private prescribers were transferred to Warinilla for the duration of the trial and returned to their care following its completion.

2.3.1.1. Methadone treatment and holding status

At the time of the pre-study assessment, subjects had been participating in a methadone maintenance program for a median of 27 months (range 1.5 – 168 months). The mean ± SD (range) daily methadone dose was 78 ± 32 mg (25-120 mg). Doses were relatively evenly distributed across the ranges of 25-49 mg (n = 5), 50-74 mg (n = 3), 75-99 mg (n = 5) and 100-125 mg (n = 6). The 18 subjects comprised equal numbers of subjects self-reporting the regular failure of their methadone dose to hold for the full 24-hour inter-dosing interval (non-holders, n = 9) and others reporting no such problem (holders, n = 9). Independent samples tests (t-test, Mann-Whitney) indicated no significant differences between the holders and non-holders in terms of age (33 ± 10 years vs. 35 ± 8 years, $t(16) = 0.37$, $p = 0.72$), gender

distribution (8/9 males vs. 7/9 males, $Z = 0.61$, $p = 0.54$), time on the methadone program ($Z = 0.04$, $p = 0.97$), or daily methadone dose (72 ± 28 mg vs. 83 ± 36 mg, $t(16) = 0.70$, $p = 0.50$). As holders and non-holders did not differ significantly on any of the demographic and treatment related variables described below, these data are presented for the subjects as a whole.

2.3.1.2. Demographics

Demographic variables are presented for all subjects in Table 2-1. All subjects were Caucasian; the majority were male (83%) and reported being hepatitis C positive (61%), educated to year 10 or less (50%), unemployed (67%), and currently with a partner (50%).

Table 2-1. Subject demographics (n=18).

Age (years: mean±SD, range)	34 ± 9 (21-48)
Gender (males, %)	15 (83)
Ethnicity	All Caucasian
Hepatitis C positive (n, %)	11 (61)
Highest level of education (n, %)	
Year 10 or less	9 (50)
Year 11	3 (17)
Year 12	1 (6)
Technical college/apprenticeship	3 (17)
University degree	2 (11)
Employment (usual occupation last 3 years) (n, %)	
Unemployed	12 (67)
Skilled/Trade	3 (17)
Student	1 (6)
Home duties	1 (6)
Imprisoned	1 (6)
Marital/parental status (n, %)	
Has partner	9 (50)
Living with partner	7 (39)
Ever married	6 (33)
Divorced/Separated	3 (17)
Have children	7 (39)

2.3.1.3. Drug use history

Subjects reported first using heroin at a mean age of 18 ± 4 (12-29) years and first using heroin on a daily basis at a mean age of 21 ± 4 (15-29) years. The mean length of consistent heroin use (no interruptions of greater than 1 week) prior to commencing the current methadone maintenance program was 2.4 ± 2.07 (0.17 – 8) years. All subjects reported daily heroin use in the month prior to treatment entry, with a mean number of 3.2 ± 1.7 (1-7) uses per day and a mean daily expenditure on heroin of AUD$227 ± 201 (50-800). The frequency with which subjects reported the use of other drug classes at any stage and in the month prior to commencing their current episode of methadone maintenance treatment is summarised in

Table 2-2. Beyond heroin, the next most commonly used drug in the month prior to treatment was tobacco, which was used by 89% of subjects with a mean number of 24 ± 15 (8-50) cigarettes per day. Use of marijuana (56%), benzodiazepines (56%), alcohol (44%), other opiates (44%) and diverted methadone (39%) was also commonly reported in the month prior to treatment entry.

Table 2-2. Frequency of life-time and month-prior-to-treatment drug use (n=18).

		Month prior to treatment entry		
	Ever used (n, %)	Used at all (n, %)	Daily use (n, %)	Days of use (mean ± SD)
Tobacco	18 (100)	16 (89)	16 (89)	27 ± 9.7
Marijuana	18 (100)	10 (56)	7 (39)	13 ± 15
Benzodiazepines	17 (94)	10 (56)	4 (22)	9.3 ± 13
Alcohol	18 (100)	8 (44)	2 (11)	5.0 ± 9.6
Other opiates[a]	16 (89)	8 (44)	2 (11)	6.6 ± 10.4
Diverted methadone	13 (72)	7 (39)	0 (0)	2.9 ± 5.5
Cocaine	16 (89)	3 (17)	1 (6)	2.4 ± 7.3
Ecstasy	1 (6)	2 (11)	0 (0)	0.3 ± 0.8
Amphetamines	16 (89)	1 (6)	0 (0)	0.2 ± 0.9
Hallucinogens	17 (94)	0 (0)	0 (0)	0 ± 0
Inhalants	5 (28)	0 (0)	0 (0)	0 ± 0

[a] Other than heroin and diverted methadone.

2.3.1.4. Drug treatment history

Drug treatment histories are summarised for all subjects in Table 2-3. All but one of the subjects reported having previously undergone treatment for opioid dependence, with the most common forms or prior treatment being clinic detoxification (78%), methadone maintenance (61%), and narcotics anonymous (39%). Previous experiences of other maintenance pharmacotherapies including naltrexone (n = 1) and LAAM (n = 2) was uncommon. Four subjects (22%) reported having undergone treatment for benzodiazepine use. One of these subjects also reported having undergone treatment for alcohol and amphetamine use.

Table 2-3. Drug treatment history (n=18).

Form of treatment	Ever tried (n,%)	Number of prior treatment episodes		
		Mean ± SD	Range	Median
Opioid dependence				
Any previous treatment	17 (94)	11 ± 13	2-46	5
Methadone maintenance	11 (61)	1.4 ± 2.1	0-8	1
Detoxification – clinic	14 (78)	3.3 ± 5.4	0-20	1
Detoxification – home (medically supervised)	5 (28)	0.6 ± 1.2	0-5	0
Drug free counselling	8 (44)	0.7 ± 1.2	0-5	0
Therapeutic community	4 (22)	0.3 ± 0.8	0-3	0
Narcotics anonymous	7 (39)	2.8 ± 6.1	0-25	0
Naltrexone	[a]2 (11)	-	0-1	0
LAAM	[a]1 (6)	-	0-1	0
Other drug classes				
Any	4 (22)	0.4 ± 1.0	0-4	0
Benzodiazepines	4 (22)	0.3 ± 0.6	0-2	0
Speed	[a]1 (6)	-	0-1	0
Alcohol	[a]1 (6)	-	0-1	0

[a] Insufficient numbers for calculation of mean ± SD.

2.3.1.5. Criminal and legal history

Criminal and legal histories are summarised for all subjects in Table 2-4. Lifetime involvement in criminal behaviour was common, with dealing of heroin (67%), dealing of other drugs (72%), and shoplifting (72%) being the most commonly reported offences. More than a third of subjects also reported involvement in break and enters (39%), assault (44%), fraud (44%), and car theft (39%) at some stage in their life. In the 6 months prior to the study, dealing of drugs other than heroin (39%) and shoplifting (33%) were the most common offences.

Consistent with these high rates of criminality, subjects showed a high level of past and present contact with law enforcement and the judiciary system. A very high proportion of subjects reporting having been arrested (94%), cautioned (94%), or placed in the 'lock up' (94%) by police. All subjects reported having court appearances and being required to undertake community service, with nearly two-thirds (61%) also having been imprisoned at some stage. More than a quarter of subjects reported a court appearance (33%), arrest (28%), or police caution (33%) in the 6 months prior to the study, indicating continuing criminal behaviour amongst some subjects. The mean age of first occurrence for most of the criminal and law enforcement events described above generally coincided with the mean age at which heroin use was initiated.

Table 2-4. Criminal and legal history (n=18).

	Frequency (n , %)			Age 1st occurrence (yrs)	
	Ever	Last 6 months	Last 12 months	Mean±SD	Range
Crime / behaviour					
Dealing heroin	12 (67)	4 (22)	5 (28)	22 ± 7	16 - 38
Dealing other drugs	13 (72)	7 (39)	8 (44)	19 ± 5	11 - 30
Break/enter – domestic	7 (39)	3 (17)	4 (22)	19 ± 7	9 - 29
Break/enter – commercial	7 (39)	1 (6)	1 (6)	16 ± 4	9 - 22
Snatch and grab	4 (22)	0 (0)	0 (0)	19 ± 6	15 - 28
Injurious assault	8 (44)	1 (6)	2 (11)	18 ± 5	10 - 27
Fraud	8 (44)	0 (0)	0 (0)	21 ± 7	11 - 32
Shoplifting	13 (72)	6 (33)	6 (33)	13 ± 6	5 - 26
Prostitution	1 (6)	0 (0)	0 (0)	18	n/a
Armed robbery	3 (17)	0 (0)	0 (0)	19 ± 5	15 - 25
Stolen car	7 (39)	0 (0)	0 (0)	17 ± 4	11 - 25
Contact with police/courts					
Police caution	17 (94)	6 (33)	9 (50)	16 ± 5	8 - 30
Police lock-up	17 (94)	2 (11)	4 (22)	20 ± 5	10 - 29
Arrested	17 (94)	5 (28)	8 (44)	18 ± 6	10 - 29
Imprisoned	11 (61)	0 (0)	1 (6)	20 ± 6	15 - 30
Community service	13 (72)	2 (11)	3 (17)	26 ± 9	15 - 40
Court appearance	18 (100)	6 (33)	8 (44)	17 ± 5	8 - 30

2.3.1.6. Attitudes towards methadone maintenance treatment

Attitudes towards methadone maintenance treatment are presented for all subjects and the methadone holder and non-holder subgroups in Table 2-5. Of the 33 statements for which subjects were asked to indicate their degree of agreement, 15 showed mean ratings indicating a significant degree of either agreement or disagreement, as determined by a single-sample t-test comparison with the scale midpoint (i.e., rating of "3"). Subjects generally expressed positive attitudes towards the recipients and providers of methadone maintenance, disagreeing with statements that "people who use methadone have given up" and "are lazy", and agreeing

with statements that "people on methadone are strong" and that "methadone clinic staff are helpful". Significant agreement was also found for the statement that "methadone stops you from hanging out", suggesting that subjects generally considered methadone an effective means of suppressing withdrawal. However, attitudes towards many other aspects of methadone maintenance were unfavourable. A number of items suggested that subjects perceived methadone as more addictive and dependence-inducing than heroin, as evidenced by significant agreement to statements such as "methadone is more addictive than heroin", "methadone replaces one addiction with another", "hanging out is worse from methadone than heroin", "methadone is worse for you than heroin", "the sooner a person stops taking methadone the better" and "its harder to get off methadone than it is to get off heroin". Attitudes towards the requirements of treatment (e.g., supervised dosing, clinic attendance) were similarly suggestive of low patient acceptability, as evidenced by significant agreement with the statements that "being on methadone interferes with my daily activities (daily life)" and "picking up methadone everyday is a hassle". Subjects disagreed with the statement that "methadone keeps you high for 24 hours".

Notably, many of these negative attitudes towards methadone maintenance were common to both holders and non-holders, suggesting that the achievement of adequate withdrawal suppression does not guarantee patient acceptability of treatment. Independent t-tests indicated that there were only 3 items for which ratings differed significantly for holders and non-holders. Consistent with their self-reported holding status, non-holders showed stronger disagreement than holders with the statements that methadone "keeps you high for 24 hours" and "is stronger than heroin". Interestingly, non-holders also showed stronger disagreement with the statement that "methadone is too expensive".

Table 2-5. Attitudes towards methadone maintenance for all subjects (n=18) and the methadone holder (n=9) and non-holder (n=9) subgroups.

Item	All subjects	Holders	Non-holders
A person is better off taking methadone than heroin	2.8 ± 1.6	2.8 ± 1.2	2.8 ± 1.9
People who use methadone have given up	*3.7 ± 1.1	3.6 ± 1.2	*3.9 ± 0.9
Methadone keeps you high for 24 hours	***4.2 ± 1.2	†3.6 ± 1.2	†***4.8 ± 0.7
People who use methadone are lazy	*3.7 ± 1.4	3.7 ± 1.4	3.7 ± 1.4
Methadone is stronger than heroin	3.2 ± 1.5	†2.3 ± 1.1	†4.0 ± 1.4
Methadone has bad side-effects	2.8 ± 1.7	2.3 ± 1.7	3.2 ± 1.8
Being on methadone interferes with my daily activities (daily life)	*2.3 ± 1.2	2.4 ± 1.2	*2.1 ± 1.2
Methadone helps you lead a normal life	2.6 ± 1.4	2.6 ± 1.7	2.6 ±1.2
Methadone is more addictive than heroin	**1.9 ± 1.3	***1.4 ± 0.7	2.3 ± 1.7
Methadone is the best treatment for heroin users	3.6 ± 1.4	3.3 ± 1.2	3.8 ± 1.6
Picking up methadone everyday is a hassle	***1.6 ± 1.1	***1.6 ± 0.7	*1.7 ± 1.4
Methadone replaces one addiction with another	***1.8 ± 1.2	*2.0 ± 1.0	*1.6 ± 1.3
Once you're on methadone you have to keep taking it	**1.9 ± 1.3	***1.8 ± 0.0	2.1 ± 1.7
It's better being abstinent than taking methadone	2.8 ± 1.3	3.1 ± 1.1	2.6 ± 1.6
People on methadone are strong	**3.8 ± 0.9	*3.7 ± 0.9	*3.9 ± 0.9
It is easy to get on a methadone program	2.8 ± 1.4	3.2 ± 1.2	2.3 ± 1.5
Hanging out (withdrawal) is worse from methadone than heroin	***1.8 ± 1.1	*1.6 ± 1.0	*2.2 ± 1.2
Methadone clinic staff are helpful	**2.3 ± 1.0	2.3 ± 1.1	*2.2 ± 1.0
Methadone has done a lot more good for people than bad	2.4 ± 1.1	2.6 ± 1.2	2.3 ± 1.1
Methadone makes you feel normal	2.5 ± 1.2	*2.0 ± 1.0	3.0 ± 1.2
Methadone rules are unfair	3.3 ± 1.1	2.9 ± 0.9	3.8 ± 1.1
People on methadone are more active than people who use heroin	2.9 ± 1.4	3.1 ± 1.4	2.8 ± 1.5
People would not stay off heroin if they didn't take methadone	2.7 ± 1.3	2.7 ± 1.2	2.8 ± 1.4
I would be too ashamed to use methadone	***4.4 ± 1.2	4.0 ± 1.5	***4.8 ± 0.7
Methadone is too expensive	2.6 ± 1.5	†**1.8 ± 1.0	†3.3 ± 1.7
With methadone you can eventually get off the drugs if you want to	2.4 ± 1.2	2.7 ± 1.5	*2.2 ± 1.0
People on methadone would not make it on the street	3.3 ± 0.8	2.6 ± 1.1	3.0 ± 0.0
Methadone is worse for you than heroin	*2.2 ± 1.4	2.1 ± 1.5	2.3 ± 1.4
The sooner a person stops taking methadone, the better	**2.1 ± 1.2	**2.0 ± 0.7	2.1 ± 1.6
People on methadone are healthier than people who use heroin	3.0 ± 1.4	2.6 ± 1.3	3.4 ± 1.4
In the long run, methadone is more helpful than harmful	2.8 ± 1.2	1.4 ± 1.4	2.7 ± 1.0
Methadone stops you from hanging out	***1.5 ± 0.9	***1.6 ± 0.7	**1.4 ± 1.0
It's harder to get off methadone than it is to get off heroin	***1.3 ± 0.6	***1.4 ± 0.7	***1.1 ± 0.3

Values are mean ± SD. Response categories: 1 = strongly agree, 2 = somewhat agree, 3 = neither agree nor disagree, 4 = somewhat disagree, 5 = strongly disagree. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (significantly different from '3 = neither agree nor disagree' scale midpoint), † $p < 0.05$ (holders vs. non-holders).

2.3.2. Subject compliance and attrition

2.3.2.1. Completion rates

Completion rates varied for each of the three main phases of data collection in the present study. Although all 18 subjects were transferred from methadone to SROM, 3 (all males; 2 non-holders, 1 holder) dropped-out of the study prior to undertaking the 24-hour inter-dosing interval assessment for either methadone or SROM. Two of these subjects (id. numbers: 4 and 18) decided that methadone was preferable to SROM and elected to resume methadone maintenance without completing the study. A third subject (id. no. 12) wished to detoxify from maintenance treatment for reasons relating to employment and was transferred back to methadone in order to do so. This subject had also twice failed to attend for scheduled 24-hour inter-dosing interval assessments for SROM and was considered unlikely to have satisfactorily completed the study in any case. Further details of these cases and their reasons for discontinuing the study are presented in Chapter 7.

In addition to these 3 drop-outs, a fourth subject (id. no. 3: male, holder), who completed all phases of data collection in the study, was excluded from all pharmacokinetic and pharmacodynamic analyses due to evidence of significant additional opioid intake prior to the inter-dosing interval assessment for both methadone and SROM. For the methadone assessment, the baseline plasma sample for this subject was positive for morphine, although the concentration was very low (1.2ng/mL). Evidence of significant additional heroin use was more notable for the SROM assessment, for which plasma morphine concentrations showed a 10-fold continuous decline from 230ng/mL to 23ng/mL between the time of dosing and 23 hours post-dose (Figure 2-1). Excluding this subject, the primary analyses of pharmacokinetic and pharmacodynamic data presented in Chapters 3 to 6 are based on a sample of 14 (11 male, 3 female) methadone maintenance patients, comprising 7 holders and 7 non-holders. There were no significant differences between the 4 excluded subjects and this primary cohort of 14 subjects in terms of age (30 ± 10 yrs vs. 34 ± 9 yrs), daily methadone

dose (83 ± 31 mg vs. 76 ± 33 mg), or any of the major demographic and treatment variables (e.g., drug use and treatment history) summarised above.

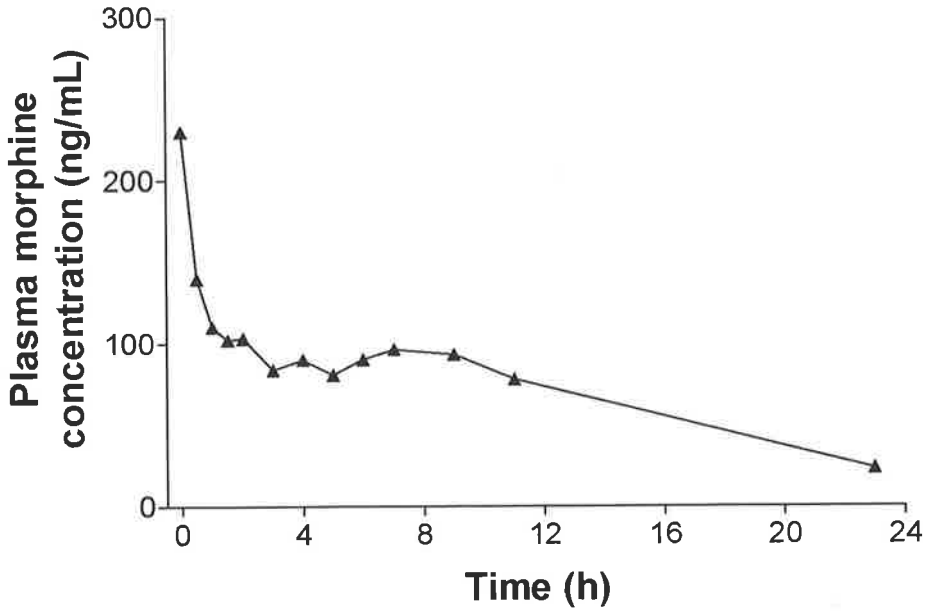

Figure 2-1. Plasma morphine concentrations during a 24-hour inter-dosing interval for SROM in a single subject suspected of additional heroin use prior to testing.

The subject showing evidence of significant additional opioid use of opioids prior to the SROM assessment (id. no. 3) was not excluded from assessments of clinical outcomes in the month prior to assessment, presented in Chapter 7, yielding a sample of size of 15 for these analyses. Similarly, since 1 of the 3 drop-outs satisfactorily completed withdrawal questionnaires during the transition from methadone to SROM, and dosage information during this transition period was available for all subjects, greater samples sizes (n = 16 to 18) were permitted for certain analyses (Chapter 8). Due to above-mentioned drop-outs and other specific instances of non-compliance (described in Chapter 8), withdrawal data for the transition from SROM back to methadone were only available for 11 subjects. A flow chart detailing subject recruitment and attrition during the study is presented in Figure 2-2.

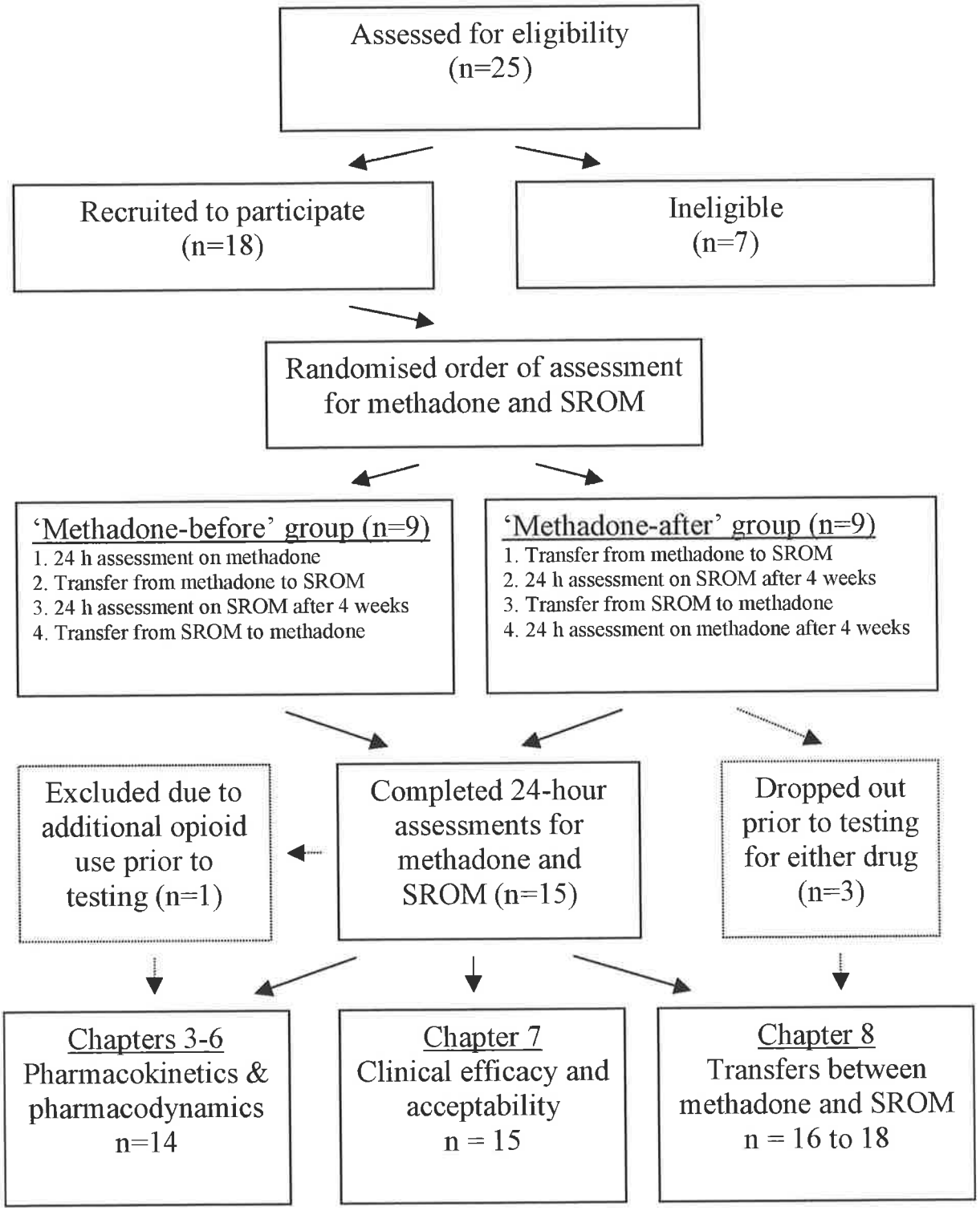

Figure 2-2. Flow chart of subject recruitment, randomisation and sample sizes (n) for data presented in Chapters 3-8.

2.3.2.2. Assessment order and duration

The order of assessments for methadone and SROM was randomised such that equal numbers of subjects were to be assessed on methadone prior to ('methadone-before' group: n = 9) and subsequent to ('methadone-after' group: n = 9) the SROM maintenance phase, as outlined earlier. Due to 3 subjects dropping out of the study, however, the numbers of subjects in the 'methadone-before' 1 (n = 9) and 'methadone–after' (n = 6) groups were slightly different. Nevertheless, independent samples t-tests and chi-square tests indicated that there were no significant differences between the two groups in distributions of age (33 ± 8 yrs vs. 40 ± 9 yrs, p = 0.13), daily methadone dose (72 ± 35 mg vs. 83 ± 29 mg, p = 0.56), methadone holding status (4/6 vs. 4/9 holders, p = 0.40), and gender (male:female, 7:2 vs. 5:1, p = 0.79). To this extent, the occurrence of subject drop-outs did not significantly compromise the experimental design on key demographic and treatment variables.

Subjects were maintained on SROM for a mean of 43 ± 14 days (32-87 days), with a mean of 42 ± 14 days (30-85 days) separating the assessments for SROM and methadone. Variation in these measures reflects variability in (1) the time it took to achieve stabilisation on SROM and re-stabilisation on methadone, (2) constraints regarding access to clinical (e.g., inpatient bed and staff availability) and research (e.g., testing rooms) resources, and (3) subject compliance. In particular, it is noteworthy that one subject (id. no. 3) cancelled scheduled assessment days for SROM on two occasions before eventually completing the study requirements for that treatment phase nearly 3 months following its commencement. Although the subject stated unforeseen circumstances (relating to employment as a shift-worker) as the reason for these delays, it is possible that other motivations, including the subject's desire to remain on SROM, were contributing factors. Variation between subjects in the time spent maintained on SROM (30-55 days) and the interval between methadone and SROM assessments (32-57 days) was considerably less amongst the primary cohort of 14

patients, which did not include the above-mentioned subject (excluded due to evidence of additional heroin use).

2.3.2.3. Unsanctioned drug use on day of assessments

Frequencies of additional drug detection in urine and plasma samples taken on the day of the inter-dosing interval assessments for methadone and SROM are summarised in Table 2-6 for the 14 subjects included in all pharmacodynamic and pharmacokinetic analyses. Urinalysis indicated that the most commonly detected drugs for both methadone and SROM on testing days were benzodiazepines (57% vs. 64%) and cannabinoids (50% vs. 36%)). There were also significant correlations between methadone and SROM in the frequencies with which cannabinoids ($r = 0.75$, $p = 0.002$) and benzodiazepines ($r = 0.56$, $p = 0.002$) were detected in urine. For methadone, morphine detection in urine (36%) and plasma (21%) suggested possible recent heroin use in some subjects, although plasma samples showed no positive results for the heroin metabolite 6-mono-acetylmorphine for either methadone or SROM. The concentrations of morphine detected in the trough plasma samples for 3 subjects at the start of the methadone testing session were sufficiently low (3.9, 4.6 and 11.4 ng/mL) to preclude exclusion of these subjects' data. No subjects returned positive urinalyses results for cocaine or barbiturates for either methadone or SROM, whilst a small number showed positive results for sympathomimetic amines (14% methadone vs. 21% SROM).

Table 2-6. Frequency of additional drug detection in urine and plasma samples taken immediately prior to 24-hour inter-dosing assessments for methadone and SROM (n=14).

Drug	Methadone (n, %)	SROM (n, %)
Urine sample		
Morphine	5 (36)	14 (100)
Methadone	14 (100)	1 (7)
Benzodiazepines	8 (57)	9 (64)
Barbiturates	0 (0)	0 (0)
Cannabinoids	7 (50)	5 (36)
Sympathomimetic Amines	2 (14)	3 (21)
Cocaine	0 (0)	0 (0)
Plasma sample		
6-monoacetylmorphine	0 (0)	0 (0)
Morphine	3 (21)	14 (100)
Benzodiazepines[a]	6 (43)	8 (57)

[a] Benzodiazepines detected included diazepam, desmethyldiazepam, oxazepam, temazepam and nitrazepam.

2.4.Discussion

The primary aim of the present research was to compare methadone and SROM as maintenance pharmacotherapies for opioid dependence with respect to their comparative pharmacokinetics, pharmacodynamics, clinical efficacy and patient acceptability. The methodology used to achieve this aim consisted of a crossover clinical trial of methadone and SROM in eighteen methadone maintenance patients, half of whom reported inadequate withdrawal suppression prior to the study (non-holders) and half of whom reported no such problem (holders). Results pertaining to six distinct areas of enquiry featured in the study design are presented in Chapters 3 to 8. To facilitate comprehension of later sections, the present chapter provided an overview of the trial methodology and research participants; in particular, those aspects of the study that are common to all subsequent chapters. In the following discussion, issues pertaining to the ethical and scientific integrity of the present study are addressed in reference to the trial methodology and design.

2.4.1. Ethical considerations

The primary ethical consideration in the design of the present study related to the small evidence base for SROM maintenance and, conversely, the preponderance of evidence supporting the use of methadone in maintenance programs for opioid dependence. From this perspective, it was ethically desirable that the study be designed in such a way as to minimise the likelihood that transfer from methadone to SROM maintenance would compromise the well-being of research participants. A number of elements of the study design are notable in this regard.

Firstly, by sampling methadone maintained volunteers, the study design ensured that all participants had already been exposed to the most effective known treatment for opioid dependence prior to their choosing to transfer to SROM. Secondly, half of the sample were already reporting inadequate treatment efficacy whilst maintained on methadone (i.e., the non-holders) and were thus less likely to be compromised by a change in the maintenance

medication. Thirdly, the study design featured the use of an experimentally powerful crossover design. To the extent that individual differences are held constant in within-subject studies, a greater degree of statistical power is achieved and hence fewer subjects are required in comparison to between-group comparisons (Hills & Armitage, 1979; Jones & Lewis, 1995; Palmer & Rosenberger, 1999). Fourth, the duration of the SROM evaluation phase was limited to the minimum amount of time thought to be necessary to achieve an accurate assessment of outcomes following the achievement of a stable dose and to allow for a sufficient 'washout' period following transfers between methadone and SROM (i.e., at least 4 weeks on a stable dose).

These characteristics of the study were particularly advantageous in limiting the number of patients for which transfer from methadone to SROM would be required and the likelihood that this change of medication would deleteriously impact on patient outcomes. The study was further characterised by an emphasis on determining whether or not the magnitude and duration of opioid effects between doses for SROM were comparable to that achieved with methadone and thus sufficient for once-daily dosing. Addressing this question was considered imperative in obtaining 'proof in principle' evidence regarding the likely clinical utility of SROM in maintenance programs. To the extent that such evidence of SROM's efficacy was forthcoming in a relatively small number of subjects, it was intended that this study would provide ethical justification for further evaluation and clinical implementation of SROM maintenance using larger sample sizes and standard treatment outcome indicators (Simon, Thall, & Ellenberg, 1994).

2.4.2. Methods of statistical inference

Another important methodological consideration that relates to both the ethical and scientific integrity of the present study concerns the methods of statistical inference used to draw conclusions about the significance of observed differences and relationships. For certain research questions, the practice of reducing the alpha level when making multiple

comparisons has been advocated in the past as a means of keeping the overall probability of a Type 1 error rate (false-positive) as low as possible. The Bonferroni method, for example, involves decreasing the alpha level in proportion to the number of comparisons made to yield the adjusted alpha level. A number of problems associated with this approach, particularly when applied to the evaluation of clinical outcomes, have been highlighted. These problems include (1) the untenable scenario whereby the number of tests performed rather than the data itself determines the outcome of the decision making process (e.g., "a patient's packed cell volume might be abnormally low, except if the doctor also ordered a platelet count, in which case it could be deemed normal") (Perneger, 1998) and (2) ambiguities and impracticalities about which tests should be included in the adjustment (e.g., tests performed but not published, tests published but in a separate journal) (Perneger, 1998). Moreover, although Bonferroni adjustments preserve the Type 1 error rate, the likelihood of Type 2 errors (i.e., whereby a difference exists but is not detected; false-negative) and hence the number of subjects required to execute a powerful study increases accordingly. For these reasons, the practice of correcting alpha levels for multiple comparisons is sometimes disadvantageous from an ethical and practical viewpoint in exploratory evaluations of novel treatments (Perneger, 1998). To avoid these problems and ambiguities, an alpha level of 0.05 is used uniformly throughout this thesis as the criterion for statistical significance. Consideration of Type 1 errors is taken into account, where applicable, in discussions of the clinical importance of observed differences and relationships.

2.4.3. Internal and external validity

To the extent that ethical and practical constraints were applicable in the design and conduct of the present study, it is important that possible threats to the internal and external validity of the study methodology are identified and discussed. A number of facets of the study require attention in this regard.

One possible threat to the validity of the present study's findings concerns the use of an open-label design. Ordinarily, double-blind methodologies are preferable in that they conceal treatment conditions from both patients and staff, thus limiting the likelihood that expectations and other biases may influence results. Use of a double-blind methodology was not considered feasible in the present study for the following reasons. Firstly, it was considered likely that subjects would experience clinically significant differences in subjective effects (e.g., withdrawal) upon transfer between the medications and because of the differences in the time-course of effects for each drug between doses. These differences between the two treatments would limit the likelihood of effective blinding. Second, it was considered preferable for safety reasons that clinic staff and the researcher be aware of both the maintenance drug and dosage, particularly given the limited evidence base for SROM maintenance. Third, at the time the study was commenced, placebo versions of the Kapanol™ capsules were not readily available. Finally, it should also be noted that many of the primary outcome measures for the present study were objective and physiological in nature (e.g., plasma drug concentrations, drug concentrations in hair, pupil diameter; described below) and thus relatively unsusceptible to potential biases (e.g., patient expectations and attitudes).

The use of a crossover design also entails certain threats to the internal validity of the present study. As such designs involve exposure of each subject to each experimental condition (i.e., methadone or SROM), their main disadvantage is the possibility of interactions between the two treatments; that is, the possibility that responses to one treatment may be affected by exposure to the other treatments (Senn, 1994). To control for possible order effects in the present study, the order of outcome assessments for methadone maintenance was randomised to occur either before or after the SROM maintenance phase of the study. Additionally, assessments of outcomes for each drug were made after at least 4 weeks on a stable dose of each drug, thus limiting the likelihood of significant carry-over effects from the previous medication. The advantages of a crossover design in maximising statistical power and hence

minimising subject numbers were deemed to outweigh potential threats to the internal validity of results due to order effects.

Another important methodological consideration concerns the methods of sampling used in the present study. Given the small existing evidence base for SROM maintenance, it was considered ethically advisable that the sample comprise methadone-maintained volunteers, freely consenting to participate and with at least six weeks prior exposure to methadone maintenance. A disadvantage of this approach relates to the risk of self-selection biases, whereby patients electing to participate may differ from those electing not to participate in a way that compromises the representativeness of the sample and thus the external validity of the study. Examples of potential biases include the possibility that patients with particularly unfavourable opinion of methadone maintenance treatment, irrespective of their status as holders or non-holders, may be more motivated to participate in the evaluation of an alternative treatment such as SROM than patients who are satisfied with methadone maintenance. Alternatively, volunteers may be characterised by other motivations such as curiosity in a new option such as SROM or the desire to facilitate improvements in clinical practice. Although the possibility of selection biases needs to be considered when interpreting the results of the present study, it should also be noted that similar selection biases may also apply in real clinical settings where patients are given a choice between methadone or SROM. To this extent, possible differences between the study sample and the wider population of methadone maintenance patients do not necessarily entail a significant threat to the external validity of the study.

In some instances, ethical and practical constraints involved a choice between the internal and external validity of the study design. Variation between subjects in terms of the maintenance dose, the time they were maintained on SROM and methadone, and their use of additional drugs, in particular, deserve attention in this regard. For each of these variables, the

achievement of homogeneity across subjects may eliminate possible sources of variation in the patient outcomes considered but would also limit the applicability of the findings to clinical settings and compromise the ethical integrity of the study. Failure to adopt an individualised and flexible approach to dosing, whereby maintenance doses are decided in consultation between patient and clinicians, would be inconsistent with policies of treatment delivery in South Australia and hence severely limit the applicability of the findings. From this perspective, the use of standardised doses (e.g., standardised SROM:methadone dose ratios) would also jeopardise the ethical integrity of the study and the well-being of its participants, given evidence of significant variation in disposition and effects for both methadone and morphine. Variation between subjects in the number of days they were maintained on SROM and the number of days between assessments was unavoidable due to practical constraints (e.g., access to research and clinical facilities) and patient compliance (e.g., subjects cancelling scheduled assessments), but was kept to a minimum.

Participants' use of additional drugs (e.g., heroin, cannabinoids, benzodiazepines) is potentially problematic in that some drug classes (e.g., cannabis, benzodiazepines) may have clinically significant effects on certain patient outcomes measured in this study (e.g., severity of opioid withdrawal). However, since poly-drug use is common amongst methadone maintenance patients, exclusion of patients on the basis of minor additional drug use may have adversely impacted on the representativeness of the sample. Furthermore, although drugs such as caffeine and tobacco (use of which was permitted in the present study) are similarly capable of influencing pharmacodynamic measures, requiring subjects to abstain from using these agents may have resulted in caffeine and nicotine withdrawal syndromes and thus similarly interfered with the measurement of certain patient outcomes.

In addressing problems relating to subjects' use of additional drugs, several measures were taken in the present study. Firstly, subjects showing excessive use of non-opioid drugs such as

benzodiazepines were excluded to ensure that opioids were the primary drug of dependence for all subjects. Second, subjects were instructed to refrain from using psychoactive drugs (e.g., opioids, cannabis, benzodiazepines) within the period immediately leading up to and during collection of pharmacodynamic data, to minimise the likelihood that additional drug use would produce clinically significant effects during testing. However, the use of drugs such as caffeine and tobacco was permitted during the testing period given the likelihood that abstinence from these agents would adversely compromise the representativeness of any results obtained. Third, urine samples taken at the commencement of testing were assayed for the detection of additional drug classes, thus allowing for statistical exploration of any potential effects.

For both methadone and SROM, benzodiazepines (50% and 37%) and cannabinoids (57% vs. 64%) were the most commonly detected drugs in urine. However, since urinary detection of benzodiazepines ($r = 0.56$, $p = 0.04$) and cannabinoids ($r = 0.75$, $p = 0.002$) was highly correlated for methadone and SROM, and occurred at similar overall frequencies for each assessment, it is likely that any effects of this additional drug use were relatively constant across experimental conditions. Similarly, although five subjects showed urinalyses positive for morphine, only three of these subjects also showed traces of morphine in plasma samples. The concentrations of morphine observed were sufficiently low to preclude the likelihood of significant opioid action and hence data for these subjects were not excluded. Of the fourteen subjects included in pharmacodynamic and pharmacokinetic analyses, none showed plasma samples positive for 6-mono-acetylmorphine for either methadone or SROM. With the exception of the subject who was excluded from pharmacodynamic and pharmacokinetic analyses (i.d. no. 3), this suggests that significant heroin use did not occur shortly prior to testing in any subject. Collectively, these results suggest that the patterns of additional drug use observed during assessments for methadone and SROM in the present study is unlikely to

pose a major threat to the internal or external validity of findings regarding the value of each medication in maintenance programs for opioid dependence.

A final threat to the internal and external validity of the research findings relates to subject attrition. In the present study, three subjects dropped-out prior to undertaking outcome assessments for either methadone or SROM and a fourth subject was excluded from pharmacokinetic and pharmacodynamic analyses due to additional opioid consumption. The use of a crossover design means that these cases of non-compliance do not represent a major threat to internal validity, since comparisons for most measures were only made for subjects in whom data for both methadone and SROM was available. To the extent that exclusion of these subjects reduced the representativeness of the sample, their non-compliance may pose a comparatively greater threat to the external validity of the study. However, these individuals showed no significant differences compared to the remainder of the sample in terms of key demographic and treatment variables such as age and daily methadone dose. It should also be noted that inclusion of data for these subjects was permitted for certain outcomes considered (e.g., treatment preference, withdrawal during the transfer between medications).

2.4.4. Characteristics and representativeness of the sample

Characteristics of the subject sample used in the present study are consistent with previous large-scale surveys of methadone maintenance patients in South Australia (Dyer & White, 1997; Ryan & White, 1996). Subjects were predominantly male (83%), unemployed (61%), hepatitis C positive (61%) and showed a long history of poly-drug use, criminal behaviour, contact with law enforcement (i.e., police, judiciary system), and unsuccessful prior treatment episodes. Consistent with the South Australian DASC policy of individualised methadone dosing, daily methadone doses showed a wide range (20 mg to 120 mg), but mean levels (78mg) were above putative lower limits for effective treatment (> 50mg) (Ward, Mattick, & Hall, 1998c). As intended, half of the recruited subjects reported the regular failure of their methadone dose to hold (non-holders, n = 9) prior to commencing the study and the remainder

reported no such problem (holders, n = 9). Methadone holders and non-holders were not differentiated by age, methadone dose, time on the program or any other demographic or treatment related variable.

Subjects' ratings of attitudinal statements about methadone maintenance revealed an interesting pattern of findings. In general, ratings indicated that attitudes towards methadone patients and treatment providers were generally positive or at least satisfactory, as evidenced by significant disagreement with statements that "people who use methadone have given up" and "are lazy", and agreeing with statements that "people on methadone are strong" and that "methadone clinic staff are helpful". However, attitudes towards methadone itself appeared less favourable and indicated a strong perception that methadone was in some respects no better than heroin and that eventual cessation of treatment was an important goal. This pattern of attitudes was evidenced by significant agreement with items such as "methadone is more addictive than heroin", "methadone replaces one addiction with another", "hanging out (withdrawal) is worse from methadone than heroin", "methadone is worse for you than heroin", "the sooner a person stops taking methadone the better" and "its harder to get off methadone than it is to get off heroin". Negative attitudes towards the impracticalities of treatment requirements (e.g., supervised dosing, clinic attendance) were also indicated by significant agreement with the statements that "being on methadone interferes with my daily activities (daily life)" and "picking up methadone everyday is a hassle". These negative attitudes were expressed despite agreement with the statement that "methadone stops you from hanging out", indicating that adequate withdrawal suppression does not guarantee treatment satisfaction.

2.4.5. Summary

The present study evaluated the clinical utility of SROM as an alternative to methadone for maintenance treatment of opioid dependence. The study featured the use of a crossover design and sampled eighteen methadone maintenance patients reporting either adequate (holders) or

inadequate (non-holders) withdrawal suppression between doses. This approach was ethically advantageous in maximising the statistical power of the study whilst minimising the number of subjects in whom treatment outcomes may have been compromised following transfer from methadone to SROM. Although practical and ethical considerations (e.g., likelihood that blinding would be ineffective, availability of placebo capsules) precluded the use of a double-blind methodology, the limitations associated with the use of an open label design are nonetheless unlikely to apply to many of the objective pharmacokinetic and physiological indicators considered in this study. Additionally, it is notable that use of additional drugs (benzodiazepines, cannabinoids) (a) was consistent across experimental conditions, (b) is unlikely to have produced pharmacokinetic interactions with morphine and methadone, and that (c) exclusion of subjects on this basis may have adversely impacted on the representativeness of the sample. The use of individualised maintenance doses is similarly justified on the grounds of external validity, as this is required in the methadone program from which subjects were sampled. Characteristics of the patient sample were consistent with previous surveys of this patient population (Dyer & White, 1997; Ryan & White, 1996) and highlighted the need for alternatives to methadone to be evaluated. In addition to evidence of ongoing crime and drug use in some patients, the sample as a whole expressed negative attitudes towards methadone including the belief that it was in some respects worse than heroin (e.g., more addictive, more difficult to get off) and the perception of maintenance treatment as being inconvenient (e.g., due to requirements for supervised daily dosing). The methodological approach of the present study represents a scientifically and ethically appropriate means of evaluating SROM as a possible alternative to methadone in this regard.

3. PHARMACOKINETICS OF METHADONE AND SROM

3.1.Introduction

Methadone has a number of dispositional characteristics that make it highly amenable for use as a maintenance pharmacotherapy for opioid dependence. Its long half-life and high oral bioavailability, in particular, facilitate sustained suppression of opioid withdrawal symptoms in the majority of patients maintained on once-daily oral dosing regimens (Dole, 1988). Nevertheless, there are a number of ways in which the pharmacokinetic profile of methadone limits its efficacy, safety and patient acceptability as a maintenance treatment option. The high degree of observed inter-individual variability in methadone disposition (Boulton, Arnaud, & DeVane, 2001; Eap et al., 2002; Foster et al., 2000; Garrido & Troconiz, 1999; Gourlay et al., 1986; Quinn et al., 1997), in particular, presents a number of clinical challenges. Since methadone has a narrow therapeutic index, evidenced by a high incidence of adverse effects within the dose and plasma methadone concentration ranges associated with adequate withdrawal suppression (Judson and Goldstein, 1982; Kreek, 1991), variability between individuals in methadone disposition necessitates an individualised approach to dosing in order to maintain treatment efficacy and safety (Eap et al., 2002). Careful and individualised dose management is especially important during the induction phase of treatment when accumulation of methadone is associated with risks of delayed opioid toxicity (Caplehorn & Drummer, 1999; Drummer et al., 1992; Williamson et al., 1997; Zador & Sunjic, 2000; Zador & Sunjic, 2002). However, even when an individualised approach to dosing is utilised, a significant proportion of methadone patients report sub-optimal treatment outcomes, including adverse effects (Judson & Goldstein, 1982; Kreek, 1991) and the failure of their methadone dose to suppress withdrawal for the duration of the inter-dosing interval (Dyer et al., 1999; Dyer & White, 1997). These problems highlight the need for alternative maintenance pharmacotherapies to be evaluated.

Like methadone, SROM permits infrequent, oral dosing of an opioid agonist (Gourlay et al., 1997) and is thus likely to have clinical utility as an alternative treatment option in methadone maintenance programs. The pharmacokinetics of SROM have been assessed in single-dose studies with healthy volunteers (Bochner et al., 1999; Broomhead et al., 1997b; Broomhead et al., 1997c; Maccarone et al., 1994) and in one chronic dosing study conducted in patients with moderate to severe pain (Gourlay et al., 1997), but have not been previously characterised in opioid dependent individuals receiving maintenance treatment. Since morphine disposition may differ between these populations due to a number of factors (e.g., age, effects of disease states) (Andersen, Christrup, & Sjogren, 2003), pharmacokinetic evaluations of SROM in a methadone maintenance population are required. The purpose of the present study was to compare the steady-state pharmacokinetics of methadone and the once-daily SROM formulation Kapanol™ in a sample of methadone maintenance patients, in order to ascertain the suitability of the latter for once-daily dosing in maintenance programs for opioid dependence.

3.1.1. Pharmacokinetic characteristics of maintenance pharmacotherapies

The effectiveness of maintenance pharmacotherapies for opioid dependence is partly determined by the extent to which plasma concentrations of the therapeutic agent are maintained within the range whereby therapeutic effects (e.g., suppression of cravings and withdrawal) are maximal and adverse effects (e.g., respiratory depression, sedation) are minimal. The suitability of an opioid agonist for achieving such stabilisation is subject to several considerations relating to both the pharmacokinetic properties of the drug and practical constraints applicable to treatment delivery (e.g., requirements for supervised dosing, cost-effectiveness of treatment). The route of administration, length of the inter-dosing interval, and degree to which key pharmacokinetic parameters (e.g., clearance, volume of distribution) vary between individuals are particularly important considerations, as these factors impact significantly on the degree to which treatment can be delivered in a manner

that is safe, efficacious, cost-effective and acceptable to patients. Opioids that show sustained plasma concentration-time profiles and are permissive of infrequent oral dosing are normally advantageous in this regard, as such medications generally minimise the cost, inconvenience, and intensity of opioid effects associated with dosing. Individual variability in drug disposition may impact on the need for an individualised approach to dosing (Eap et al., 2002), with potentially negative consequences regarding the cost-effectiveness and patient acceptability of treatment. In the sections that follow, the suitability of methadone and morphine as maintenance pharmacotherapies for opioid dependence is discussed in reference to the above considerations.

3.1.2. Methadone pharmacokinetics

Methadone exhibits a number of dispositional properties that make it highly amenable for use in maintenance programs for opioid dependence (Dole, 1988). Its principal advantages are its high oral bioavailability (approximately 80%) (Gourlay et al., 1986) and long half-life (e.g., >33 h for racemic methadone) (Wolff et al., 1997), which enable the achievement of relatively stable plasma methadone concentrations using oral dosing regimens with a much longer oral dosing interval (normally 24 h) than is possible with most other opioids (e.g., for morphine, approximately 4-6 h) (King & Miller, 1998). Methadone is a highly lipophilic drug with a disassociation constant (pKa) of 9.2. Following oral administration, absorption of methadone is rapid and almost complete, with bioavailability estimates of up to 95% (Garrido & Troconiz, 1999). It binds extensively to plasma proteins, particularly alpha 1-acid glycoprotein (AAG), and at tissue sites throughout the body including the brain (Inturrisi, Colburn, Kaiko, Houde, & Foley, 1987; Wilkins et al., 1997). Pharmacokinetic studies in patients maintained on racemic methadone have reported low unbound fractions for (R)- and (S)-methadone of approximately 3.6% and 2.1% respectively (Foster et al., 2000), and large volumes of distribution of up to 6.7 L/kg (Kristensen et al., 1996; Wolff, Hay, Raistrick, & Calvert, 1993). Elimination of methadone, which primarily involves biotransformation in the liver by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19 (Foster et al., 2000), does

not result in the production of any active metabolites. The main metabolite of methadone is 2-ethylidene-1,5-dimethyl1-3,3-diphenylpyrrolidine (EDDP). Following oral dosing at steady-state, peak plasma (R)-methadone concentrations are normally reached after 3 hours at concentrations approximately 1.8 times greater than baseline (Foster et al., 2000).

A number of disadvantages associated with the use of methadone relate to individual variability in its dispositional characteristics. This variation arises from multiple sources including considerable variability in plasma protein binding and hepatic metabolism (Eap et al., 2002). Previous studies have indicated up to 6-fold variation in the unbound fraction of methadone in plasma (Romach, Piafsky, Abel, Khouw, & Sellers, 1981; Wilkins et al., 1997). This variation is partly accounted for by variability in AAG levels, which show significant variation in response to physiological or pathological conditions such as stress (Abramson, 1982; Olsen, 1973). Determinants of methadone elimination also show considerable variability. CYP3A4 is an inducible enzyme for which *in vitro* activity levels in the liver have been shown to vary by as much as 30-fold between individuals (Ketter et al., 1995), resulting in adaptive changes in methadone pharmacokinetics during the course of treatment (Rostami-Hodjegan et al., 1999). Total methadone clearance, for example, was found to increase 3.5-fold between the first dose and steady-state in opioid dependent individuals commencing methadone maintenance treatment (Rostami-Hodjegan et al., 1999). A number of concomitant medications are also known to alter the elimination kinetics of methadone, including carbamazepine, phenytoin, rifampicin, zidovudine, barbiturates, spironolactone, verapamil, diethylstilboestrol, and amitriptyline (Wolff et al., 1993). Furthermore, although methadone elimination is mediated primarily by hepatic metabolism, as much as 30% of the methadone dose can be excreted via the renal route when the urinary pH is below 6 (Anggard et al., 1975). The above factors are associated with clinically significant variation in oral bioavailability (36%-100%), volume of distribution (2-5 L/kg for elimination phase), EDDP formation (e.g., 15-fold variation in methadone:EDDP ratios in urine), plasma clearance (7-

fold), and half-life (10-80 h) (Eap et al., 2002). In a recent study of methadone maintenance patients, weight-adjusted methadone dose explained 46% of the variance in the area under the plasma concentration-time curve for (R)-methadone (Foster et al., 2000). Other reviews have concluded that up to 17-fold variation exists between individuals in the plasma methadone concentration associated with a given dosage (Eap et al., 2002).

A particularly noteworthy type of variability in methadone disposition concerns dispositional differences between (R)- and (S)-methadone. Foster et al. (2000) assessed the pharmacokinetics of (R)- and (S)- methadone in 18 opioid dependent individuals maintained on racemic methadone and found that substantial stereoselectivity was evident for most pharmacokinetic parameters. Compared to (S)-methadone, (R)-methadone was associated with a significantly higher unbound fraction and total clearance. When differences in protein binding were considered, (R)-methadone was associated with significantly lower clearance of the unbound drug, resulting in a significantly greater area under the plasma concentration-time curve (AUC), compared to (S)-methadone. Plasma concentration-time curves indicated that (S)-methadone shows more pronounced temporal changes during the inter-dosing interval compared to (R)-methadone, including approximately 30% greater variation from peak to trough and a significantly higher maximum plasma concentration. Other studies have reported longer mean elimination half-lives for (R)- compared to (S)-methadone (e.g., 48 h vs. 31 h) (Kreek, Hachey, & Klein, 1979; Nakamura, Hachey, Kreek, Irving, & Klein, 1982). In addition to intra-patient variability in the relative abundance of (R)- and (S)-methadone in plasma during the inter-dosing interval, other studies have shown up to 5-fold inter-patient variability in enantiomeric ratios in plasma samples taken at single time points (Eap et al., 1996; Hiltunen et al., 1999). Since (R)-methadone is known to account for most if not all of methadone's opioid actions (Scott et al., 1948), stereoselectivity in methadone disposition highlights the need to use stereoselective methadone assays when attempting to relate treatment response to plasma methadone concentrations.

Variability in methadone disposition between individuals presents a number of clinical challenges. Above all, this variation contributes to the need for an individualised approach to dosing to be used in order to ensure treatment efficacy and safety (Eap et al., 2002). To the extent that an individualised approach to dosing involves increased costs for treatment providers and greater inconvenience for treatment recipients (e.g., more frequent contact between clinicians and patients), it may impact negatively on the cost-effectiveness and patient acceptability of treatment. The need for such an approach is particularly pertinent during the induction phase of treatment. The long and variable half-life of methadone can lead to an accumulation of methadone with repeated-dosing prior to the achievement of steady-state concentrations (Gourlay et al., 1986). This accumulation contributes to an increased risk of delayed opioid toxicity and has been implicated as an important causal factor in a number of fatalities associated with the commencement of methadone maintenance (Drummer et al., 1992). These risks are curtailed to some extent by limiting the magnitude of initial methadone doses and the rate at which they are increased each day (Ward et al., 1998c). However, to the extent that inadequate withdrawal suppression may lead to compensatory use of other sedatives (e.g., heroin, alcohol, benzodiazepines), overly conservative dosing during methadone induction is also associated with risks of opioid toxicity.

Although many of the challenges associated with variability in methadone disposition can be overcome with an individualised approach to dosing, this is not always the case. Even in methadone maintenance programs that adopt an individualised approach to treatment, a significant number of patients report adverse effects or the failure of their methadone dose to 'hold' (suppress opioid withdrawal) for the entire 24-hour inter-dosing interval (Dyer et al., 1999; Dyer & White, 1997). Two previous investigations have sought to characterise the pharmacokinetic basis of 'non-holding'. Each of these studies arrived at similar conclusions.

In the first study of interest, Nilsson et al. (1983) examined the pharmacokinetics of methadone in eight patients classified as 'therapeutic failures', as evidenced by complaints of withdrawal, the presence of unprescribed drugs in urine, and demonstration of insufficient progress in social rehabilitation as outpatients. An unselected group of twelve patients who had been maintained on oral methadone for 25 days served as a control group. Subjects were admitted to an inpatient setting and administered their oral methadone dose daily at 8am for the first seven days of the study. On the morning of day eight, the methadone dose was administered intravenously as deuterated methadone, and blood samples were subsequently taken for 48 hours following dosing to permit quantification of plasma methadone concentrations. Results indicated that the therapeutic failures had similar plasma methadone concentrations, but significantly smaller volumes of distribution during the post-distribution phase, compared to the control group. The authors suggest that a smaller volume of distribution will result in a more rapid peak and decline in plasma methadone concentrations following oral dosing, resulting in a shorter period during which the patient is "straight" at the start of the inter-dosing interval and a greater likelihood of withdrawal appearing prior to the next dose. In patients showing this type of methadone disposition, an increase in dose is likely to result in unacceptable variation in plasma methadone concentrations between dosing. A more appropriate solution, Nilsson et al. suggest, is to shorten the inter-dosing interval.

In the second study of interest, Dyer et al. (1999) compared the plasma pharmacokinetics of racemic methadone in 18 methadone maintenance patients, including 9 holders and 9 non-holders. Plasma samples were collected on 13 occasions for 23 hours following oral administration of racemic methadone. The non-holder group showed significantly greater withdrawal scores than the holder group, despite having similar methadone doses and plasma concentration-time profiles. When two subjects whose pre-study urinalyses indicated the use of additional opioids were excluded, the non-holders were differentiated from the holders by a greater maximum rate of decline in plasma methadone concentration during the period from

peak concentration to trough (42 ng/mL/h vs.75 ng/mL/h). A significant correlation between the maximal rate of decline in plasma methadone concentration and the average number of withdrawal symptoms during this period was also observed ($r = 0.60$). Thus, these results are consistent with the conclusions of Nilsson et al. (1983) in suggesting that rapid changes in plasma methadone concentration during the inter-dosing interval may be associated with unacceptable variation in pharmacodynamic response.

The investigations of Nilsson et al. (1983) and Dyer et al. (1999) are consistent in suggesting that some methadone maintenance patients may report the failure of their dose to hold for 24 hours despite apparently adequate doses and plasma methadone concentrations. These studies suggest that the severity of withdrawal responses is related to the degree of change in plasma methadone concentrations during the inter-dosing interval. To this extent, increasing the methadone dose may sometimes be an inappropriate response to withdrawal complaints. This is partly because an increase in dose may result in greater fluctuation in plasma methadone concentrations and hence greater variation in pharmacodynamic response across the inter-dosing interval. Accordingly, some patients may experience adverse effects at times of peak plasma methadone concentrations (e.g., respiratory depression, sedation) but also experience withdrawal at times of trough plasma methadone concentrations. Moreover, some patients may resist dose increases for fear of prolonging eventual detoxification from treatment (Bell et al., 1995). In such cases, alternatives strategies such as shortening the methadone dosing interval (e.g., twice-daily dosing) or transferring patients to an alternative long-acting maintenance medication may be indicated. It should be emphasised that other factors that were not examined in these two studies may also contribute to complaints of inadequate withdrawal suppression. As noted by Dyer et al. (1999), for example, a full pharmacokinetic characterisation of holders and non-holders needs to account for stereoselectivity in methadone disposition. Their finding that non-holders exhibit a greater maximal rate of decline in plasma racemic methadone concentration than holders is difficult to interpret

without controlling for the fact that (S)-methadone shows greater variation from peak to trough than (R)-methadone (Foster et al., 2000).

In summary, although methadone has a number of dispositional characteristics that are highly amenable to once-daily dosing in maintenance programs (e.g., high oral bioavailability, long half-life), other aspects of its pharmacokinetic profile are problematic. Individual variability in methadone disposition necessitates an individualised approach to dosing, particularly during the early dose-finding stages of treatment. Even when the strategy of individualised dosing is applied, a significant number of patients experience poor outcomes such as the failure of their methadone dose to suppress withdrawal for the entire 24-hour inter-dosing interval. The severity of such withdrawal complaints has been related to an increased rate of decline in plasma racemic-methadone concentrations towards the end of the inter-dosing interval. In patients for which dose increases may precipitate unacceptable variation in pharmacodynamic responses between doses, alternative strategies such as a reduction in the length of the methadone dosing interval (e.g., twice daily dosing) or transfer to other long-acting alternative pharmacotherapies (e.g., buprenorphine, LAAM) may be indicated. However, there are limitations associated with each of these options, which were outlined in Chapter 1. Problems regarding the safety of LAAM, in particular, underscore the need for alternative opioid agonist options to methadone permissive of infrequent oral dosing regimens.

3.1.3. Morphine pharmacokinetics

In comparison to methadone, the pharmacokinetic profile of morphine makes it relatively unsuitable for use as a maintenance pharmacotherapy for opioid dependence. Its primary disadvantage is its short (approximately 2 h) and variable half-life when administered orally (Osborne, Joel, Trew, & Slevin, 1990; Sawe, 1986), which often necessitates 4 to 6 dose administrations per day when used for the management of pain (Thirlwell et al., 1989). In comparison to methadone, morphine is also less lipid soluble and binds less extensively to

plasma proteins (approximately 30-40%) (Olsen, 1975), with volume of distribution estimates ranging from 2.1 L/kg to 4.0 L/kg (Milne, Nation, & Somogyi, 1996). Due primarily to extensive first-pass metabolism in the liver, only a small portion of absorbed morphine reaches the systemic circulation, with mean bioavailability estimates ranging from 19% to 47% (Lotsch, Weiss, Ahne, Kobal, & Geisslinger, 1999; Osborne et al., 1990; Sawe, Dahlstrom, Paalzow, & Rane, 1981; Sawe, Kager, Svensson Eng, & Rane, 1985; Vater, Smith, Aherne, & Aitkenhead, 1984).

Morphine metabolism occurs mainly in the liver, primarily involving conjugation with uridine diphosphate glucuronic acid to form morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) (Milne et al., 1996). M6G and M3G are up to 9 and 56 times more abundant than morphine in plasma after oral dosing, respectively (Andersen et al., 2003) and show significant passage across the blood-brain barrier despite their polar, hydrophilic nature (Samuelsson, Hedner, Venn, & Michalkiewicz, 1993; Wolff, Samuelsson, & Hedner, 1995). Both of these metabolites are pharmacologically active and may thus influence responses to morphine, although the clinical significance of these effects is unclear. M6G shows high affinity for mu opioid receptors and produces significant analgesic effects in both humans (Murthy, Pollack, & Brouwer, 2002; Osborne et al., 1992; Skarke, Darimont, Schmidt, Geisslinger, & Lotsch, 2003) and animals (Frances, Gout, Monsarrat, Cros, & Zajac, 1992; Paul, Standifer, Inturrisi, & Pasternak, 1989), although the clinical importance of these effects is yet to be fully elucidated (Andersen et al., 2003; Quigley, Joel, Patel, Baksh, & Slevin, 2003). M3G has low affinity for opioid receptors, but in some studies has been found to act as a functional antagonist of morphine and M6G (Yaksh & Harty, 1988; Yaksh, Harty, & Onofrio, 1986) and produce other effects such as hyperalgesia, allodynia, and myoclonus (Andersen et al., 2003; Gong, Hedner, Hedner, Bjorkman, & Nordberg, 1991). Median elimination half-lives of 7.2 and 7.7 hours have been reported for M6G and M3G, respectively, following oral morphine administration (Osborne et al., 1990). For once-daily

SROM dosing at steady-state, the plasma concentration-time profiles for M6G and M3G have been shown to be highly congruent with that of morphine (Gourlay et al., 1997).

As for methadone, individual variability in the pharmacokinetics of morphine and its metabolites can be managed using an individualised approach to dosing. To this extent, the primary impediment to the use of morphine as an alternative to methadone in maintenance programs is its short half-life and the consequent requirement for frequent dosing. These problems may be overcome with the advent of SROM preparations. Recently developed SROM formulations such as Kapanol™ provide sustained and stable plasma morphine concentrations following dosing permissive of once-daily dosing in the treatment of moderate to severe pain (Gourlay et al., 1997). To this extent, it is likely that Kapanol™ may also have clinical utility as an alternative once-daily agonist option to methadone for maintenance treatment of opioid dependence. However, studies of morphine disposition following Kapanol™ administration in opioid dependent maintenance patients have not been previously undertaken.

The pharmacokinetics of morphine after Kapanol™ dosing have been the subject of five previous investigations, including 4 singe-dose studies involving a total of 149 healthy volunteers (Bochner et al., 1999; Broomhead et al., 1997b; Broomhead et al., 1997c; Maccarone et al., 1994) and one multiple-dosing study at steady-state in 24 patients with moderate to severe cancer pain (Gourlay et al., 1997), each of which were reviewed in detail in Chapter 1. Means and coefficients of variation from these studies for the area under the plasma morphine concentration-time curve (AUC), maximum plasma concentrations (Cmax), time to reach maximum plasma concentrations (Tmax), time associated with plasma concentrations greater than 75% of Cmax (T>75%Cmax; a measure of the efficiency of control slow-release formulations exert over drug-release rate) (Gourlay, 1998), and estimated terminal half-life ($T_{1/2}$) following Kapanol™ administration are summarised in Table 3-1.

These data indicate that the pharmacokinetics of morphine as Kapanol™ are linear across the dose range of 30 mg to 100 mg, and are relatively unaffected by food, except for a small increase in Tmax. Normalised to a 100mg SROM dose, pharmacokinetic parameters showed a high degree of consistency across these different investigations.

Table 3-1. Summary of previous pharmacokinetic evaluations of morphine as Kapanol™

Ref	Design	Dose mg	Food intake	AUC ng/mL•hr	$AUC_{0-\infty}$ ng/mL•hr	Cmax ng/mL	Tmax hr	T½ hr	T>75 hr
Single-dose studies with volunteers									
1	2-way (n=30) 48 hours	50	Fed	250 (33)	304 (32)	13.8 (32)	10.1 (34)	17.0 (31)	8.3 (90)
		50	Fasted	240 (34)	306 (37)	14.6 (48)	8.5 (53)	18.3 (45)	6.7 (101)
	4-way (n=24) 48 hours	30	Fasted	265 (25)	363 (24)	14.0 (42)	7.8 (62)	20.7 (39)	n.s.
		50	Fasted	266 (24)	342 (30)	14.8 (36)	7.2 (36)	19.4 (41)	n.s.
		70	Fasted	274 (23)	339 (28)	17.1 (34)	8.4 (31)	17.5 (41)	n.s.
		100	Fasted	266 (25)	328 (28)	16.7 (36)	8.4 (36)	18.7 (49)	n.s.
	1-way (n=24) 48 hours	50	Fasted	266 (20)	358 (16)	15.2 (24)	8.6 (41)	19.5 (36)	6.3 (59)
2	2-way (n=22) 48 hours	60	Fed	268 (18)	305 (19)	16.3 (34)	11.4 (31)	14.9 (28)	n.s.
		60	Fasted	273 (17)	308 (18)	18.2 (22)	8.3 (22)	14.7 (31)	n.s.
3	2 x 2 (n=25) 48 hours Capsules (C) vs. pellets (P)	50 (C)	Fed	306 (34)	352 (33)	19.4 (43)	11.6 (12)	15.1 (21)	n.s.
		50 (C)	Fasted	310 (33)	364 (32)	20.0 (40)	7.4 (20)	17.0 (29)	n.s.
		50 (P)	Fed	298 (33)	344 (31)	16.6 (45)	11.6 (33)	15.0 (19)	n.s.
		50 (P)	Fasted	310 (34)	358 (34)	21.2 (57)	7.9 (25)	16.3 (27)	n.s.
4	1-way (n=24) 36 hours	60	Fasted	212 (39)	n.s.	16.2 (62)	7.9 (34)	n.s.	4.9 (45)
Summary of single-dose studies (48 hour studies only for AUC)									
Weighted average				270 (26)	333 (26)	16.2 (40)	8.9 (35)	17.4 (34)	6.3 (69)
Steady-state study in cancer patients with severe pain									
5	1-way 24 hours (n=24)	199±275	Fed	501 (39)	n.s.	37.3 (38)	10.3 (32)	n.s.	6.0 (50)

All data have been normalised to a 100 mg dose and are expressed as mean (%CV). 1. Maccarone et al. (1994) 2. Broomhead et al. (1997b) 3. Broomhead et al. (1997c) 4. Bochner et al. (1999) 5. Gourlay et al. (1997). AUC = area under plasma concentration-time curve. Cmax = maximum plasma concentration. Tmax = time to reach plasma concentration. T½ = terminal half-life. T>75= time associated with plasma concentrations > 75% of Cmax. n.s. = not specified.

The studies summarised in Table 3-1 highlight a number of important factors regarding the suitability of Kapanol™ for use in maintenance programs for opioid dependence. Firstly, in comparison to immediate-release morphine solution, it can be estimated that Kapanol™ reduces Cmax by a factor of between 5 and 8 and increases both Tmax and T>75%Cmax by a factor of approximately 8 (Bochner et al., 1999; Maccarone et al., 1994). These estimates are consistent with a previous meta-analysis (Collins, Faura, Moore, & McQuay, 1998). Second, in comparison with MS Contin™, Kapanol™ was associated with a significantly longer Tmax (8.6 h vs. 2.5 h, Maccarone et al., 1994; 10.3 h vs. 4.4 h, Gourlay et al., 1997), and significantly less fluctuation in plasma morphine concentrations during the inter-dosing interval (calculated as Cmax - Cmin as a ratio of the average steady-state concentration: 1.4 vs. 1.6) (Gourlay et al., 1997). Third, in comparison to data previously reported for (R)-methadone in maintenance patients (Foster et al., 2000), Kapanol™ is associated with a significantly longer Tmax (3 h vs. 8h) and similar individual variability (coefficients of variation: methadone vs. SROM) for AUC (53% vs. 40%), Cmax (27% vs. 40%), and Tmax (53% vs. 35%).

In summary, although the short half-life of morphine has traditionally precluded its use as an alternative agonist option to methadone in maintenance programs for opioid dependence, this restriction may be overcome with the advent of SROM. Kapanol™ is associated with more sustained and stable plasma morphine concentrations in comparison to other shorter-acting morphine formulations routinely used for the management of pain (Gourlay, 1998). In comparison to methadone, the dispositional profile of morphine following once-daily Kapanol™ dosing is characterised by a significantly longer Tmax and similar individual variability on key pharmacokinetic parameters. These findings suggest that Kapanol™ may be suitable for once-daily dosing in maintenance populations, particularly as an alternative treatment option for patients reporting inadequate withdrawal suppression whilst maintained on methadone. However, morphine disposition varies according to factors including hepatic

and renal function (Andersen et al., 2003) and age (Owen et al., 1983) that are likely to differ for opioid dependent maintenance patients in comparison to healthy volunteers and cancer patients. Accordingly, pharmacokinetic evaluations of Kapanol™ in opioid dependent maintenance patients are required, but are yet to be undertaken. To the extent that pharmacokinetic factors may contribute to complaints of the dose 'not-holding', it is also important that such an evaluation establish the extent to which the pharmacokinetics of methadone and morphine differ for those reporting adequate (holders) and inadequate (non-holders) withdrawal suppression whilst maintained on methadone.

3.1.4. The present study

The purpose of the present study was to compare the steady-state pharmacokinetics of (R)- and (S)-methadone (administered as racemic methadone) and morphine (administered as Kapanol™) in a crossover study of opioid dependent individuals receiving methadone maintenance treatment for opioid dependence. The study included subjects reporting adequate (holders) and inadequate (non-holders) withdrawal suppression between doses and featured the collection of 13 blood samples across a 24-hour inter-dosing interval for each medication after at least 4 weeks on a stable dose of each drug.

3.1.4.1. Aims

Specific aims of the investigation were as follows:

- To characterise dispositional differences between (R)- and (S)-methadone and morphine associated with once-daily oral dosing of racemic methadone and SROM.
- To characterise the degree of individual variability in pharmacokinetic parameters, including the relationship between dose and plasma drug concentrations, for (R)-methadone and morphine.

- To investigate the pharmacokinetic basis of complaints of 'non-holding' during methadone maintenance by characterising dispositional differences for (R)- and (S)-methadone in methadone holders and non-holders.

3.1.4.2. Hypotheses

1. The time to reach maximum plasma concentrations (Tmax) will be significantly later in the inter-dosing interval for morphine compared to (R)- and (S)-methadone.
2. The dispositional properties of (R)- and (S)- methadone will show significant differences, as evidenced by significant variation in the ratio of (S)- to (R)-methadone during the inter-dosing interval.
3. Area under the plasma concentration-time curve (AUC) will be significantly proportional to dose for both (R)-methadone and morphine.

3.2.Methods

3.2.1. Subjects and procedures

The subjects and general procedures for this aspect of the study were as described in Chapter 2. The pharmacokinetics of methadone and SROM during a single 24-hour inter-dosing interval were assessed in 14 opioid-dependent volunteers undergoing maintenance treatment after at least 4 weeks on a stable dose of each drug in an open-label, randomly-ordered, crossover design. Blood samples were collected on 13 occasions at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 11 and 23 hours after administration of the maintenance dose. The intravenous line was cleared with saline immediately following sample collection. Blood samples were placed in heparin gel containing tubes and centrifuged at 3000rpm. Plasma was separated and samples stored at -20^0C until later analysis by HPLC. Pharmacodynamic responses were recorded at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11 and 23 hours following dosing.

3.2.2. Analysis of plasma samples

Plasma concentrations of (R)- and (S)-methadone and morphine during the inter-dosing interval for methadone and SROM, respectively, were determined using the procedures described in Chapter 2. Plasma concentrations of M6G and M3G were not determined for SROM in the present study. These metabolites could potentially be important in the interpretation of pharmacodynamic responses, although it should be noted that their time-courses in plasma have been shown to be highly congruent with that of morphine following once-daily dosing with Kapanol™ (Gourlay et al., 1997).

3.2.3. Pharmacokinetic and statistical analyses

Pharmacokinetic analyses were based on non-compartmental methods (Rowland & Tozer, 1995). The area under the plasma concentration versus time curve (AUC) from 0-23 hours was determined using the linear trapezoidal method. Steady-state plasma concentrations (Css) were determined by dividing AUC by the sampling interval (0-23 h). Time to reach maximum

plasma concentration (Tmax), maximum plasma concentration (Cmax), and minimum plasma concentration (Cmin) were obtained by direct observation of subjects' data. AUC, Css, Cmax, and Cmin were normalised to 70 mg racemic methadone and 300 mg SROM, respectively. The stability of plasma concentrations over the inter-dosing interval were quantified by the peak to trough ratios (calculated by dividing Cmax by Cmin) and the time over which plasma concentrations exceeded 75%Cmax (T>75%Cmax). Coefficients of variation (%CV) were calculated for all pharmacokinetic parameters. Paired t-tests were used to contrast pharmacokinetic parameters according to the maintenance drug and for each methadone enantiomer. Independent t-tests were used to compare pharmacokinetic parameters according to methadone holding status. Pearson correlation coefficients were used to examine the relationship between dose and AUC and the relationship between pharmacokinetic parameters for (R)- and (S)-methadone and morphine. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). All significance tests were two-tailed and used an alpha level of 0.05. Data are presented as mean ± SD (range) unless otherwise indicated.

3.3.Results

3.3.1. Pharmacokinetics of methadone and SROM

3.3.1.1. Comparisons for all subjects

Figure 3-1 shows plasma concentrations of (R)- and (S)-methadone and morphine during the inter-dosing interval, normalised to 70 mg racemic methadone and 300 mg SROM doses, respectively. These data indicate a different profile of temporal changes in plasma concentrations following dosing for methadone compared to SROM. Mean plasma concentrations for both (R)- and (S)-methadone increased rapidly following dosing, reaching peak levels after 2-3 hours, before declining for the remainder of the inter-dosing interval. In comparison, mean plasma morphine concentrations showed a more gradual pattern of temporal changes following dosing. Morphine concentrations showed only a minimal increase in the first two hours and remained relatively stable between 3 and 11 hours following dosing.

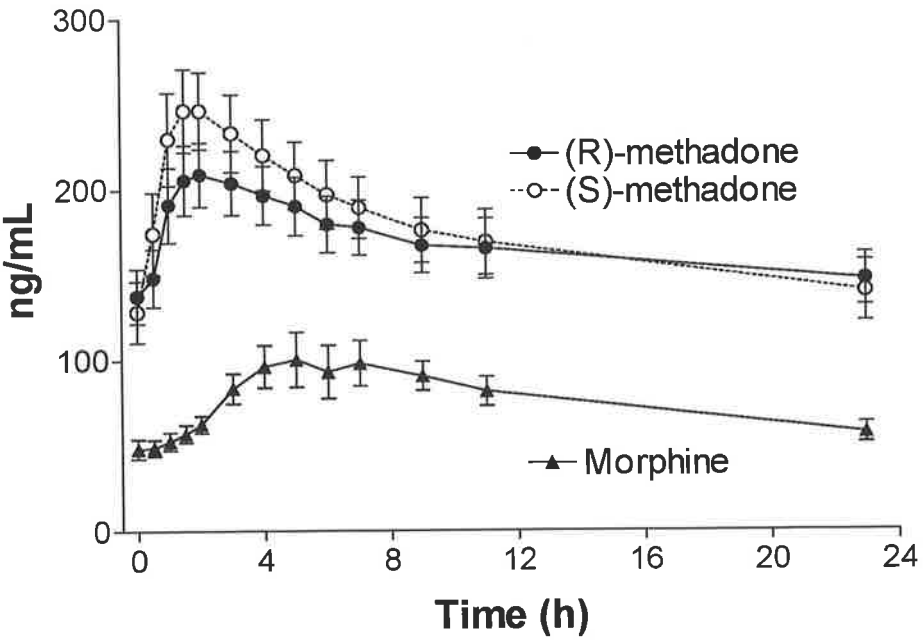

Figure 3-1. Plasma concentrations of (R)- and (S)-methadone and morphine during a 24-hour inter-dosing interval for methadone and SROM (n=14). Concentrations have been normalised to 70 mg and 300 mg doses for racemic methadone and SROM, respectively. Data are presented as mean ± SE.

Pharmacokinetic parameters for (R)- and (S)-methadone and morphine are presented in Table 3-1. Tmax was significantly longer for morphine (6.5 ± 2.3 h) compared to (R)-methadone

(2.5 ± 1.4 h). T>75%Cmax was similar for (R)-methadone and morphine (10.0 ± 7.8 h vs. 7.8 ± 4.7 h, p = 0.40). The P/T ratio was significantly less for methadone (1.83 ± 0.35) compared to SROM (3.2 ± 1.81), although the value for SROM is exaggerated by an outlying value of 8.8. Median P/T ratios for methadone and SROM were 1.8 and 2.6.

Table 3-2. Pharmacokinetic parameters for (R)- and (S)-methadone and morphine during a 24-hour inter-dosing interval for methadone and SROM (n=14).

		Methadone			Morphine		
Parameter		Mean	Range	%CV	Mean	Range	%CV
Dose (mg)[a]		78	25-120	41	349	120-570	39
Dose/weight (mg/kg)[a]		1.10	0.43-2.07	48	4.96	1.73-8.64	43
AUC (mg.L/hr)	(R)-	3.84	2.17-6.92	37	1.76	1.01-2.77	33
	(S)-	4.16	1.90-7.16	40			
Cmax (ng/mL)	(R)-	†232	119-405	32	121	60-122	45
	(S)-	†273	137-486	32			
Cmin (ng/mL)	(R)-	133	66-264	43	40	20-64	33
	(S)-	126	53-261	53			
Css (ng/mL)	(R)-	169	95-301	37	76	44-120	33
	(S)-	177	83-311	40			
P/T	(R)-	*†1.83	1.32-2.43	19	*3.2	1.6-8.8	56
	(S)-	†2.41	1.37-3.57	27			
Tmax (h)	(R)-	**2.5	1-5	53	**6.5	3-11	35
	(S)-	2.6	1-6	60			
T>75%Cmax	(R)-	**10.0	1.2-22.5	78	7.8	2.0-19.2	60
	(S)-	**7.5	1.1-22.3	93			
Max. decline (ng/mL/hr)	(R)-	†48	3-160	102	20	4-37	58
	(S)-	†64	9-192	92			

Values are mean (%CV). [a] Doses are for racemic methadone and morphine sulphate. AUC = area under the plasma concentration-time curve 0-23 h; Tmax = time to reach maximum plasma concentration; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; Css = average steady-state plasma concentration; P/T = peak to trough ratio (Cmax/Cmin); Max. decline = maximum decline in plasma concentration from peak to trough. AUC, Cmax, Cmin, and Css have been normalised to 70 mg racemic methadone and 300 mg SROM doses* $p < 0.05$ ** $p < 0.01$ ((R)-methadone vs. morphine: Tmax and P/T only), † $p < 0.01$ ((R)- vs. (S)-methadone).

Inspection of ranges and coefficients of variation for the pharmacokinetic parameters presented in Table 3-2 indicate a similar degree of individual variability for (R)-methadone and morphine. Variation across individuals, expressed as a ratio of maximum to minimum values, was slightly greater for (R)-methadone compared to morphine for AUC (3.2 vs. 2.7), Cmax (3.4 vs. 2.0), and Cmin (4.0 vs. 3.2). Correlation coefficients indicated a stronger

relationship between weight-adjusted dose (mg/kg) and AUC for morphine ($r = 0.93$, $p < 0.001$) compared to (R)-methadone ($r = 0.63$, $p = 0.018$). These relationships are shown in Figure 3-2. There were no significant relationships (Pearson r) between (R)-methadone and morphine values for AUC (0.01), Tmax (-0.44), Cmax (0.14), Cmin (0.02), or P/T ratios (0.21).

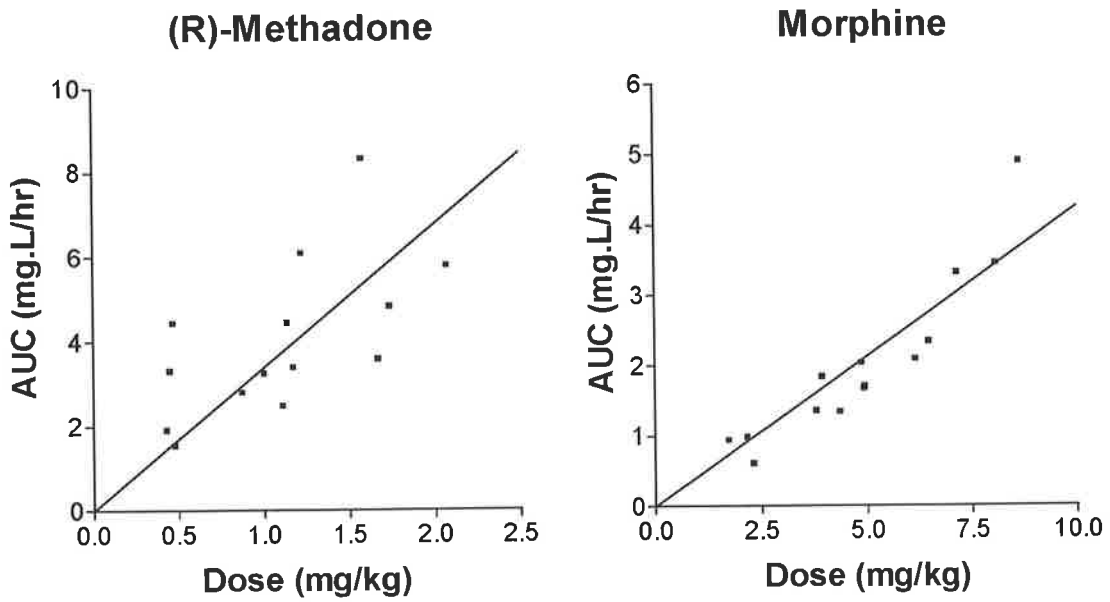

Figure 3-2. Relationship between maintenance dose for methadone and SROM and area under the plasma concentration-time curve for (R)-methadone and morphine.

Table 3-2 also highlights stereoselectivity in the pharmacokinetics of methadone. The time-course and magnitude of plasma concentrations differed for each enantiomer during the inter-dosing interval: compared to (R)-methadone, (S)-methadone was associated with a significantly greater Cmax, a greater P/T ratio, a shorter T>75%Cmax, and a greater rate of maximal decline in the period from peak to trough. Ratios of maximum to minimum values suggested slightly greater individual variability for (S)- compared to (R)-methadone for AUC (3.8 vs. 3.2), Cmax (3.5 vs. 3.4), Cmin (4.9 vs. 4.0), T>75%Cmax (20.3 vs. 18.8) and P/T ratios (2.6 vs. 1.8). The ratio of (S)- to (R)-methadone also varied considerably between and within-subjects. The mean ratio of (S)- to (R)-methadone AUC values was 1.04 ± 0.13 and ranged from 0.83 to 1.33. Variation in the ratio of (S)- to (R)-methadone during the inter-dosing interval, as measured by the ratio of maximum to minimum values for each subject,

showed a mean value of 2.4 ± 0.93 and ranged from 1.6 to 5.4. The mean ratio of (S)- to (R)-methadone during the inter-dosing interval is shown in Figure 3-3.

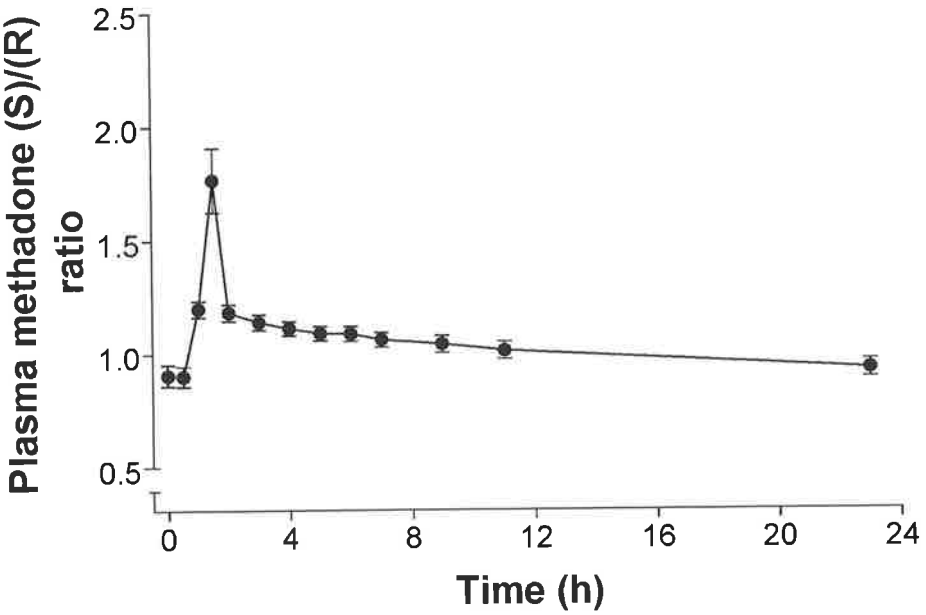

Figure 3-3. Plasma (S)-/(R)-methadone ratio during a 24-hour inter-dosing interval for methadone (n=14). Data are presented as mean ± SE.

3.3.1.2. Comparisons for methadone holders and non-holders

Figure 3-4 shows plasma concentrations of (R)- and (S)-methadone during the inter-dosing interval for methadone holders and non-holders. Mean plasma (R)-methadone concentrations were greater for non-holders compared to holders at each time point during the methadone dosing-interval, with statistically significant differences evident prior to dosing and at 1 hour following dosing. A similar pattern was observed for dose normalised plasma methadone concentrations (Figure 3-4). At trough, the mean plasma racemic (R+S)-methadone concentration was significantly greater for the non-holders (342 ± 127, range 187-566) compared to the holders (199 ± 88, range 99-354) ($t(12) = 2.45$, $p = 0.03$).

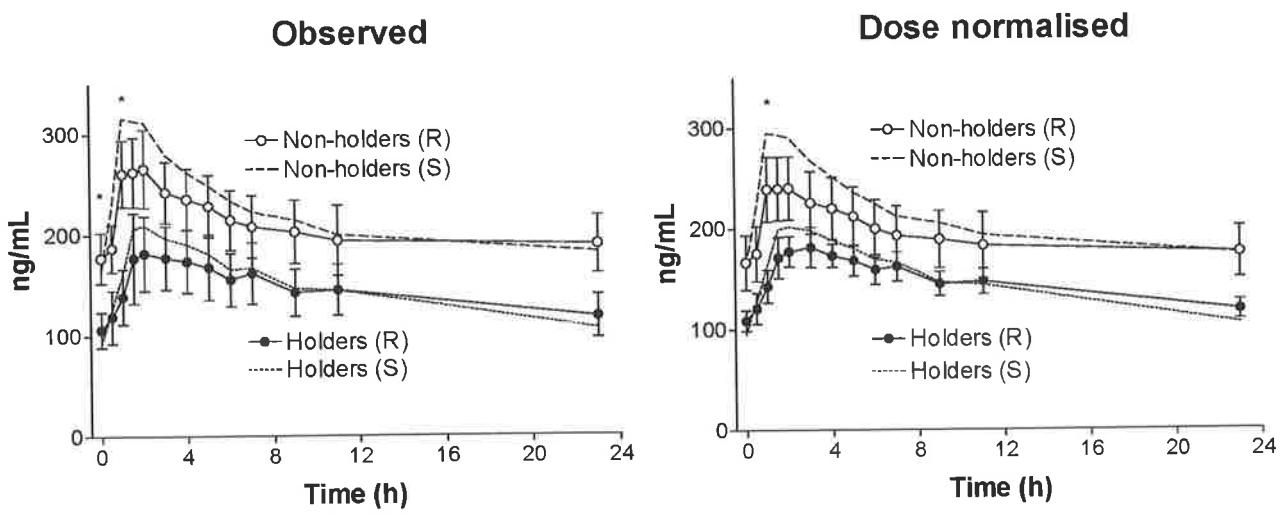

Figure 3-4. Observed and dose normalised (70 mg racemic methadone) plasma concentrations for (R)- and (S)-methadone during a 24-hour inter-dosing interval for methadone: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. Error bars for (S)-methadone have been excluded for clarity in data presentation. * $p < 0.05$ (holders vs. non-holders for (R)-methadone).

Figure 3-5 shows plasma morphine concentrations during the SROM inter-dosing interval for methadone holders and non-holders. As for methadone, the non-holders showed higher mean plasma morphine concentrations throughout the inter-dosing interval, with statistically significant differences at 6, 7 and 11 hours following dosing. Dose normalised concentrations also showed higher means for the non-holders compared to the holders throughout most of the inter-dosing interval, although this difference was significant only at 11 hours (Figure 3-5).

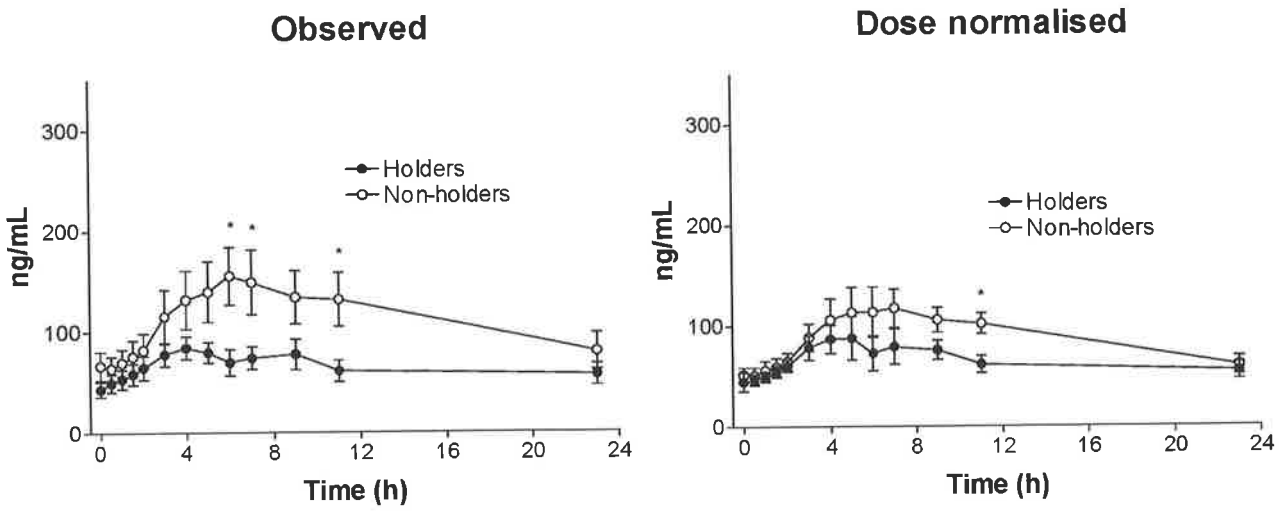

Figure 3-5. Observed and dose normalised (300 mg SROM) plasma morphine concentrations during a 24-hour inter-dosing interval for SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. * $p < 0.05$ (holders vs. non-holders).

Pharmacokinetic parameters for (R)- and (S)-methadone and morphine are shown for methadone holders and non-holders in Table 3-3. Mean normalised values for AUC, Css, Cmax and Cmin were greater for the non-holders compared to the holders for both methadone and SROM, but these differences were not statistically significant. The non-holders showed a significantly shorter Tmax compared to the holders for both (R)- and (S)-methadone, and a greater increase in Tmax for (R)-methadone compared to morphine (5.6 ± 2.3 h vs. 2.4 ± 3.1 h, $t(12) = 2.19$, $p = 0.049$). Individual variability, as measured by coefficients of variation, was greater for the non-holders compared to the non-holders for most pharmacokinetic parameters.

Table 3-3. Pharmacokinetics of (R)- and (S)-methadone and morphine in methadone holders (n=7) and non-holders (n=7).

		Methadone		Morphine	
Parameter		Holders	Non-holders	Holders	Non-holders
Dose (mg)		72 (31)	83 (42)	321 (46)	3.77 (34)
Dose/weight (mg/kg)		0.94 (36)	1.26 (52)	4.17 (36)	5.74 (44)
AUC (mg.L/hr)	(R)-	3.33 (22)	4.41 (40)	1.48 (24)	2.03 (33)
	(S)-	3.35 (19)	4.78 (43)		
Cmax (ng/mL)	(R)-	206 (26)	259 (33)	106 (48)	137 (57)
	(S)-	232 (24)	313 (32)		
Cmin (ng/mL)	(R)-	106 (26)	160 (40)	36 (31)	45 (33)
	(S)-	92 (27)	161 (49)		
Css (ng/mL)	(R)-	145 (22)	192 (40)	65 (23)	88 (33)
	(S)-	145 (19)	207 (43)		
Tmax (h)	(R)-	*3.36 (34)	†*1.71 (41)	5.71 (41)	†7.29 (28)
	(S)-	*3.50 (46)	*1.64 (46)		
T>75%Cmax	(R)-	9.5 (85)	10.6 (78)	6.5 (63)	9.2 (57)
	(S)-	6.4 (79)	8.6 (102)		
P/T	(R)-	1.96 (19)	†1.70 (17)	3.32 (75)	†3.15 (31)
	(S)-	2.56 (20)	2.23 (32)		
Max. decline (ng/mL/hr)	(R)-	44 (116)	51 (97)	23 (54)	16 (59)
	(S)-	59 (116)	69 (77)		

Values are mean (%CV). [a] Doses are for racemic methadone and morphine sulphate. AUC = area under the plasma concentration-time curve 0-23 h; Tmax = time to reach maximum plasma concentration; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; Css = average steady-state plasma concentration; P/T = peak to trough ratio (Cmax/Cmin); Max. decline = maximum decline from peak to trough. AUC, Cmax, Cmin, and Css have been normalised to 70 mg racemic methadone and 300 mg SROM doses * $p < 0.05$ (holders vs. non-holders), † $p < 0.01$ ((R)-methadone vs. morphine).

3.4.Discussion

The purpose of the present study was to establish whether the pharmacokinetics of SROM, administered as Kapanol™, are suitable for use as an alternative maintenance pharmacotherapy to methadone in the treatment of opioid dependence. The steady-state pharmacokinetics of (R)- and (S)-methadone and morphine were assessed across a 24-hour inter-dosing interval in 14 methadone maintenance patients after at least 4 weeks on a stable dose of each drug. Results indicated that SROM was effective in providing a relatively stable profile of plasma morphine concentrations during the inter-dosing interval and, moreover, was associated with a similar degree of individual variability as methadone for most pharmacokinetic parameters. These findings suggest that the dispositional properties of SROM, administered as Kapanol™, are amenable for use an alternative once-daily agonist option to methadone for maintenance treatment of opioid dependence.

The suitability of methadone and SROM for use as maintenance pharmacotherapies for opioid dependence in part depends on the extent to which sustained and relatively stable plasma concentrations are achieved using once-daily oral dosing regimens. Methadone is usually well-suited to this purpose due to its long half-life and high oral bioavailability in comparison to other opioids (Dole, 1988). By comparison, the clinical utility of morphine has traditionally been limited by its short-half life and the consequent requirement for a short dosing interval (e.g., 4 to 6 h) in order to avoid unacceptable variation in plasma morphine concentrations between doses. The present study found that mean time to reach maximum plasma concentrations (Tmax) following SROM dosing was 6.5 hours and ranged from 3 to 11 hours. This is considerably longer than Tmax values reported for immediate-release morphine (1 h) and shorter-acting (e.g., twice-daily) SROM formulations (3 h) in a previous meta-analysis of SROM pharmacokinetics (Collins et al., 1998) and indicates that Kapanol™ is highly effective in prolonging the time-course of plasma morphine concentrations between dosing. Consistent with hypothesis 1, the Tmax for SROM was also significantly greater than for (R)-

methadone (mean difference 4 h, range –2 to 9 h). To the extent that opioid effects have been related to plasma concentrations for both methadone and morphine (Gourlay et al., 1986; Hill et al., 1990), these results indicate that SROM may be characterised by a delayed onset of action following dosing relative to methadone.

The pharmacokinetic profile of SROM also differed from that of (R)-methadone by showing significantly greater fluctuation in plasma concentrations from peak to trough. Interpretation of the clinical significance of this finding is complicated by several factors. Firstly, despite the difference in overall peak to trough variation, the other main measure used to quantify the stability of plasma concentrations over an inter-dosing interval, T>75%Cmax, showed similar means for (R)-methadone and morphine (10.0h vs. 7.8h). Furthermore, greater overall variation in plasma concentrations does not necessarily entail a greater degree of pharmacodynamic variation between doses for SROM compared to methadone. Morphine exhibits reduced *in vitro* intrinsic efficacy relative to methadone in animal tissues (Adams et al., 1990) and may thus entail less intense opioid effects in response to changing plasma concentrations. A number of studies further indicate that opioid effects following morphine administration may show a delayed time-course relative to that of plasma morphine concentrations (Charway, Calvey, Williams, & Murray, 1985; Howard, Murray, Calvey, & Williams, 1985). This may be partly due to the action of M6G. Both M3G and M6G exhibit plasma concentration-time profiles that are highly congruent with the parent drug but slightly delayed due to the time associated with their formation (Gourlay et al., 1997). M3G and M6G also have reduced lipid solubility in comparison to morphine and thus exhibit less rapid passage through the blood brain barrier (Wu, Kang, Bickel, & Pardridge, 1997). Moreover, whereas morphine enters brain cells, M6G is almost exclusively located in extra-cellular fluid following slow diffusion across the blood-brain barrier and may thus durably bind to opioid receptors (Stain-Texier, Boschi, Sandouk, & Scherrmann, 1999). These factors have been postulated to contribute to a delayed opioid action for morphine and M6G relative to that

which would be evidenced by inspection of plasma concentration-time profiles alone (Lotsch, Skarke, Schmidt, Grosch, & Geisslinger, 2001; Stain-Texier et al., 1999; Wu et al., 1997). It is also notable that in the only other multiple-dose pharmacokinetic study of Kapanol™ (Gourlay et al., 1997), conducted in pain patients, the mean fluctuation in plasma morphine concentrations (defined as Cmax-Cmin divided by Css) was similar, although slightly greater, than observed in the present study (1.4 ± 0.4 vs. 1.0 ± 0.4).

In addition to achieving a stable profile of plasma concentrations during the inter-dosing interval, the clinical utility of methadone and SROM for use as maintenance pharmacotherapies for opioid dependence also depends on the degree to which the dispositional properties of each drug vary between individuals. Even when variation in doses was taken into account, the pharmacokinetic parameters considered in the present study showed considerable variation for both (R)-methadone and morphine. Although coefficients of variation were within a similar range for both drugs (32%-45%), the range of values across subjects (ratio of maximum to minimum) indicated somewhat greater variation for (R)-methadone compared to morphine for the area under the plasma concentration time-curve (AUC) (3.2 vs. 2.7) and both maximum - (3.4 vs. 2.0) and minimum- (4.0 vs. 3.2) plasma concentrations.

Consistent with hypothesis 3, AUC values for (R)-methadone and SROM were directly proportional to the weight-adjusted maintenance dose. The relationship between dose and plasma concentrations was stronger for morphine compared to (R)-methadone. The maintenance dose, corrected for body weight, explained 86% of the variance in AUC for morphine but only 40% of the variance in AUC for (R)-methadone. These results are in agreement with previous studies by Thirwell et al. (1989) and Foster et al. (2000) who reported that 88% and 46% of the variance in AUC were explained by dose for SROM and methadone in their respective studies of cancer pain and methadone maintenance patients.

Collectively, these findings indicate that individual variability in disposition of the maintenance drug was less for SROM compared to methadone. Moreover, to the extent that plasma concentrations are predictive of treatment response for methadone and morphine, this suggests that there may be a stronger dose-response relationship for SROM compared to methadone. However, larger sample sizes are needed to address this issue.

Consistent with previous investigations (Dyer et al., 1999), the present study found no evidence that complaints of withdrawal towards the end of the inter-dosing interval were associated with lower methadone doses or plasma concentrations. To the contrary, subjects self-identifying as non-holders at the commencement of the study showed higher mean methadone doses and plasma methadone concentrations throughout the methadone inter-dosing interval in comparison to those identifying as holders. These groups were further differentiated according to the time associated with peak plasma concentrations for (R)-methadone, which occurred twice as rapidly for the non-holders compared to the holders (1.7h vs. 3.4h). For SROM maintenance, there were no significant mean differences on any pharmacokinetic parameters for holders and non-holders. As for methadone, however, the non-holders tended to show higher mean plasma concentrations throughout the inter-dosing interval; a pattern that was still evident when differences in SROM doses for each group were taken into account. Additionally, it was evident that the increase in Tmax for SROM compared to methadone was significantly greater for the non-holders compared to the holders.

Differences in methadone disposition for methadone holders and non-holders observed in the present study are partly congruent with two earlier studies that have investigated the pharmacokinetic basis of withdrawal complaints. Nilsson et al. (1983) found that patients classified as therapeutic failures were characterised by a smaller volume of distribution relative to an unselected control group. On the basis of this finding, these authors predicted that patients reporting inadequate withdrawal suppression between doses might be

characterised by more rapid changes in plasma methadone concentrations during the inter-dosing interval. Consistent with this postulation, Dyer et al. (1999) found that the maximal rate of decline in racemic methadone concentrations from peak to trough correlated significantly with withdrawal severity and was greater for non-holders compared to holders. Although mean decline in plasma (R)-methadone concentrations was also greater for non-holders compared to holders in the present study, this difference was not significant. Notably, coefficients of variation for this measure were high for both the holder (116%) and non-holder (97%) groups. This result indicates that a significantly larger sample than that used in the present study would be necessary to achieve statistical significance, based on the observed difference. Nevertheless, the findings that (R)-methadone concentrations peaked more rapidly and tended to be higher for a given dose for non-holders compared to holders are compatible with suggestions that non-holders are characterised by more rapid changes in methadone concentrations, possibly due to a smaller volume of distribution (Nilsson et al., 1983).

The present study builds also upon earlier attempts to characterise the pharmacokinetic basis of non-holding by taking into account stereoselectivity in the pharmacokinetics of methadone. Consistent with hypothesis 2 and previous research (Foster et al., 2000), the present study found differences in the disposition of (R)- and (S)-methadone during the inter-dosing interval. Specifically, in comparison to (R)-methadone, (S)-methadone was associated with a significantly higher maximum plasma concentration, a greater peak to trough ratio, and a greater rate of maximal decline from peak to trough. The latter finding is especially relevant in interpreting the finding of Dyer et al. (1999) that methadone non-holders were differentiated from holders by a greater rate of decline in racemic methadone concentrations from peak to trough, since the rate of decline is likely to have been disproportionately influenced by the 'inactive' (S)-methadone enantiomer.

Analyses further indicated that there was considerable between- and within-subject variation in the ratio of (S)- to (R)-methadone. The AUC ratio of (S)- to (R)-methadone ranged from 0.83 to 1.33, indicating approximately 60% variation across subjects in their relative exposure to each enantiomer. The ratio of (S)- to (R)-methadone also varied more than 2-fold on average during the methadone inter-dosing interval, with one subject showing more than 5-fold variation. This variation in exposure to (R)- and (S)-methadone raises a number of important issues. Firstly, since only (R)-methadone enantiomer has significant opioid action, variation in exposure to (R)-methadone in relation to the racemic methadone dose is likely to obscure a dose response relationship and contribute to the need for individualised dosing. Secondly, variation in the enantiomeric ratio may be associated with variability in treatment response owing to the distinct pharmacological actions of (S)- and (R)-methadone. Whereas (R)-methadone shows greater opioid potency (Scott et al., 1948) and a greater capacity to inhibit serotonin and noradrenaline re-uptake compared to (S)-methadone (Codd et al., 1995), both enantiomers are relatively potent NMDA antagonists (Ebert et al., 1998; Gorman et al., 1997). This may result in different patterns of clinical responses in response to variation in the ratio of (S) to (R)-methadone during the inter-dosing interval. This possibility is explored further in Chapter 5.

Another important pharmacokinetic consideration during maintenance treatment concerns the accumulation of the maintenance drug with multiple dosing. In the case of methadone, its long half-life and extensive tissue distribution are associated with a risk of accumulation across doses (Gourlay et al., 1986). During the induction phase of treatment, in particular, it is necessary to increase doses carefully in order to avoid delayed opioid toxicity (Eap et al., 2002). By comparison, morphine has a short-half life and in immediate-release and shorter-acting SROM formulations (e.g., twice-daily) shows little accumulation across doses in comparison to methadone (Gourlay et al., 1986; Savarese, Goldenheim, Thomas, & Kaiko, 1986). A meta-analysis by Collins et al. (1998), for example, found very little difference in

estimates of Cmax between single- and multiple-dosing studies of morphine pharmacokinetics. However, once-daily SROM formulations were not included in this analysis. Based on the results of the five previous investigations of Kapanol™ presented in Table 3-1 and those of the present study (dose corrected to 100 mg SROM), the following comparisons are relevant in this regard. Firstly, the present study and the only other multiple dosing study reported for Kapanol™ (Gourlay et al., 1997) yielded similar values for both AUC (587 ng/mL*hr vs. 501 ng/mL*hr) and Cmax (40.3 ng/mL vs. 37.3 ng/mL) (data normalised to 100 mg SROM dose). Secondly, by comparison, the four previous single-dosing Kapanol™ studies showed approximately 2-fold smaller values for AUC (range 212 – 274 ng/mL·hr; 24-hour studies only) and Cmax (13.8 – 21.2 ng/mL). Although possible differences in morphine disposition between patients and healthy volunteers (e.g., effects of disease states on hepatic and renal function) (Andersen et al., 2003) must be taken into account, these differences indicate that accumulation of morphine does occur with multiple-dosing.

To the extent that both methadone and SROM show accumulation across doses, an individualised and careful approach to dosing is necessitated for both drugs upon commencement of maintenance treatment. However, a number of factors suggest the risks of drug accumulation may be less pronounced and easier to overcome for SROM compared to methadone. Firstly, it is evident that although SROM formulations drastically increase the half-life of morphine (from 2 to >15 h), the half-life of methadone is nonetheless much longer on average (>30 h) (Gourlay et al., 1986; Wolff et al., 1993). Second, in the case of SROM, shorter-acting morphine solutions may be used to titrate doses rapidly and safely, prior to switching to a slow-release formulation (Hoskin, Poulain, & Hanks, 1989). The issue of SROM induction is addressed in more detail in Chapter 8.

In summary, the present study has shown that the dispositional characteristics of SROM, administered as Kapanol™, are amenable to once-daily dosing in patients undergoing maintenance treatment for opioid dependence. SROM was associated with a stable and prolonged profile of plasma morphine concentrations during the inter-dosing interval and exhibited a similar degree of individual variability to methadone for key pharmacokinetic parameters including AUC. To this extent, SROM may be particularly advantageous as an alternative once-daily agonist option to methadone for patients reporting the failure of their methadone dose to hold for the entire 24-hour inter-dosing interval. Consistent with previous studies (Dyer et al., 1999; Nilsson et al., 1983), complaints of withdrawal towards the end of the inter-dosing interval were associated with more rapid changes in plasma methadone concentrations (e.g., shorter Tmax), rather than inadequate methadone doses or plasma concentrations. Increasing the methadone dose may be an inappropriate clinical response to some cases of 'non-holding' given the possibilities that it may fail to ameliorate withdrawal, exacerbate adverse methadone effects, or be resisted by patients who fear prolonging eventual detoxification from treatment. There are also limitations associated with strategies including a reduction in the methadone inter-dosing interval (e.g., impractical for supervised dosing) and transfer to alternative to long-acting maintenance medications such as LAAM (e.g., risk of cardiac abnormalities) and buprenorphine (e.g., precipitation of opioid withdrawal).

The major clinical implication of the present study is that it identifies SROM as another opioid agonist with dispositional characteristics suitable for once-daily dosing in maintenance programs. It may thus facilitate better treatment outcomes in maintenance programs, particularly in instances where the existing range of treatment options is ineffective, unsafe or unacceptable to the patient. The realisation of such benefits that may be possible with wider implementation of SROM is subject to further large-scale evaluations of its effectiveness. Such evaluations may also provide an opportunity for further characterisation of the pharmacokinetic profile of SROM in relation to its clinical utility in maintenance programs.

4. OPIOID WITHDRAWAL, PHYSIOLOGICAL RESPONSES, AND SYMPTOM COMPLAINTS DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SROM

4.1. Introduction

Maintenance pharmacotherapies seek to reduce use of illicit opioids by suppressing opioid withdrawal and blocking the effects of additional illicit opioids that may be used by the patient. The determination of a methadone dose that provides an optimal balance between withdrawal suppression, adverse effects, and blockade of additional opioids is thus a primary objective during treatment. As a strategy for achieving this goal, the suitability of once-daily oral methadone dosing varies considerably between individuals. Many methadone maintenance patients report problems including adverse effects attributable to treatment (e.g., constipation, sweating) (Dyer & White, 1997; Goldstein & Judson, 1973; Judson & Goldstein, 1982; Kreek, 1973; Longwell et al., 1979) and the frequent failure of their methadone dose to adequately suppress withdrawal for the duration of the 24-hour inter-dosing interval (Dyer & White, 1997). Since there are limitations associated with each of the strategies currently available for addressing these problems (discussed in Chapter 1), the likelihood of positive outcomes resulting from treatment is likely to be compromised in a significant number of patients. To the extent that once-daily SROM is as effective as methadone in suppressing opioid withdrawal between doses in the absence of significant adverse effects, it is likely to be advantageous as a new alternative treatment option for patients responding poorly to methadone maintenance. The present study explored this possibility by comparing the magnitude and duration of opioid effects (opioid withdrawal and physiological responses) and overall prevalence of symptom complaints for methadone and SROM across a standard 24-hour inter-dosing interval.

4.1.1. Prevalence, causes and patterns of methadone symptom complaints

The clinical utility of once-daily SROM for use in maintenance programs depends partly on the frequency with which patients respond poorly to methadone and the likelihood that

transfer to SROM would facilitate better outcomes for such individuals. Studies investigating the prevalence of symptom complaints during methadone maintenance have reported similar results. The most commonly reported symptoms include constipation, sweating, painful joints and bones, insomnia, general malaise, sexual dysfunction (e.g., reduced libido), and menstrual irregularities, each of which have been reported to occur in excess of 50% of cases (Dyer & White, 1997; Goldstein & Judson, 1973; Judson & Goldstein, 1982; Kreek, 1973; Longwell et al., 1979). The causes of these symptom complaints, and hence appropriate clinical responses, are sometimes difficult to determine due to the multiplicity of factors that may contribute to their presentation. These factors can be classified into the following two categories (Dyer & White, 1997).

First, symptom complaints may be directly related to the pharmacological actions of methadone. This includes direct opioid effects to which tolerance has not fully developed. Although tolerance to some of the adverse effects of methadone can develop during treatment, it has been shown that many of these symptoms are prevalent even amongst long-term methadone maintenance patients. In a study by Kreek (1973), for example, excess sweating and constipation were reported by 48% and 17%, respectively, of high-dose methadone maintenance patients after three or more years of treatment. In addition to direct effects of methadone, other symptom complaints may represent experiences of opioid withdrawal, for example, amongst patients exhibiting a rapid decline in plasma methadone concentrations prior to the end of the inter-dosing interval (Dyer et al., 1999).

Second, symptom complaints may derive from characteristics of patients' psychology and health that are unrelated to the pharmacological effects of the maintenance drug or any other aspect of treatment. Opioid dependence is associated with a high prevalence of comorbid psychological (e.g., depression, anxiety disorders) and medical (e.g., HIV, hepatitis C) disorders that may independently contribute to deficits in health and the frequency of

symptom complaints during methadone maintenance treatment (Crofts et al., 1993; Piccolo et al., 2002; Ward et al., 1998b). Moreover, the features of opioid dependence and other comorbid disorders may also interact in a synergistic way to increase the frequency of symptom presentation. Negative mood states, for example, have been found to increase the perceived severity of opioid withdrawal symptoms in experimental settings (Childress et al., 1994; Phillips, Gossop, & Bradley, 1986). Other psychological factors including attempts by patients to gain a dose increase (Whitehead, 1974) and misinformation about the effects of methadone (Stancliff et al., 2002) may also contribute to the high rate of symptom presentation and negative attitudes towards treatment in methadone maintenance patients.

The question of whether symptom complaints during methadone maintenance are related to the effects of methadone is important for two main reasons. Firstly, knowing the cause of symptom complaints is important in determining the most appropriate clinical response. Depending on whether symptoms are attributable to methadone or not, adjustments in the methadone dosing regimen (e.g., adjustment of dose or dosing interval) or transfer to alternative maintenance medications may or may not be indicated. Second, a knowledge of which symptoms and outcomes are related to the pharmacological actions of methadone is important in identifying patient outcomes that can be used to directly compare maintenance pharmacotherapies such as methadone and SROM. By distinguishing symptoms that are attributable to opioid effects from those that are not, a more sensitive measurement of changes in patient outcomes attributable to changes in dose or the maintenance medication is possible. In attempting to relate patient outcomes to the pharmacological actions of methadone, two major approaches have been utilised. These are summarised in the next two sections.

4.1.2. Methadone dose, plasma concentrations and treatment outcomes

Numerous studies have sought to ascertain whether there is a relationship between dose and clinical outcomes during methadone maintenance treatment (Strain & Stitzer, 1999; Ward et

al., 1998c). These studies have typically involved either comparisons of groups randomised to receive different methadone doses (e.g., 'high' and 'low' dose groups) (Johnson, Jaffe, & Fudala, 1992; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling, Wesson, Charuvastra, & Klett, 1996; Strain et al., 1993) or observational studies in which patient outcomes (e.g., withdrawal symptoms, retention in treatment, urinary indicators of heroin use, HIV status) have been correlated with methadone dose (Caplehorn & Bell, 1991; Caplehorn, Dalton, Cluff, & Petrenas, 1994; McGlothlin & Anglin, 1981; Torrens, Castillo, & Perez-Sola, 1996). Reviewers of the literature have generally concluded that methadone doses of at least 50 mg per day are associated with better outcomes than lower doses on measures including retention in the program, heroin use, HIV status and withdrawal symptoms (Ward et al., 1998c).

On the basis of these findings, some authors have proposed the notion of a minimum plasma methadone concentration associated with effective maintenance (Dole, 1988; Loimer & Schmid, 1992). Direct measurement of plasma concentrations is advantageous in that it partially accounts for variability in the pharmacokinetics of methadone that may obscure a dose-response relationship (Eap et al., 2002). A small number of studies have reported an inverse relationship between plasma methadone concentrations and outcome measures including illicit drug use and withdrawal severity (Horns et al., 1975; Tennant et al., 1984), whilst others suggest that withdrawal is likely when plasma concentration falls below 50 ng/mL (Bell et al., 1988; Wolff et al., 1991). In contrast, other studies have found no clear evidence of a concentration-response relationship for methadone maintenance (Bell, Bowron, Lewis, & Batey, 1990; deVos, Vanwilgenburg, Vandenbrink, Kaplan, & Devries, 1996; Schall, Pries, Katta, Kloppel, & Gastpar, 1996b; Torrens et al., 1998). Notably, complaints of adverse effects and inadequate withdrawal suppression have also been found to be highly prevalent across a range of methadone doses, including those within or above the putative therapeutic range (e.g., >50 mg) (Dyer & White, 1997; Goldstein & Judson, 1973).

These findings have important implications for treatment delivery and research. Although many indicators of treatment outcome (e.g., heroin use, withdrawal) are related to the adequacy of the methadone dose and plasma concentration, the nature of these relationships is neither linear nor strong. Withdrawal and heroin use are likely when the methadone dose is low (Bell et al., 1988; Wolff et al., 1991), but many patients experience symptom complaints and inadequate withdrawal suppression despite high and even very high doses of methadone (Byrne, 1996; Dyer et al., 1999; Dyer & White, 1997). In one report, daily methadone doses of up to 350 mg were found to be necessary to achieve consistent abstinence from heroin use in some patients (Byrne, 1996). Given the many pharmacokinetic (e.g., methadone clearance) and pharmacodynamic (e.g., tolerance) factors that may explain variation in response to a given methadone dose (Eap et al., 2002), the absence of a strong dose-response relationship is not surprising. As a consequence of this variability, it is necessary to use an individualised approach to dosing in order to achieve an optimal balance between withdrawal suppression and adverse effects. In cases where an individualised approach to methadone dosing fails to yield the desired outcome, transfer to alternative maintenance medications such as once-daily SROM may be necessary.

4.1.3. Temporal changes in opioid effects and plasma drug concentrations

An alternative method for investigating the relationship between methadone administration and patient outcomes involves studying how fluctuations in the plasma methadone concentrations within individuals during the inter-dosing interval influence treatment response (Curran et al., 2001; Dyer et al., 1999; Dyer & White, 1997; Eissenberg, Stitzer, Bigelow, Buchhalter, & Walsh, 1999; Hiltunen et al., 1999; McCaul, Bigelow, Stitzer, & Liebson, 1982). This approach normally incorporates repeated and concurrent measurement of both subjective and physiological indices of opioid effects, in addition to plasma methadone concentrations, following methadone dosing. This technique takes advantage of the fact that plasma methadone concentrations vary approximately 2-fold on average between

doses, resulting in clinically significant and detectable changes in both the frequency and intensity of symptom presentation and other physiological indices known to reflect opioid action, including pupil diameter, respiration rate, heart rate and blood pressure (Dyer et al., 1999; Dyer & White, 1997; Eissenberg et al., 1999; McCaul et al., 1982; Walsh et al., 1995). Since the adequacy of withdrawal suppression associated with the maintenance dose is considered a major determinant of long-term treatment outcomes, the magnitude of opioid effects during a single inter-dosing interval can be viewed as a model of long-term treatment efficacy and safety. The sensitivity of this model to the effects of the maintenance drug within-subjects (i.e., across the 24-hour inter-dosing interval) has the advantage of requiring few subjects in order for the effects of treatment to be detected. Studies reported by Dyer and colleagues (Dyer et al., 1999; Dyer & White, 1997; Dyer et al., 2001) provided the methodological framework for the present comparison of methadone and SROM, featuring comparisons of methadone patients reporting adequate (holders) and inadequate (non-holders) withdrawal suppression between doses, and will therefore be reviewed as exemplars of the approach described above.

In their first study, Dyer and White (1997) investigated the temporal pattern of symptom complaints and opioid effects during a 24-hour inter-dosing interval in 51 methadone maintenance patients (mean dose 54 mg, range 15-140 mg; 55% male). The frequency and intensity of symptom complaints were assessed using the Methadone Symptoms Checklist (MSC), comprising three subscales of 16 items each: (1) direct opioid effect symptoms; (2) opioid withdrawal symptoms; (3) mixed / unclear symptoms (which could be characteristic of both direct effects and withdrawal). The intensity of symptoms was measured using a 5-point Likert scale with the following categories: none, mild, moderate, severe and extreme. The Morphine Benzedrine Group scale (MBG) of the Addiction Research Centre Inventory (Haertzen & Hickey, 1987) was used to assess positive opioid effects (e.g., euphoria). Both questionnaires were administered pre-dose, every two hours up to 12-hours post-dose, then

again immediately prior to the next methadone dose. The mean total intensity for the 16 withdrawal items (maximum score = 64) peaked immediately prior to the methadone dose (11.8), declined to a minimum at 2 hours post-dose (4.7) before returning to higher scores at 12 hours post-dose (10.8) and immediately prior to the next dose (13.6). Mean scores for the MBG and some of the direct opioid effect symptoms (e.g., itchy skin, itchy nose, pleasant feeling in stomach, feeling 'high') showed an inverse pattern, peaking 2 hours post-dose and showing minimum scores at dosing times. Other direct effect symptoms such as constipation and dry mouth remained stable throughout the inter-dosing interval. A median split of peak withdrawal intensity was used to divide subjects into subgroups of holders (n = 26) and non-holders (n = 25). Mean withdrawal intensity was low and stable for the holders, but showed higher levels and pronounced temporal changes for the non-holders. Compared to the holders, the non-holders also showed lower mean MBG scores after the peak that occurred two hours post-dose for both groups. Differences between the groups were not attributable to differences in the daily methadone dose or dose-to-weight ratios. However, in the absence of pharmacokinetic data the possibility that variations in plasma methadone concentrations may have accounted for the observed differences between holders and non-holders could not be excluded.

In a second study, Dyer et al. (1999) conducted a pharmacokinetic and pharmacodynamic assessment of eighteen methadone maintenance patients, comprising nine holders and nine non-holders as identified by self-report. A control group of 10 drug-free volunteers was also included. The study design featured the collection of blood samples on 13 occasions throughout a single inter-dosing interval. These were assayed for plasma racemic methadone concentrations. Subjective and physiological measures of opioid effect were assessed on 11 of these occasions. The subjective measures included withdrawal severity (MSC), direct opioid effects (MBG), and the threshold at which increasing electrical stimulation of the ear lobe

became painful (designated 'pain threshold'; measure in volts). Changes in pupil diameter were measured as a physiological index of opioid effect.

Dyer et al. (1999) found that plasma methadone concentrations were inversely related to withdrawal severity and pupil diameter and directly related to MBG scores and pain threshold. Whereas the methadone maintenance patients showed changes in indices of opioid effect (including withdrawal) consistent with fluctuating plasma methadone concentrations, the control group showed no such changes. Plasma concentration versus effect relationships were also analysed by fitting each subjects' data to the Sigmoid Emax model. These analyses revealed a very steep slope-factor (N) for subjective responses for withdrawal responses (N = 5.4), such that relatively small changes in plasma methadone concentrations were associated with large changes in the severity of withdrawal, although these relationships could only be determined for 50% of the sample. Consistent with their earlier study (Dyer & White, 1997), withdrawal severity during the inter-dosing interval remained low and stable for the holders but showed higher and less stable values for the non-holders. There were no significant differences between the groups in racemic methadone doses or trough plasma concentrations, but when two patients whose urinalyses were positive for additional opioid use were excluded, the mean rate of decline in plasma methadone concentrations from peak to trough was greater for non-holders compared to holders (75 ng/mL/h vs. 42 ng/mL/h). There was also a significant correlation between the mean rate of decline in plasma methadone concentration and withdrawal severity during the period from peak to trough ($r = 0.60$).

The investigations of Dyer and colleagues (1999; 1997) are consistent with other studies demonstrating significant changes in pharmacodynamic response following methadone dosing in maintenance patients (Curran et al., 2001; Eissenberg et al., 1999; Hiltunen et al., 1999; McCaul et al., 1982; Walsh et al., 1995). However, Dyer and colleagues were the first to show such changes for the duration of a 24-hour inter-dosing interval, including comparisons of

methadone holders and non-holders. This experimental approach, and, in particular, the measurement of subjective withdrawal severity, was shown to be a highly effective means of distinguishing holders and non-holders using relatively small numbers of patients. In the evaluation of novel treatment strategies such as slow-release oral morphine, for which the existing evidence base is limited, this approach is likely to be advantageous in limiting the numbers of subjects required to achieve a sensitive measurement of the relative efficacy of methadone and SROM in suppressing opioid withdrawal between doses.

4.1.4. The present study

The evidence reviewed above indicates that the suitability of once-daily oral methadone dosing as an intervention for opioid dependence varies considerably between individuals. A significant proportion of methadone maintenance patients report inadequate withdrawal suppression, even when apparently adequate methadone doses and plasma concentrations doses are achieved and an individualised approach to dosing is utilised (Dyer et al., 1999; Dyer & White, 1997). Moreover, even when adequate withdrawal suppression is achieved, other symptoms complaints are highly prevalent (e.g., excessive sweating, constipation, lethargy, dry mouth, and reduced libido) (Dyer & White, 1997; Goldstein & Judson, 1973) and may reflect direct pharmacological effects of methadone. In patients for whom a satisfactory balance between withdrawal suppression and unwanted effects is difficult to achieve with once-daily methadone dosing, transfer to an alternative maintenance pharmacotherapy may yield better outcomes.

Like methadone, morphine is primarily selective for the mu opioid receptor and thus produces a similar pattern of pharmacological effects. These include analgesia, respiratory depression, miosis, euphoria, sedation, constipation, nausea and vomiting, alterations of the endocrine and autonomic nervous system, pruritus, and flushing of the skin (Andersen et al., 2003). Pharmacodynamic evaluations of once-daily SROM formulations such as Kapanol™ have been reported for the management of pain (Gourlay et al., 1997) and in healthy volunteers

(Bochner et al., 1999; Broomhead et al., 1997a; Broomhead et al., 1997b; Broomhead et al., 1997c; Floter et al., 1997; Kerr & Tester, 2000; Maccarone et al., 1994). These studies, reviewed in Chapter 1, indicated that once-daily Kapanol™ was similarly effective and safe compared to short-acting SROM formulations in providing analgesia in the absence of significant adverse effects. This suggests that Kapanol™ provides sustained opioid effects with once-daily dosing and may therefore be effective in suppression opioid withdrawal without significant adverse effects in patients undergoing maintenance treatment for opioid dependence. Nevertheless, although pain and opioid withdrawal are primarily mediated by the same (mu) opioid receptor, these effects involve distinct neural pathways. There may also be clinically important differences between the pain management and methadone maintenance patient groups (e.g., renal and hepatic function, opioid tolerance) (Andersen et al., 2003; Eap et al., 2002) that influence the pharmacokinetics and pharmacodynamics of methadone and SROM for each group.

For these reasons, an assessment of the extent to which SROM is efficacious in suppressing opioid withdrawal in the absence of significant adverse effects is necessary to determine its suitability for once-daily dosing in maintenance programs for opioid dependence. Moreover, to the extent that SROM may be particularly advantageous as an alternative for patients reporting the failure of their methadone dose to 'hold' for 24 hours, it is necessary to determine whether those who experience inadequate withdrawal suppression on methadone also experience the same problem whilst maintained on SROM. As demonstrated by Dyer et al. (1999; 1997), the concurrent measurement of physiological and subjective indices of opioid effect, in addition to plasma concentrations of the maintenance drug, provides an experimentally powerful means of addressing such questions. In determining the suitability of SROM for use as a maintenance pharmacotherapy, such an approach is ethically advantageous in limiting the number of subjects in whom transfer to an unproven treatment is required.

The present study compared the magnitude and duration of opioid effects (subjective and physiological) and overall prevalence of symptom complaints for methadone and SROM across a 24-hour inter-dosing interval in a crossover study of opioid dependent individuals receiving methadone maintenance treatment for opioid dependence. The study included methadone maintenance patients reporting adequate (holders) and inadequate (non-holders) withdrawal suppression between doses and featured the repeated measurement of subjective (withdrawal severity, symptom complaints) and physiological (pupil diameter, respiration rate, heart rate, blood pressure) indices of opioid effect and treatment safety throughout a 24-hour inter-dosing interval for each drug. As reported in Chapter 3, plasma drug concentrations for (R)- and (S)-methadone and morphine were collected at each measurement time and were used to examine the pharmacokinetic basis of observed patterns of pharmacodynamic responses.

4.1.4.1. Aims

Specific aims of the investigation were as follows:

- To determine whether the magnitude of opioid effects and overall prevalence of symptom complaints during the 24-hour inter-dosing interval differ for methadone and SROM.
- To determine whether patients reporting the failure of their dose to hold for 24-hours whilst maintained on methadone also experience the same problem whilst maintained on SROM.
- To characterise the pharmacokinetic basis of any such differences in pharmacodynamic responses to methadone and SROM.

4.1.4.2. Hypotheses

1. Temporal patterns of subjective and physiological opioid effects for methadone and SROM will be consistent with plasma concentration-time profiles for (R)-methadone and morphine.

4.2.Methods

4.2.1. Subjects and procedures

The subjects and general procedures for this aspect of the study were described in Chapter 2. The pharmacodynamics of methadone and SROM during a single 24-hour inter-dosing interval were contrasted in fourteen opioid-dependent volunteers undergoing maintenance treatment after at least 4 weeks on a stable dose of each drug in an open-label, randomly-ordered, crossover design. Pharmacodynamic responses were recorded on 11 occasions at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, and 23 hours after administration of the maintenance dose.

4.2.2. Measures

At each of the above times, the following measures of treatment efficacy and safety were obtained. Subjects completed the Methadone Symptoms Checklist (MSC) (Dyer & White, 1997). This version of the MSC consisted of 52 symptoms (see Table 4-3, p. 162) for which subjects provided a rating from 0 ("none") to 4 ("extreme") according to the presence and severity of that symptom. Of these, 16 items were designated as withdrawal symptoms based on previous studies (Dyer et al., 1999; Dyer & White, 1997). For each completed MSC, the number of opioid withdrawal symptoms and total intensity of opioid withdrawal (calculated by adding severity of all 16 withdrawal items) were calculated (maximum score = 64).

In addition to the MSC, the following physiological indices of treatment efficacy and safety were measured. Pupil diameter was measured using a video camera (Panasonic NV-RX33, Tokyo, Japan) under constant lighting conditions (65 lux adjacent to camera lens) with a ×2 magnification. Subjects held a metric ruler immediately below the eye for approximately 10 seconds of recording to enable measurement of the pupil diameter (to the nearest 0.25mm) during playback on a 68cm television screen. Respiration rate was measured for 1 minute by direct observation of the subject without their awareness after at least 10 minutes of rest. Heart rate was measured manually by recording the subjects' pulse at the wrist for 1 minute.

Systolic and diastolic blood pressures were recorded manually using a sphygmomanometer and blood pressure cuff. Other subjective measures of opioid effect (mood states, pain detection and threshold) taken at the same times are presented in later chapters.

4.2.3. Statistical analyses

Repeated-measures analysis of variance (ANOVA) was used to examine the effects of the maintenance dose, the time since dosing and methadone holding status on pharmacodynamic responses. Additional analyses of pharmacodynamic responses according to the maintenance drug and methadone holding status used paired and independent t-tests, respectively. Pearson correlation coefficients and scatter plots were used to examine linear relationships between paired variables. Comparisons of symptom frequency according to the maintenance drug and methadone holding status used McNemar and Chi-square tests, respectively. Cronbach's alpha was used to assess the internal consistency of the MSC withdrawal scale. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). An alpha level of 0.05 was used for all analyses. Data are presented as mean ± SD (range) unless otherwise indicated.

4.3.Results

4.3.1. Indices of opioid effect during the inter-dosing interval

4.3.1.1. Comparisons for all subjects

Temporal patterns of opioid withdrawal during the 24-hour inter-dosing interval for methadone and SROM are contrasted for all subjects in Figure 4-1. These data indicate that SROM was at least as effective as methadone overall in suppressing opioid withdrawal. In comparison to methadone maintenance, SROM maintenance was associated with a lower number ($t(13) = 2.07$, $p = 0.06$; marginally non-significant) and intensity ($t(13) = 2.43$, $p = 0.03$) of withdrawal symptoms prior to dosing. There were no significant differences between methadone and SROM for either withdrawal measure at any other time point. The severity of opioid withdrawal declined following dosing of each drug, reaching minimal levels after 4-6 hours for methadone and after 7-9 hours for SROM before returning to higher levels at the end of the inter-dosing interval. Assessments of scale reliability for the 16 withdrawal items of the MSC indicated a high level of internal scale consistency (Cronbach alpha = 0.85).

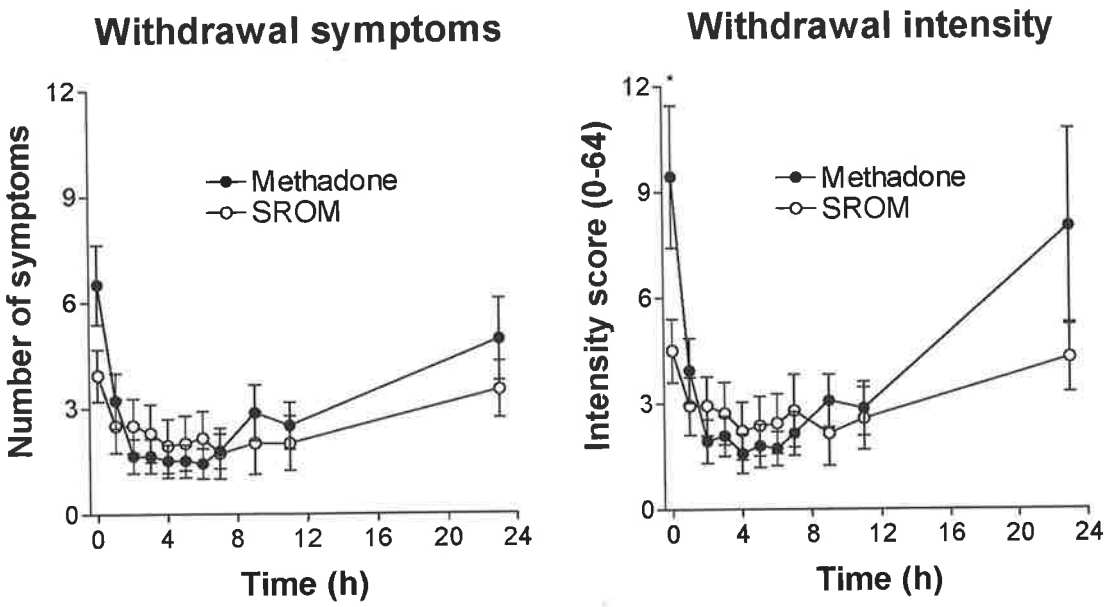

Figure 4-1. Opioid withdrawal during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean ± SE. * $p < 0.05$ (methadone vs. SROM).

Repeated-measures ANOVA used to examine the effects of the maintenance drug and the time since dosing on opioid withdrawal severity and physiological responses are summarised in Table 4-1. Temporal changes in both the number and intensity of withdrawal symptoms during the inter-dosing interval were significant for both methadone and SROM. There was no significant maintenance drug effect for either the number of intensity of withdrawal symptoms. However, maintenance drug × time since dosing interactions for both the number and intensity of withdrawal symptoms indicated that temporal patterns of withdrawal during the inter-dosing interval were significantly different for methadone and SROM.

Table 4-1. Repeated-measures ANOVA for subjective and physiological indices of opioid effects (n=14).

Effect[b]	Df	Pharmacodynamic responses[a]						
		WD Number	WD Intensity	Pupil Diam.	Respir. Rate	Heart rate	Systol BP	Diast BP
		Within drug conditions						
Time								
Methadone	10,130	***10.1	***6.98	***13.6	***8.35	**2.50	1.70	***3.32
SROM	10,130	***3.23	**2.56	***3.17	1.22	**2.82	***3.33	*1.95
		Between drug conditions						
Drug	1, 13	0.32	0.94	0.29	0.15	4.50	0.37	0.37
Drug × Time	10,130	**2.67	***3.17	***3.90	*2.24	0.65	1.31	1.53

Values are F ratios. [a] Number of withdrawal (WD) symptoms; intensity of withdrawal symptoms; pupil diameter, respiration rate; heart rate; systolic blood pressure (BP); diastolic blood pressure. [b] ANOVA effects were time since dosing (Time) and the maintenance drug (Drug). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Temporal changes in physiological indices of opioid effects and safety during the inter-dosing interval for methadone and SROM are contrasted for all subjects in Figure 4-2. Consistent with results observed for measures of opioid withdrawal, the data for pupil diameter and respiration rate, in particular, indicate that the magnitude and duration of opioid effects

following dosing was comparable if not greater overall for SROM compared to methadone. Results for each of these measures will now be considered.

In comparison to methadone, SROM was associated with a significantly smaller mean pupil diameter both prior to dosing ($t(13) = 2.76$, $p = 0.02$) and 23 hours following dosing ($t(13) = 2.98$, $p = 0.01$). Mean pupil diameter declined relative to baseline after dosing for both drugs, reaching minimal levels at 3 hours for methadone (1.0 mm below baseline) and 6 hours for SROM (0.34 mm below baseline). ANOVA indicated significant main effects for time since dosing for both methadone and SROM, and a significant maintenance drug × time since dosing interaction, but there was no main effect for the maintenance drug (Table 4-1). Thus, in comparison to methadone, SROM produced a similar if not greater overall level of pupillary constriction, but this effect tended to be more gradual in onset and more stable across the inter-dosing interval.

Patterns of changes in respiration rate similarly suggested a more stable overall opioid effect between doses for SROM compared to methadone. For methadone, mean respiration rate showed an abrupt decline from maximal levels at baseline to minimal levels 2 hours following dosing (2.63 breaths/min below baseline), before ascending rapidly back towards pre-dose levels for the remainder of the inter-dosing interval. By comparison, the decline following dosing was less marked (1.43 breaths/minute below baseline at both 2 and 11 hours post-dose) and more temporally stable for SROM. ANOVA indicated a significant main effect for time since dosing for methadone but not SROM and a significant maintenance drug × time since dosing interaction, but no overall differences between the two drugs (Table 4-1).

In comparison to the above parameters, heart rate and blood pressure appeared less sensitive to changes in plasma concentrations of (R)-methadone and morphine following dosing with racemic methadone and SROM, respectively. Temporal changes in mean heart rate are

suggestive of a decline following dosing, with notable increases occurring approximately 3 hours and 6-7 hours after dosing for both methadone and SROM. These time points correspond with the timing of subjects' meals (lunch and dinner). ANOVA indicated significant effects for time since dosing for both methadone and SROM, a non-significant maintenance drug × time since dosing interaction, and a marginally non-significant effect for the maintenance drug (Table 4-1). The latter result reflects the slightly higher mean respiration rates found for SROM compared to methadone at most points.

Temporal changes in blood pressure for methadone and SROM, as mentioned, were not strongly associated with changes in plasma concentrations of (R)-methadone and morphine following dosing. For systolic blood pressure, ANOVA indicated significant time since dosing effects for SROM but not methadone, and no significant effects for the maintenance drug or the maintenance drug × time since dosing interaction (Table 4-1). For diastolic blood pressure, ANOVA indicated significant time since dosing effects for both methadone and SROM, but no significant effects for the maintenance drug or the maintenance drug × time since dosing interaction (Table 4-1).

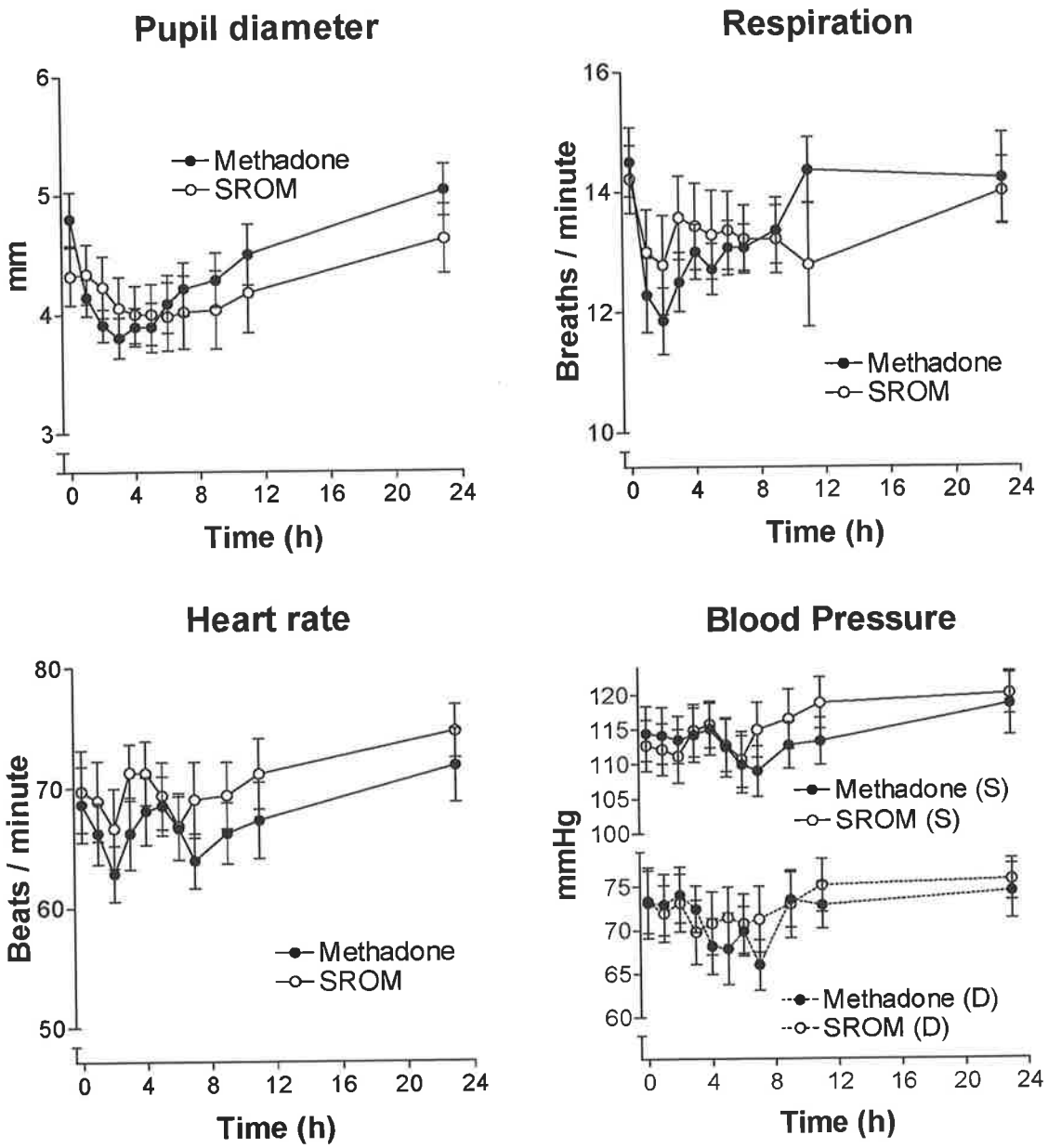

Figure 4-2. Physiological indices of opioid effects and safety during a 24-hour inter-dosing interval for methadone and SROM: pupil diameter, respiration rate, heart rate, systolic (S) and diastolic (D) blood pressure (n=14). Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone vs. SROM).

4.3.1.2. Comparisons for methadone holders and non-holders

Temporal patterns of opioid withdrawal during the inter-dosing interval for methadone and SROM are contrasted for methadone holders and non-holders in Figure 4-3. During methadone maintenance, non-holders showed a significantly greater number and intensity of withdrawal symptoms in comparison to holders prior to dosing ($t(12) = 2.70$, $p = 0.02$; $t(12) = 2.53$, $p = 0.03$) and 23 hours following dosing ($t(12) = 3.05$, $p = 0.01$; $t(12) = 2.23$, $p = 0.046$). Both groups showed similar levels of withdrawal for approximately 6 hours post-dose, at which point withdrawal began to increase in the non-holder group but remained stable in

the holder group. During SROM maintenance, there were no significant differences between holders and non-holders on either withdrawal measure at any stage during the inter-dosing interval ($p > 0.33$). The mean number of withdrawal symptoms was approximately 3 or less for the duration of the inter-dosing interval in both groups. These findings indicate that both groups experienced an equivalent and satisfactory degree of withdrawal suppression between doses whilst maintained on SROM. The holders showed no significant changes at any time point for either withdrawal measure during SROM maintenance in comparison to methadone maintenance. However, compared to methadone maintenance, the non-holders showed significant reductions during SROM maintenance in both the number ($t(6) = 4.04$, $p = 0.01$) and intensity ($t(6) = 2.26$, $p = 0.03$) of opioid withdrawal symptoms prior to dosing. Scatter plots relating the maximal rate of decline in plasma concentrations for (R)-methadone and morphine and average withdrawal severity in the period from peak trough for both methadone and SROM, respectively, indicated no relationship between these variables, precluding the need for further analysis.

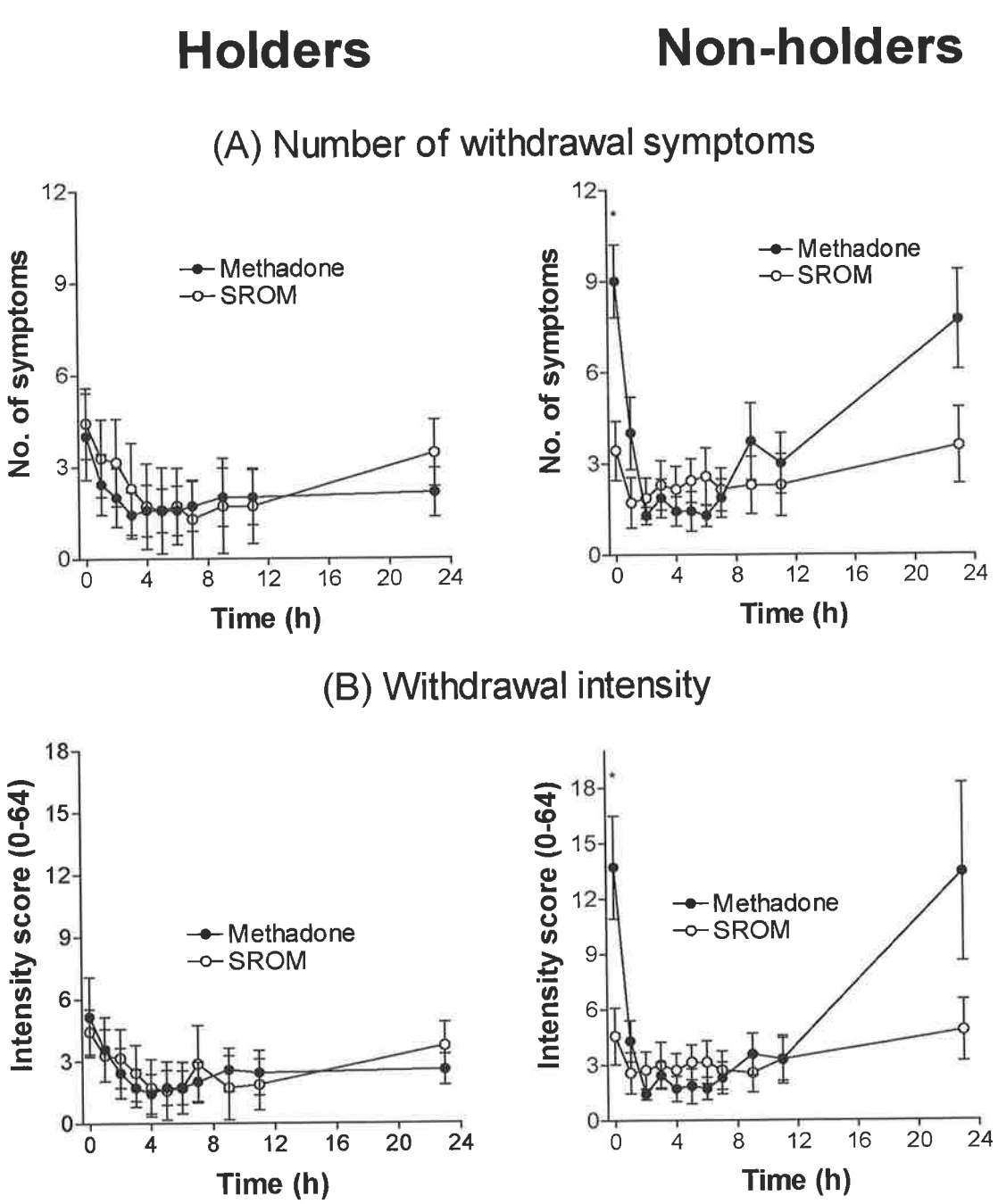

Figure 4-3. Opioid withdrawal during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. * p < 0.05 (methadone vs. SROM).

Repeated-measures ANOVA used to determine differences in subjective and physiological indices of opioid effect according to methadone holding status are summarised in Table 4-2. Significant maintenance drug × holding status × time since dosing interactions were evident for both the number and intensity of withdrawal symptoms. Analysed separately for each drug, a significant holding status × time since dosing interaction was found for methadone but not SROM. These results indicated that holders and non-holders showed significantly

different patterns of opioid withdrawal during methadone but not SROM maintenance. There were no main effects for holding status during either methadone or SROM maintenance. However, it should be noted that the differences between these two groups were pronounced at the end of the inter-dosing interval, whereas most assessments of withdrawal occurred during the middle and early stages of the inter-dosing interval, when withdrawal suppression was maximal for both groups.

Table 4-2. Repeated-measures ANOVA for subjective and physiological indices of opioid effects according to methadone holding status (n=14).

Effect[b]	Df	Pharmacodynamic responses[a]						
		WD Number	WD Intensity	Pupil Diam.	Respir. Rate	Heart rate	Systolic BP	Diastolic BP
		Within drug conditions						
Hold								
Methadone	1,12	1.61	2.32	0.06	0.02	0.60	0.15	0.07
SROM	1,12	0.00	0.16	0.30	2.49	2.38	1.37	1.07
Time × Hold								
Methadone	12,120	***5.70	***4.61	0.78	1.40	1.03	0.86	0.91
SROM	12,120	1.41	0.64	0.51	1.15	0.31	0.70	0.84
		Between drug conditions						
Drug × Hold	1,12	1.76	1.32	0.56	*6.37	2.39	1.92	2.59
Drug × Time × Hold	10,120	***4.78	***3.70	1.22	1.06	0.57	0.25	0.87

Values are F ratios. [a] Number of withdrawal (WD) symptoms; intensity of withdrawal symptoms; pupil diameter, respiration rate; heart rate; systolic blood pressure; diastolic blood pressure. [b] ANOVA effects were time since dosing (Time), methadone holding status (Hold) and the maintenance drug (Drug). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

In contrast to the marked differences in withdrawal patterns shown by holders and non-holders, physiological indices of opioid effect revealed less pronounced differences between these groups. Blood pressure and heart rate, as described above, were comparatively insensitive to change associated with administration of the maintenance dose. Pupil diameter and respiration rate were more informative regarding the time-course of opioid effects and are

contrasted according to methadone holding status for methadone and SROM in Figure 4-4. Declines in pupil diameter and respiration following dosing were evident for both holders and non-holders. Repeated-measures ANOVA indicated a significant holding status × maintenance drug interaction for respiration rate. For the holder group, mean respiration rate was marginally higher for SROM compared to methadone throughout the inter-dosing interval. For the non-holder group, mean respiration rate tended to be similar if not lower for SROM compared to methadone. There were no other significant effects for holding status on any physiological measure (Table 4-2).

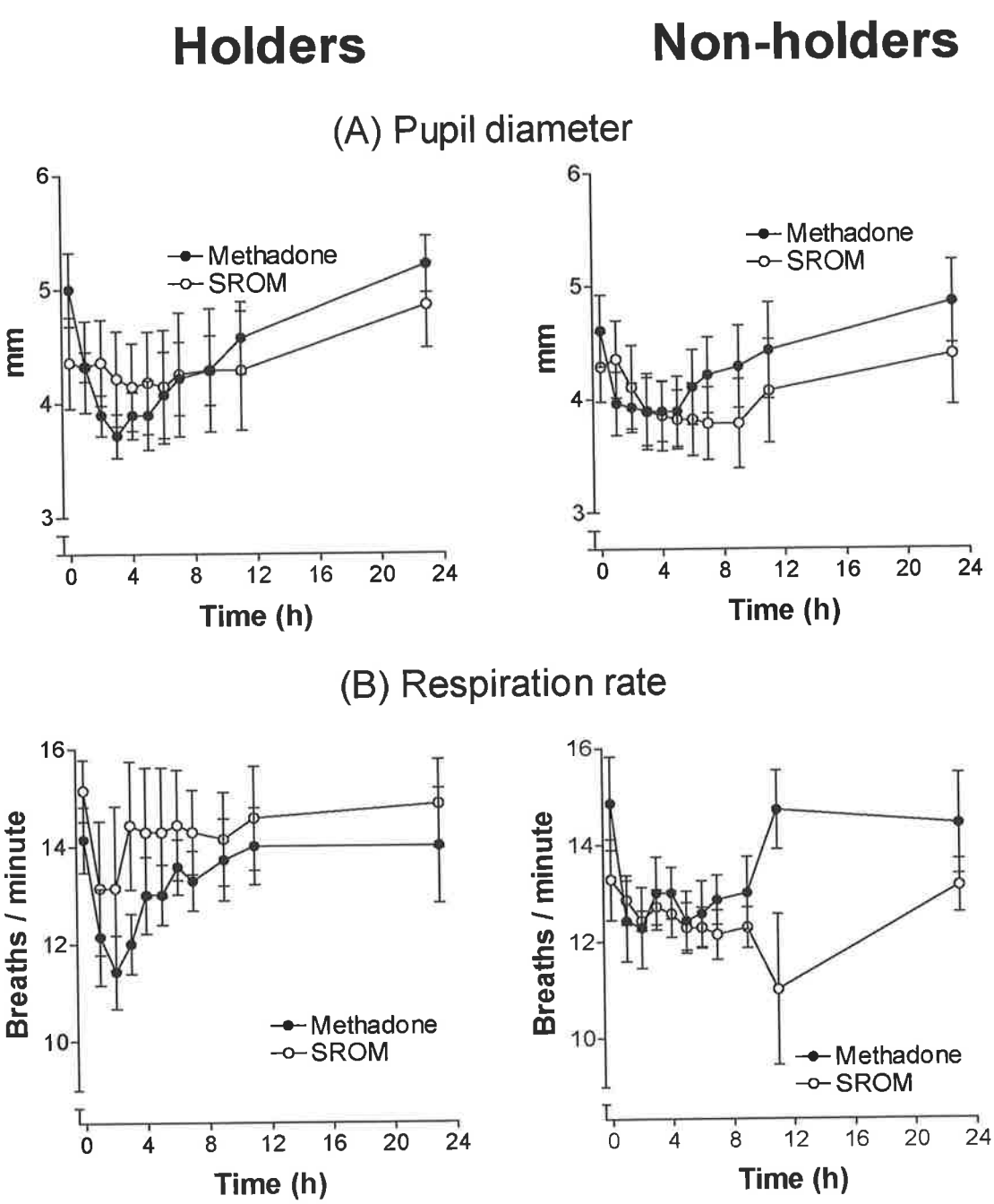

Figure 4-4. Pupil diameter and respiration rate during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone vs. SROM).

4.3.2. Frequency of symptoms complaints

The frequencies with which subjects reported specific symptom complaints on at least one occasion during the inter-dosing interval for methadone and SROM are presented in Table 4-3. During methadone maintenance, the most commonly reported symptoms were complaints of the methadone dose not-holding, runny nose, feeling tired, decreased appetite, sweating, hot flushes, and constipation, each of which were reported by greater than 79% of

the sample. It is particularly notable that 6 of the 7 holders, in addition to all 7 non-holders, reported that their dose was not holding them on at least one occasion during the methadone inter-dosing interval. More generally, it is also evident that the holder group, despite showing significantly less withdrawal than the non-holders, nonetheless experienced a high prevalence of symptom complaints whilst maintained on methadone. At the end of the SROM maintenance phase, 5 of the 14 subjects self-identified as SROM non-holders, including 3 methadone holders and 2 methadone non-holders.

The frequency of symptom complaints associated with methadone and SROM was strongly correlated across the 52 items in Table 4-3 ($r = 0.89$), indicating a highly similar overall pattern of symptom presentation for each drug. However, the overall frequency of symptom complaints was reduced for SROM compared to methadone. The number of MSC items reported by 50% or more of the sample was 27 for methadone compared to 15 for SROM. Symptoms that were reported with significantly greater frequency for methadone than SROM included the dose not-holding (13 vs. 7), hot flushes (11 vs. 5), decreased appetite (12 vs. 6), and blurred vision (7 vs. 1). No symptoms were reported with significantly greater overall frequency for SROM compared to methadone.

The mean total number of symptoms (out of 52) for SROM compared to methadone was similar for the holders (15.1 ± 8.9 vs. 17.6 ± 10.1, $t(6) = 1.34$, $p = 0.23$) but significantly less for the non-holders (18.4 ± 7.7 vs. 28.9 ± 8.8, $t(6) = 3.21$, $p = 0.02$). This indicates that reductions in symptom frequency for SROM were primarily attributable to the non-holder group. Specific symptoms reported more frequently by non-holders relative to holders during methadone maintenance, all of which were classified as withdrawal symptoms, included feelings of coldness (7 vs. 3), nervousness (6 vs. 2), aches and pains (6 vs. 2), and craving (6 vs. 1). During SROM maintenance, non-holders reported urinary urgency (5 vs. 0) and decreased appetite (5 vs. 1) at a significantly greater frequency than holders.

Table 4-3. Frequency of symptom complaints during a 24-hour inter-dosing interval for methadone and SROM: comparisons for all subjects (n=14) and the methadone holder (n=7) and non-holder (n=7) subgroups.

	Methadone			SROM		
	All	Holders	Nonholders	All	Holders	Nonholders
Opioid withdrawal						
Dose not-holding	***13**	6	7	***7**	4	3
Runny nose	**13**	6	7	**10**	5	5
Feeling tired	**12**	6	6	**10**	5	5
Sweating	**11**	4	7	**9**	5	4
Hot flushes	***11**	5	6	***5**	2	3
Yawning	**10**	5	5	**9**	4	5
Feelings of coldness	**10**	*3	*7	**10**	5	5
Nausea (feeling sick)	**9**	3	6	**9**	3	6
Feeling anxious	**9**	4	5	**7**	4	3
Nervousness	**8**	*2	*6	**4**	3	1
Aches and pains	**8**	*2	*6	**4**	2	2
Runny eyes	**7**	2	5	**5**	1	4
Tense muscles	**7**	2	5	**3**	3	0
Craving	**7**	*1	*6	**3**	1	2
Headache	**6**	3	3	**7**	3	4
Stomach cramps	**6**	2	4	**4**	3	1
Muscle spasms/twitching	**5**	1	4	**1**	1	0
Goose pimples	**5**	1	4	**4**	3	1
Salivation	**5**	3	2	**3**	1	2
Heart pounding	**3**	1	2	**1**	0	1
Diarrhoea	**1**	0	1	**0**	0	0
Direct opioid effects						
Constipation	**11**	6	5	**10**	6	4
Feel awake	**10**	5	5	**10**	4	6
Dry mouth	**8**	3	5	**8**	3	5
Trouble urinating	**7**	3	4	**6**	2	4
Need to urinate	**6**	2	4	**5**	*0	*5
Pleasant feeling in stomach	**5**	2	3	**5**	2	3
Itchy skin	**3**	1	2	**2**	0	2
Itchy nose	**3**	1	2	**2**	1	1
Swelling of feet or ankles	**2**	1	1	**2**	0	2
Feeling high	**2**	1	1	**2**	1	1
Mixed/Other						
Decreased appetite	***12**	5	7	***6**	***1**	***5**
Want to drink (not alcohol)	**9**	4	5	**9**	4	5
Feelings of weakness	**9**	4	5	**7**	3	4
Increased appetite	**8**	2	6	**5**	1	4
Trouble thinking clearly	**8**	4	4	**6**	3	3
Restlessness	**8**	3	5	**4**	3	1
Blurred vision	***7**	2	5	***1**	0	1
Feeling unhappy	**7**	2	5	**4**	2	2
Feeling irritable	**7**	2	5	**8**	4	4
Reduced desire for sex	**6**	2	4	**3**	2	1
Confusion	**5**	2	3	**1**	1	0
Vomiting	**3**	2	1	**1**	0	1
Chest pains	**2**	0	2	**0**	0	0
Bleeding gums	**2**	1	1	**3**	1	2
Numbness in hands or feet	**2**	0	2	**2**	1	1
Dizziness	**2**	0	2	**2**	1	1
Increased desire for sex	**2**	1	1	**3**	1	2
Hallucinations	**1**	0	1	**0**	0	0
Heartburn	**1**	0	1	**2**	1	1
Want to drink alcohol	**1**	0	1	**1**	0	1
Pain down left arm	**0**	0	0	**0**	0	0

Values are frequencies of subjects reporting symptom at least once. * $p < 0.05$ (methadone vs. SROM), * $p < 0.05$ (holders vs. non-holders). Symptom classification modified from (Dyer & White, 1997).

4.4.Discussion

The purpose of the present study was to compare the magnitude and duration of opioid effects and overall prevalence of symptom complaints following dosing for methadone and SROM. Subjective and physiological indices of opioid effect and treatment safety were measured throughout a 24-hour inter-dosing interval on one occasion for each drug after at least 4 weeks on a stable dose in 14 methadone maintenance patients. Results indicated that SROM was at least as effective as methadone in suppressing opioid withdrawal between doses and was associated with a lower overall incidence of symptom complaints. Different patterns of responses to methadone and SROM were evident for patients self-reporting adequate (holders) and inadequate (non-holders) withdrawal suppression whilst maintained on methadone prior to commencing the study. The holders showed a satisfactory level of withdrawal suppression for both methadone and SROM and a similar incidence of symptom complaints for each drug. By comparison, the non-holders showed significant reductions in both the severity of opioid withdrawal at the end of the inter-dosing interval and the overall incidence of symptom complaints for SROM relative to methadone.

Although preliminary investigations have indicated promising results for SROM when used as an alternative to methadone (Brewer, 1995; Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002; Sherman, 1996), its efficacy in suppressing withdrawal between doses in the absence of significant adverse effects has not been previously demonstrated. In the present study, the magnitude and duration of opioid effects during the inter-dosing interval was shown to be comparable for methadone and SROM. Consistent with hypothesis 1, subjective and physiological indices of opioid effect exhibited temporal patterns of change during the methadone and SROM inter-dosing intervals that were consistent with plasma concentrations for (R)-methadone and morphine presented in Chapter 3. These patterns were most clearly evident for subjective measures of the number and intensity of withdrawal symptoms and physiological measures such as pupil diameter and respiration rate. By comparison, blood pressure and heart rate appeared less sensitive to changes in plasma concentrations of the

maintenance drug. The finding that withdrawal severity and pupil diameter were reduced for SROM compared to methadone prior to dosing and similar in the hours immediately following dosing suggests the magnitude of opioid effect across the inter-dosing interval was at least as strong for SROM as for methadone. However, the temporal profile of opioid effects differed significantly for each drug, consistent with the significantly longer time associated with maximum plasma concentrations shown for morphine compared to (R)-methadone in Chapter 3 (6.5 hours vs. 2.5 hours).

To the extent that SROM is effective in producing prolonged opioid agonist effects for a 24-hour period, it is likely to be particularly advantageous as an alternative treatment option for patients experiencing inadequate withdrawal suppression whilst maintained on methadone. Consistent with this hypothesis, subjects self-identifying as methadone non-holders prior to the commencement of the study showed significant reductions in the severity of opioid withdrawal prior to dosing for SROM compared to methadone. Subjects self-identifying as holders at the commencement of the study showed a similarly satisfactory degree of withdrawal suppression for both drugs. Contrary to previous studies in methadone maintenance patients (Dyer et al., 1999), there was no apparent relationship between the maximal rate of decline and average withdrawal severity in the time from peak to trough plasma (R)-methadone and morphine concentrations. Since there are likely to be multiple factors contributing to withdrawal complaints, it is unlikely that any single pharmacokinetic factor (e.g., rate of maximal decline in plasma concentrations) will differentiate holders from non-holders.

In addition to considering the magnitude and duration of opioid effects during the inter-dosing interval, another major aim of the present study was to compare the overall prevalence of symptom complaints for methadone and SROM. Results indicated a high prevalence of symptom complaints during methadone maintenance, the most common being complaints of

the methadone dose not-holding, runny nose, feeling tired, decreased appetite, sweating, hot flushes, and constipation, each of which were reported by greater than 79% of the sample at some stage during the inter-dosing interval. Notably, a high prevalence of symptom complaints was evident for both the holders and non-holders, indicating that treatment outcomes may be compromised even amongst those reporting adequate withdrawal suppression between doses. It is especially noteworthy that 6 of the 7 subjects self-identifying as methadone holders, in addition to all 7 non-holders, reported the failure of their dose to hold on at least one occasion during the methadone inter-dosing interval. However, only 1 of the holders, compared to 6 of the non-holders, reported cravings at any stage during the inter-dosing interval. Other symptoms reported more frequently by the non-holders than the holders included feelings of coldness, nervousness, and aches and pains, all of which were classified as withdrawal symptoms. These findings are consistent with the observed differences in withdrawal severity during the inter-dosing interval for each group and suggest that non-holders are indeed characterised by a greater risk of relapse to illicit heroin use.

The overall pattern of symptom complaints for SROM maintenance was similar to that observed for methadone. This was evidenced by a strong correlation ($r = 0.89$) in the frequency with which the 52 symptom complaints considered in the present study were reported for each drug. Despite this similarity in the types of symptoms reported, the overall prevalence of complaints was reduced for SROM compared to methadone. The number of symptoms reported by at least 50% of the sample, for example, was 27 for methadone and 15 for SROM. Specific symptoms reported less frequently for SROM compared to methadone included the dose not holding, hot flushes, decreased appetite and blurred vision. No symptoms were reported significantly more frequently for SROM compared to methadone. Reductions in the mean total number of different symptom complaints for SROM compared to methadone were most clearly evident for the non-holders (18 vs. 29) compared to the holders (15 vs. 18).

In summary, SROM was a safe and efficacious alternative once-daily agonist option to methadone for maintenance treatment of opioid dependence in the 14 patients considered in this study. Subjects reporting adequate withdrawal suppression whilst maintained on methadone showed similar patterns of withdrawal and a similar prevalence of symptoms complaints during the inter-dosing interval for both methadone and SROM. Conversely, subjects reporting inadequate withdrawal suppression whilst maintained on methadone showed significant reductions in both the severity of opioid withdrawal prior to dosing and the overall prevalence of symptom complaints whilst maintained on SROM. The high prevalence of symptom complaints evident for both these groups indicates that treatment outcomes may be compromised even when adequate withdrawal suppression is achieved. In the treatment of pain management, switching the patient to an alternative opioid is often found to be an effective means of ameliorating idiosyncratic side effects (Levy, 1996). Thus, whilst the advantages of SROM were most clearly evident for the non-holders in the present study, it may nonetheless possess significant clinical utility as an alternative for patients who show significant adverse effects despite adequate withdrawal suppression on methadone. Moreover, it should be noted that although 5 subjects classified themselves as non-holders during the SROM maintenance phase (i.e., approximately one third of the subjects), only 2 of these also reported non-holding whilst maintained on methadone. Thus, if subjects were to be given the choice between methadone and SROM, the percentage of the subjects considered in this study that would experience inadequate withdrawal suppression would decrease from 50% to 14%. These findings provide justification for further large-scale evaluations of SROM maintenance using double-blind methodologies and standard treatment outcome indicators.

5. MOOD STATES DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SROM

5.1.Introduction

Mood is an integral factor in the aetiology and treatment of opioid dependence. The rewarding mood effects associated with acute administration of heroin and other opioids, particularly by the intravenous route, play an important role in the initiation and maintenance of opioid-seeking behaviour (van Ree et al., 1999). Cellular and synaptic adaptations that accompany repeated exposure to opioids contribute to a modification of users' affective responses to the drug over time and the need for pharmacological intervention (Williams et al., 2001). These include the development of tolerance, whereby increasing doses of opioids are needed to achieve the same degree of positive mood effects, and physical dependence, whereby abstinence leads to the manifestation of opioid withdrawal symptoms. Opioid withdrawal is characterised by the occurrence of negative mood states (e.g., dysphoria, depression, irritability) that promote further compensatory drug use and increase the risk of relapse to heroin use during detoxification and other treatment episodes (Calsyn et al., 2000; Kanof et al., 1993; Krueger, 1981; Powell et al., 1992; Unnithan et al., 1992). To this extent, normalisation of mood states is an important objective during pharmacological interventions for opioid dependence and thus a vital consideration in the evaluation of new maintenance pharmacotherapies.

Although methadone facilitates normalisation of mood disturbance associated with opioid withdrawal in the majority of patients, other aspects of its pharmacokinetic and pharmacodynamic profile may have negative affective consequences. This includes evidence that significant fluctuations in mood states occur during the inter-dosing interval in response to fluctuating plasma methadone concentrations (Dyer et al., 2001; Eissenberg et al., 1999; Hiltunen et al., 1999), particularly amongst patients reporting inadequate withdrawal suppression between doses (Dyer et al., 2001; Hiltunen et al., 1999), and that chronic

exposure to opioids may be associated with a shift towards dysphoric mood states (Fraser et al., 1963; Griffith et al., 1968; Martin & Jasinski, 1970; Martin et al., 1973; McNamee et al., 1976; Mirin et al., 1976a; Mirin et al., 1976b; Wikler, 1952). In addition, methadone has multiple mechanisms of action other than those mediated by mu opioid receptors, including its actions as an NMDA antagonist (Ebert et al., 1998; Gorman et al., 1997) and inhibitor of serotonin and noradrenaline re-uptake (Codd et al., 1995), which may also have significant consequences for mood. As an alternative once-daily agonist option to methadone, SROM has different pharmacokinetic and pharmacodynamic properties that may result in a different pattern of affective responses, which have yet to be determined. The present study examined patterns and determinants of mood states for methadone and SROM during the inter-dosing interval, and begins with a review of the literature regarding the effects of methadone and other opioids on mood state.

5.1.1. Effects of methadone and other opioids on mood state

Affective problems have been cited as both a cause and a consequence of opioid dependence and other substance abuse disorders (Ward et al., 1998b). The occurrence of negative mood states, for example, is both an antecedent of opioid seeking behaviour (Kanof et al., 1993) and a consequence of the many pressures associated with an opioid dependent lifestyle (Krueger, 1981). Although causality is sometimes difficult to establish, the relationship between opioid use and affective disorders is clear. Based on population surveys in the United States, it has been demonstrated that in comparison to the general population, opioid dependent individuals are estimated to be many times more likely to be diagnosed with affective disorders (odds ratio = 5), anxiety disorders (odds ratio = 2.8), and psychiatric disorders in general (odds ratio = 6.7) (Ward et al., 1998b).

Although methadone maintenance is primarily an intervention for the physiological facets of opioid dependence, it is also associated with a reduction in the prevalence and severity of affective disorders during treatment (Callaly et al., 2001). These benefits may derive from

both pharmacological (e.g., suppression of opioid withdrawal) and non-pharmacological (e.g., provision of counselling) facets of treatment. In spite of these improvements, methadone maintenance patients continue to show a number of affective abnormalities that may compromise treatment outcome. Of further concern, however, is evidence that these abnormalities are partly attributable to the pharmacokinetic and pharmacodynamic properties of methadone itself. In the following sections, pharmacological characteristics of methadone that may impact negatively on mood states in some patients are discussed.

5.1.2. Short-term mood effects associated with methadone administration

Numerous studies have shown that administration of oral methadone in methadone maintenance patients is associated with significant changes in mood states. These mood changes have been shown to correlate with fluctuations in plasma methadone concentration (Dyer et al., 2001; Hiltunen et al., 1999), which normally increases approximately 2-fold in the first 2 to 3 hours following dosing (Foster et al., 2000). In an early study, Price et al. (1975), using the Profile of Mood States, examined the effects of methadone (dose range 20-40 mg) on mood states in 49 opioid users upon commencement of a methadone detoxification program. Significant reductions in negative mood states such as Depression and Anxiety (approximately 70%) and increases in positive mood states such as Vigour (approximately 70%) were observed within 45 minutes of methadone administration.

Other studies have demonstrated that acute changes in mood states also occur amongst stabilised methadone patients and the degree of mood change is related to the adequacy of withdrawal suppression achieved between doses. Hiltunen et al. (1999) compared the acute effects of methadone on mood states in two groups of methadone maintenance patients reporting satisfaction (n = 25) and dissatisfaction (n = 25) with the adequacy of withdrawal suppression achieved with their dose. In the first 8 hours following methadone dosing, subjective ratings of well-being were relatively stable in the satisfied group but showed

significant temporal changes in the dissatisfied group. These changes were correlated with fluctuations in plasma methadone concentrations.

More recently, Dyer et al. (2001) examined mood changes in methadone maintenance patents across an entire 24-hour inter-dosing interval and found a similar relationship between the adequacy of withdrawal suppression achieved and the degree of mood change between doses. In their study, eighteen methadone maintenance patients reporting adequate (holders, n = 9) or inadequate (non-holders, n = 9) withdrawal suppression between doses completed the Profile of Mood States (POMS) on 11 occasions over 24 hours following administration of the daily maintenance dose. Negative mood states were maximal prior to dosing and minimal at the times corresponding to peak plasma methadone concentrations (2-4 hours post-dose). Conversely, scores for Vigour, the only positive mood scale included in the POMS, showed a nadir prior to dosing and were maximal at the time of peak plasma methadone concentration. The degree of mood change was also related to the withdrawal status of the patient, such that non-holders showed considerably greater change in mood states during the inter-dosing interval compared to holders. In comparison to the methadone maintenance patients, a control group comprising drug-free volunteers showed no such evidence of significant mood change over the 24 hour period.

The occurrence of clinically significant mood changes amongst methadone maintenance patients in response to fluctuations in plasma methadone concentrations following dosing is of concern for a number of reasons. Firstly, inconsistent and negative mood states are likely to make patients less amenable to counselling and other forms of psychosocial support (Woody et al., 1984) and may impair their capacity to function effectively in personal relationships. Second, mood changes may make patients more vulnerable to drug cravings and hence poorer outcomes from treatment. Negative mood states associated with opioid withdrawal have been frequently associated with an increased risk of relapse to heroin use (Calsyn et al., 2000;

Kanof et al., 1993; Krueger, 1981; Powell et al., 1992; Unnithan et al., 1992). Even positive opioid-induced mood changes and the relief of heroin withdrawal are associated with increased craving. Curran et al. (1999) examined heroin cravings in 18 methadone maintenance patients pre and pose dose after either a 33% increase in their dose or the administration of a placebo, using a double-blind, crossover design. Additional methadone increased positive (expected positive effects) and negative (expected relief of withdrawal) cravings for heroin.

The lack of mood consistency achievable with once-daily oral methadone dosing in some patients is also problematic because of limitations associated with the alternative treatment strategies currently available for addressing this problem. Increasing the methadone dose to provide greater suppression of negative mood states associated with opioid withdrawal may be effective in some cases, but risks exacerbating mood change and other adverse effects (e.g., respiratory depression, sedation) (Kreek, 1973) associated with peak plasma methadone concentrations. These problems may be countered by using a shorter methadone inter-dosing interval, resulting in a more consistent opioid effect between doses (Nilsson et al., 1983), but this option is impractical in patients for whom supervised dosing is required. As outlined in Chapter 1, transferring patients to other long-acting maintenance medications such as buprenorphine and LAAM is also not always permissible. For these reasons, the identification of alternative strategies for facilitating consistency of mood states between doses is desirable.

5.1.3. Long-term mood effects associated with methadone administration

A second way in which methadone may deleteriously impact on patients' mood status during maintenance treatment for opioid dependence concerns the long term effects of chronic exposure to methadone and other opioids on mood states. Although the acute effects of opioid agonists on mood are frequently positive and include euphoria, it is often suggested that long-term exposure to such drugs is associated with the development of generalised dysphoric state

(Fraser et al., 1963; Griffith et al., 1968; Martin & Jasinski, 1970; Martin et al., 1973; McNamee et al., 1976; Mirin et al., 1976a; Mirin et al., 1976b; Wikler, 1952). This suggestion is consistent with the knowledge that chronic opioid exposure is associated with cellular and synaptic adaptations that include dysfunction of the mu opioid receptor system, which is known to be important in the endogenous regulation of mood states (Williams et al., 2001). Although evidence for the association between chronic opioid use and dysphoria is partly anecdotal (Gold & Johnson, 1998), there have been several attempts to investigate this phenomenon in experimental settings.

Wikler (1952) described a single-case in which a detoxified opioid user was allowed access to increasing dose of intravenous morphine over a three-month period, without having to perform any operant task. Chronic morphine exposure produced increasing dysphoria, irritability, anxiety, guilt and paranoid thinking. Similar affective changes were reported in a study by Griffith et al. (1968) in which two subjects could earn intramuscular doses of morphine for performing a lever pressing task, first while the subjects were maintained on morphine and subsequently whilst maintained on methadone. The amount of morphine given for performing the task was varied to simulate a "conflict environment". The authors reported that the subjects' affective state appeared despondent and inhibited, even when they were supplied with large doses of morphine.

In two other studies, opioids were administered on a fixed-dose, fixed-interval schedule. Fraser et al. (1963) studied five patients, who were administered doses of heroin that increased from a mean dose of 10 mg per day at the start of the study to 95 mg on day eighteen, before remaining at these levels for another six weeks. Martin and Jasinski (1970) administered morphine to ten subjects, with doses ranging up to 240 mg per day over a long period. In both studies, increasing doses of the opioids were associated with reductions in motivation, increased irritability in social situations, and hypochondria.

Martin et al. (1973) subsequently reported on six subjects who were chronically administered methadone in increasing doses, reaching a stable dose of 100 mg by the 7th week, which was maintained for a subsequent 8 week period. Whereas the acute effects of methadone included euphoria, chronic dosing was associated with increased dysphoria, lethargy, and sedation, and reduced motivation. Haertzen and Hooks (1969) examined the subjective effects of opioids in volunteers and similarly found that chronic opioid administration was less euphoric than acute administration.

Two related studies reported by Mirin et al. (1976a) and McNamee et al. (1976) involved the administration of increasing intravenous doses of heroin in a largely unregulated fashion. The early effects of heroin were to produce relief from tension and euphoria, but this gradually shifted towards increasing dysphoria over the ten day duration of the study. Notably, heroin continued to induce brief improvements in mood following dosing throughout this shift towards dysphoric mood states.

These studies suggest that chronic opioid exposure is associated with a shift towards more dysphoric and depressed mood states, in contrast to the positive and often euphoric mood changes associated with acute opioid use. This pattern is consistent with evidence that methadone maintenance patients exhibit a greater degree of mood disturbance and affective disorders in comparison to normal population (Callaly et al., 2001; Dyer et al., 2001). In contrast to this pattern of findings, a study that featured psychiatric examinations of 26 opiate-using veterans over a six-year period found no significant changes in psychopathology (Mc Lellan, Woody & O'Brien, 1979). However, the significance of this finding is difficult to determine given the observational nature of the study design, which allowed for variable and self-determined exposure to opiates and other drugs during the course of the study. Although many factors may contribute to mood deficits (e.g., genetic, environmental), it is nonetheless

evident that pharmacological factors may also be involved. An important clinical implication of this possibility is that even patients reporting adequate withdrawal suppression whilst maintained on methadone may nonetheless be predisposed towards negative mood states and thus vulnerable to poorer treatment outcomes.

5.1.4. Mood effects associated with non-opioid mechanisms of methadone action

A third aspect of methadone's pharmacological profile that may impact negatively on patients' mood states during maintenance treatment for opioid dependence relates to its non-opioid mechanisms of action. In addition to its primary actions that are mediated by the mu opioid receptor system, methadone influences several other neurotransmitter systems that are known to have important functional roles in regulating mood. These include the actions of methadone as an inhibitor of the neuronal uptake of monoamines including serotonin and noradrenaline (Codd et al., 1995) and as a non-competitive NMDA antagonist (Ebert et al., 1998; Gorman et al., 1997).

Inhibition of serotonin and noradrenaline uptake is associated with antidepressant effects and may also contribute to the antinociceptive and withdrawal suppressing capacity of methadone (Akaoka & Aston-Jones, 1993; Codd et al., 1995; Ressler & Nemeroff, 2000). The *in vitro* potency of clinically used antidepressants that selectively inhibit the re-uptake of serotonin (e.g., fluoxetine, Ki = 31 nM/L) and noradrenaline (e.g., reboxetine, Ki = 11 nM/L) (Wong et al., 2000) is significantly greater than the demonstrated potency of (R)- (Ki of 140 and 702 nM/L) and (S)- (Ki of 992 and 12700 nM/L) methadone as inhibitors of each of these two neurotransmitters, respectively (Codd et al., 1995). The clinical significance of these actions in relation to mood responses in methadone maintenance patients is therefore unclear.

NMDA antagonists have been associated with the attenuation of opioid dependence in animal models (Bisaga & Popik, 2000), but clinical use of such drugs has been impeded because of

adverse affective and cognitive disturbances observed in healthy volunteers, patients and recreational users, which sometimes resemble the symptoms of schizophrenia (Abi-Saab et al., 1998; Adler et al., 1999; Curran & Monaghan, 2001; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996). The capacity of methadone to inhibit binding of the NMDA ligand MK-801 *in vitro* (Ki of 3.4 and 7.4 μM/L for (R)- and (S)-methadone, respectively) is similar to that observed for established NMDA antagonists such as dextromethorphan (Ki = 5.0 μM/L) (Gorman et al., 1997). To this extent, the NMDA antagonist actions of methadone may potentially have clinically significant negative affective consequences during maintenance treatment for opioid dependence.

5.1.5. Mood effects associated with variability in plasma concentrations of (R)- and (S)-methadone

Another pharmacological characteristic of methadone that may adversely influence mood responses during maintenance treatment, which is related to its non-opioid mechanisms of action, concerns possible differences in the affective profiles of (R)- and (S)-methadone. Compared to (S)-methadone, (R)-methadone shows approximately 10-fold greater affinity for the mu opioid receptor (IC_{50} of 3.0 and 26.4 nM, respectively) (Kristensen et al., 1996) and 50-fold greater analgesic potency in man (Scott et al., 1948). Although the opioid effects of racemic methadone are thus attributed almost entirely to the (R)-methadone, both enantiomers show significant *in vitro* potency as NMDA antagonists, as described above (Gorman et al., 1997). Indeed, *in vivo* animal studies have shown that (S)-methadone produces significant antinociception and attenuation of morphine tolerance as a result of its NMDA antagonist characteristics (Davis & Inturrisi, 1999; Shimoyama, Shimoyama, Elliott, & Inturrisi, 1997). To the extent that NMDA antagonists have been associated with adverse mood responses (Abi-Saab et al., 1998; Adler et al., 1999; Curran & Monaghan, 2001; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996), (S)-methadone may thus have clinically significant and potentially adverse effects on mood states in methadone maintenance patients.

Evidence for different mood responses to (R)- and (S)-methadone has also been found in human studies. Administered alone in high doses (>1000 mg), (S)-methadone has been shown to produce some effects consistent with opioid activity (e.g., respiratory depression, miosis, sedation), but subjects denied having subjectively satisfying sensations and all disliked the effects (Fraser & Isbell, 1962). Moreover, chronic administration of (S)-methadone was associated with a shift towards increasingly negative subjective and symptomatic responses including nervousness, confusion, depression, insomnia, vomiting, disturbing dreams, and hallucinations (Fraser & Isbell, 1962). Other studies have reported similarly unpleasant reactions to (S)-methadone such as dizziness, sedation, and an inability to concentrate, and lethargy (Olsen et al., 1977; Scott et al., 1948).

The possibility that (S)-methadone produces clinically significant and potentially adverse effects on mood states is significant given that plasma concentrations of (R)- and (S)-methadone vary considerably between individuals (Eap et al., 1996; Hiltunen et al., 1999) and within individuals during the inter-dosing interval (Foster et al., 2000). Individual variability in the enantiomeric ratio may thus be associated with variability in mood responses, such that a relatively greater exposure to (S)- compared to (R)-methadone may be associated with a more negative profile of mood responses. To date, no published studies have examined the relationship between relative exposure to (R)- and (S)-methadone and subjective responses amongst patients maintained on racemic methadone.

5.1.6. Summary

The evidence reviewed above suggests that the pharmacokinetic and pharmacodynamic properties of methadone have a number of potentially problematic affective consequences. Clinically significant changes in mood status occur during the inter-dosing interval in response to fluctuating plasma methadone concentrations (Dyer et al., 2001; Hiltunen et al., 1999), particularly in patients reporting the failure of their dose to adequately suppress withdrawal between doses (Dyer et al., 2001; Hiltunen et al., 1999). Such changes are likely

to make patients less amenable to counselling (Woody et al., 1984) and more vulnerable to heroin cravings (Calsyn et al., 2000; Kanof et al., 1993; Krueger, 1981; Powell et al., 1992; Unnithan et al., 1992). To the extent that chronic opioid exposure results in a shift towards negative mood states (McNamee et al., 1976; Mirin et al., 1976a; Mirin et al., 1976b), even patients reporting adequate withdrawal suppression may be at risk of experiencing negative mood states and a drive to engage in compensatory drug use. Moreover, to the extent that (S)-methadone produces a clinically significant and potentially adverse profile of mood effects distinct from that of (R)-methadone (Fraser & Isbell, 1962; Olsen et al., 1977; Scott et al., 1948), individual variability in the enantiomeric ratio (Eap et al., 1996; Foster et al., 2000; Hiltunen et al., 1999) may result in a more negative profile of mood responses amongst those showing relatively greater exposure to (S)- compared to (R)-methadone. Collectively, these factors suggest that racemic methadone may produce undesirable patterns of mood response in some patients for whom alternative treatment strategies may facilitate greater normalisation of mood states.

Although SROM has purported efficacy as an alternative to methadone for maintenance treatment of opioid dependence (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), its effects on patients' mood states are yet to be investigated. The pharmacokinetic and pharmacodynamic profile of SROM differs from methadone in a number of ways that may have important affective consequences. Firstly, since the time-course of plasma concentrations following dosing differs for methadone and SROM (Foster et al., 2000; Gourlay et al., 1997), each drug is likely to show a different time-course of mood changes during the inter-dosing interval. Second, to the extent that SROM may provide more effective suppression of withdrawal in patients reporting the failure of their dose to hold whilst maintained on methadone (see Chapter 4), this may facilitate greater stability of mood between doses. Third, unlike methadone, morphine does not inhibit the binding of NMDA receptor ligands or the reuptake of serotonin and noradrenaline (Ebert et al., 1998; Gorman et

al., 1997). It further differs from methadone by showing somewhat less selectivity for the mu over the delta and kappa opioid receptors (Codd et al., 1995) and by showing reduced intrinsic efficacy at the mu opioid receptor (Adams et al., 1990). Each of these factors may result in qualitative and quantitative differences in the patterns of mood states associated with methadone and SROM during the 24-hour inter-dosing interval.

5.1.7. The present study

The present study compared mood states during the inter-dosing interval for methadone and SROM in a crossover study of opioid dependent individuals receiving methadone maintenance treatment for opioid dependence. The study included methadone maintenance patients reporting adequate (holders) and inadequate (non-holders) withdrawal suppression between doses and featured the repeated measurement of mood states throughout a 24-hour inter-dosing interval for each drug. As reported in Chapter 3, plasma drug concentrations for (R)- and (S)-methadone and morphine were collected at each measurement time and were used to characterise the pharmacokinetic basis for patterns of observed mood responses.

5.1.7.1. Aims

- To determine whether the intensity and temporal pattern of mood states during the 24-hour inter-dosing interval differs for methadone and SROM.
- To determine whether the intensity and temporal pattern of mood states during the dosing interval for methadone and SROM differs for methadone holders and non-holders.
- To characterise the pharmacological basis of any such differences in pharmacodynamic responses to methadone and SROM.

5.1.7.2. Hypotheses

1. The intensity and temporal pattern of mood states will be consistent with plasma concentration-time profiles for (R)-methadone and morphine.

2. The intensity and temporal pattern of mood states will be proportional to the severity of opioid withdrawal.

5.2.Methods

5.2.1. Subjects and procedures

The subjects and general procedures for this aspect of the study were described in Chapter 2. Affective responses for methadone and SROM during a single 24-hour inter-dosing interval were contrasted in fourteen opioid-dependent volunteers undergoing maintenance treatment after at least 4 weeks on a stable dose of each drug in an open-label, randomly-ordered, crossover design. Measures of affective states were administered on 11 occasions at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, and 23 hours after administration of the maintenance dose.

5.2.2. Measures

At each of the above times, subjects completed the following questionnaire measures of affective responses. The Profile of Mood States (POMS) (McNair et al., 1971) consists of 65 adjectives that are rated on a scale from 0 (not at all) to 4 (extremely), according to how subjects feel. These items yield scores on subscales measuring six distinct affective states (ranges in parentheses): Tension (0-36), Anger (0-48), Depression (0-60), Vigour (0-32), Fatigue (0-28), and Confusion (0-28). With the exception of Vigour, high scores indicate negative affective states. The Total Mood Disturbance (TMD) scale provides a global assessment of affective state and is calculated by adding the subscales scores with Vigour weighted negatively. TMD ranges from –32 to 200 such that high scores indicate more negative mood states.

In addition to the POMS, subjects completed a questionnaire containing two subscales from the Addiction Research Centre Inventory (Haertzen & Hickey, 1987). The Morphine Benzedrine Group (MBG) scale is an empirically derived measure of euphoric drug effects comprising 16 statements for which subjects indicate true or false according to whether the statement accurately describes how they feel. This yields a score ranging from 0 to 16 such that high scores indicate a greater degree of euphoria. The Morphine Group (MG) scale is a

measure of subjective drug effects thought to be specific to morphine and comprises 8 statements that are rated in the same manner as described for the MBG. These ratings are similarly summed to yield a score from 0 to 8.

5.2.3. Statistical analyses

Repeated-measures ANOVA was used to examine the effects of the maintenance dose, the time since dosing and methadone holding status on mood responses. Comparisons of mood responses according to the maintenance drug and the time since dosing (peak vs. trough comparisons) were made using paired t-tests. The degree of association between paired variables was examined using scatter plots, linear regression and both Pearson and Spearman correlation coefficients. Cronbach's alpha was used to assess the internal consistency of the POMS scales. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). An alpha level of 0.05 was used for all analyses. Data are presented as mean ± SD (range) unless otherwise indicated.

5.3.1. Mood states during the inter-dosing interval

5.3.1.1. Comparisons for all subjects

Temporal patterns for Total Mood Disturbance during the inter-dosing interval for methadone and SROM are shown in Figure 5-1. Mean Total Mood Disturbance was maximal prior to dosing for both drugs and showed decreases following dosing that were consistent with changes in plasma concentrations of (R)-methadone and morphine (Chapter 3). For methadone, mean Total Mood Disturbance declined from 27 prior to dosing to a minimum of 11 at 3 hours post-dose. For SROM, Total Mood disturbance declined from a mean of 21 prior to dosing to a minimum of 13 at 7 hours post-dose.

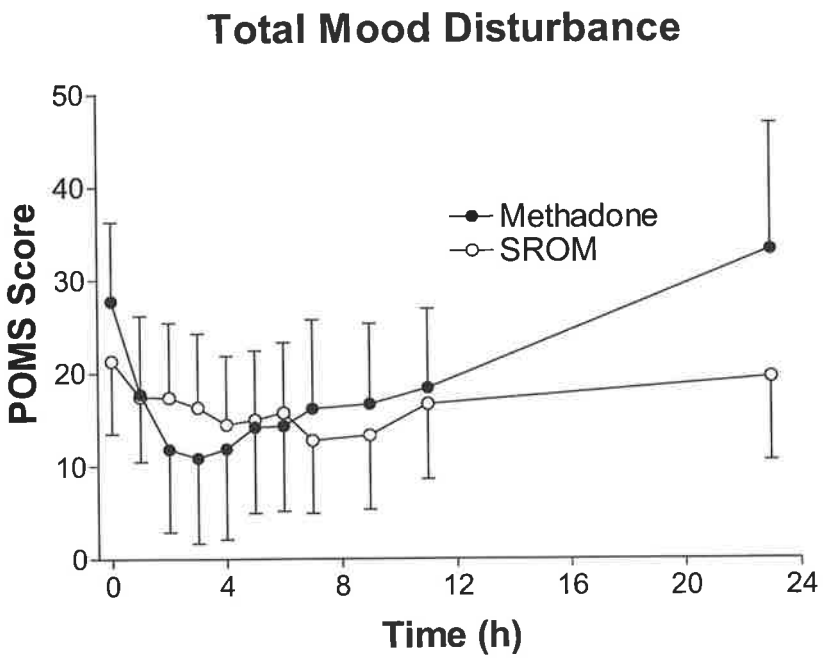

Figure 5-1. Total Mood Disturbance scores for the Profile of Mood States during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone vs. SROM).

Repeated-measures used to investigate the effects of the maintenance drug and the time since dosing for each of the POMS scales are summarised in Table 5-1. For Total Mood Disturbance, there was no main effect for maintenance drug, reflecting similar overall levels for methadone and SROM. However, a significant maintenance drug × time since dosing

interaction was found, such that the change in Total Mood Disturbance during the inter-dosing interval was significant for methadone but not SROM.

Table 5-1. Repeated-measures ANOVA for the Profile of Mood States (n=14).

		POMS scale						
	Df	TMD	Tension	Anger	Depress	Fatigue	Confus.	Vigour
Effect[a]		Within drug conditions						
Time								
Methadone	10,130	**2.37	**4.13	1.21	1.42	**2.12	1.25	*2.16
SROM	10,130	1.54	1.39	*2.27	1.37	0.27	*2.11	0.87
		Between drug conditions						
Drug	1, 13	0.24	0.50	1.65	1.59	0.01	0.23	3.38
Drug × Time	10,130	*2.08	*2.12	0.76	1.27	1.76	0.42	**2.18

Values are F ratios. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] ANOVA effects were time since dosing (Time) and the maintenance drug (Drug). TMD = Total Mood Disturbance. Conf. = Confusion.

Temporal patterns for the POMS subscales during the inter-dosing interval for methadone and SROM are shown in Figure 5-2. The patterns of change observed for each of the negative POMS subscales was similar to that observed for Total Mood Disturbance, in that the rate and degree of decline in mean levels following dosing tended to be less marked for SROM compared to methadone. Mean POMS scores reached minimal levels more rapidly following dosing for methadone compared to SROM for Tension (3 h vs. 7 h), Anger (2 h vs. 9 h), Depression (2 h vs. 9 h), and Confusion (2 h vs. 7 h), and with equivalent rapidity for Fatigue (4 h vs. 4 h). At these times the degree of decline in mean scores relative to baseline was slightly greater for methadone compared to SROM for Tension (5.0 vs. 1.9), and Depression (3.1 vs. 1.9), Fatigue (2.4 vs. 0.9), and Confusion (2.1 vs. 1.8), and slightly less for Anger (0.9 vs. 3.0). An inverse pattern was evident for the positive Vigour scale. Mean Vigour scores peaked earlier (2 h vs. 9 h) and at higher levels relative to baseline (2.7 vs. 0.1) for methadone compared to SROM, with very little temporal change evident for the latter during the inter-dosing interval.

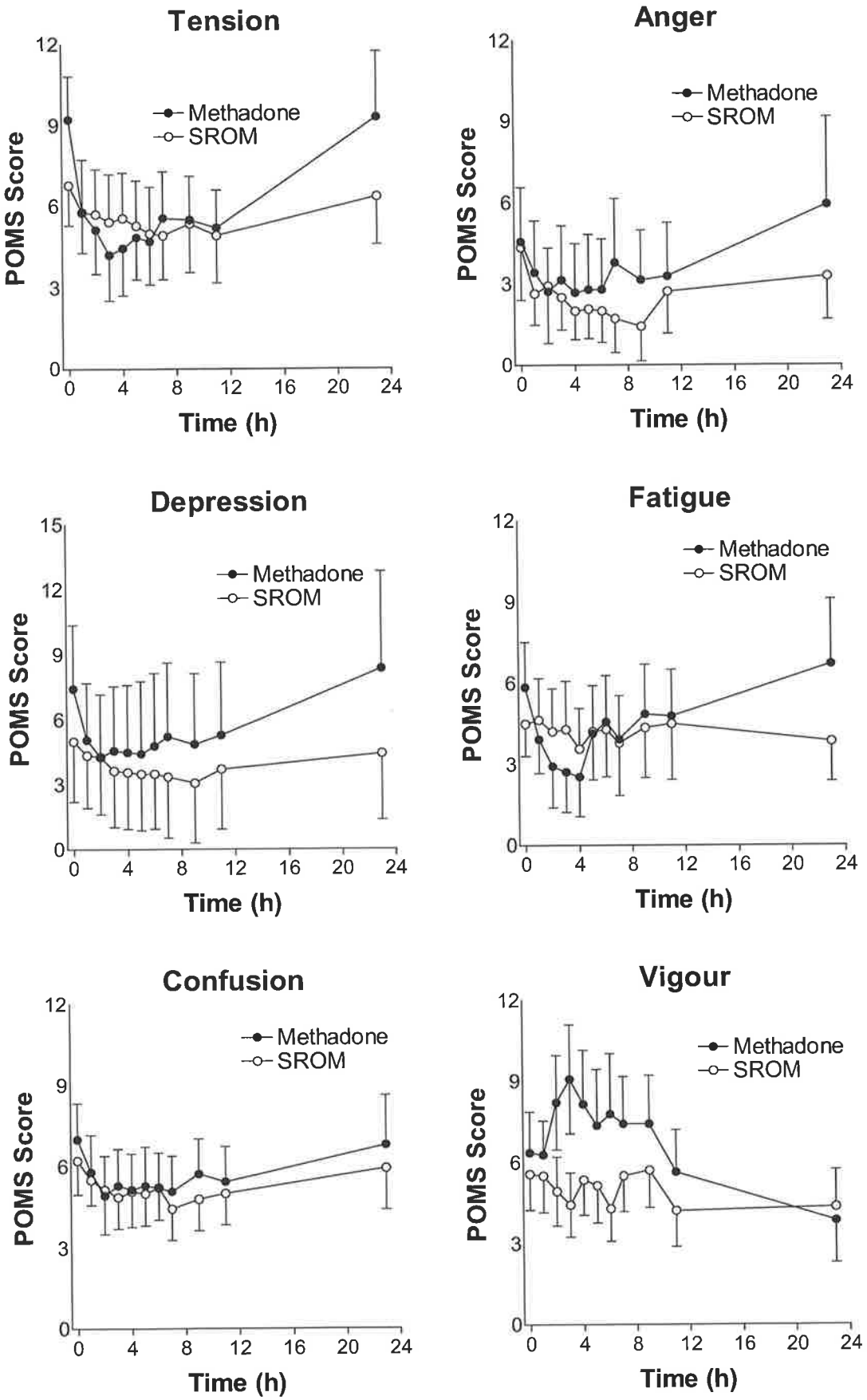

Figure 5-2. Profile of Mood States scores during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone vs. SROM).

Temporal patterns of change for the MBG and MG scales are presented in Figure 5-3. These data indicate the magnitude of subjectively positive opioid effects was very low overall for both drugs and did not show clinically significant change during the inter-dosing interval. Although mean scores for MBG tended to be slightly higher post-dose relative to baseline, the magnitude of these increases was negligible. Temporal patterns for the MG scale showed no discernible changes in response to fluctuating plasma concentrations for (R)-methadone or morphine.

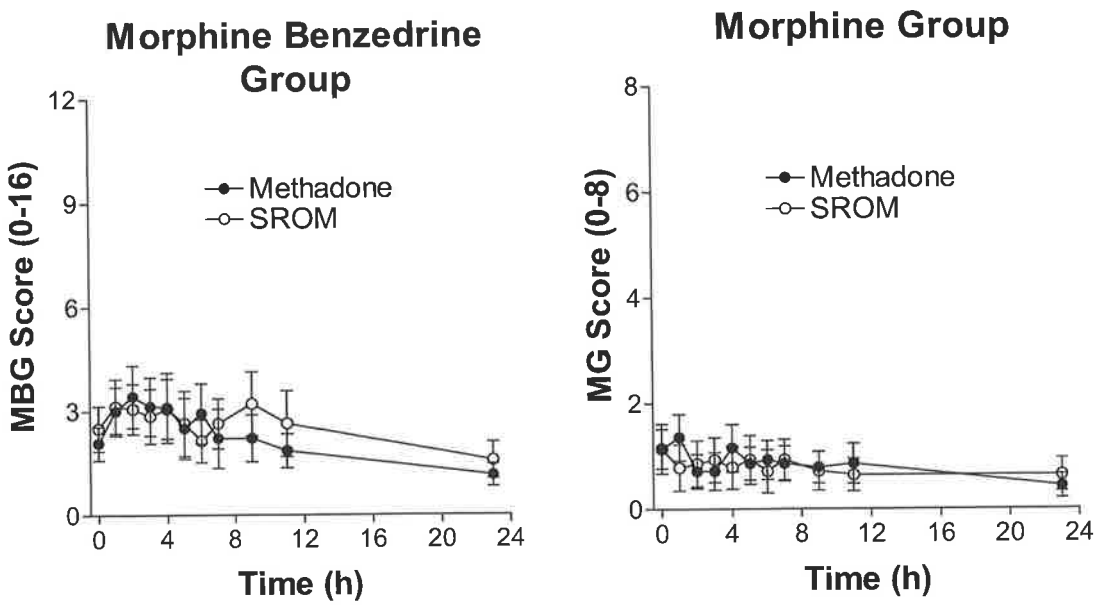

Figure 5-3. Morphine Benzedrine Group and Morphine Group scale scores from the Addiction Research Centre Inventory during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean ± SE. p > 0.05 for all differences (methadone vs. SROM).

5.3.1.2. Comparisons for methadone holders and non-holders

Temporal patterns for Total Mood Disturbance and Tension during the inter-dosing interval for methadone and SROM are contrasted for methadone holders and non-holders in Figure 5-4. These data indicate that the observed differences between methadone and SROM in the temporal profiles for Total Mood Disturbance (Figure 5-1) and Tension (Figure 5-2) were predominantly due to the non-holder group. The holders showed similar and relatively stable mood patterns for both methadone and SROM, characterised by small declines (minimal levels compared to baseline) in Total Mood Disturbance (9.3 vs. 9.3) and Tension (3.9 vs.

2.3) for each drug. By comparison, the non-holders showed much greater mood fluctuations for methadone compared to SROM, as evidenced by a greater degree of decline following dosing in mean scores for both Total Mood Disturbance (26 vs. 10) and Tension (7.0 vs. 2.0). These findings indicate a relationship between the severity of opioid withdrawal (Chapter 4) and mood responses during the inter-dosing interval.

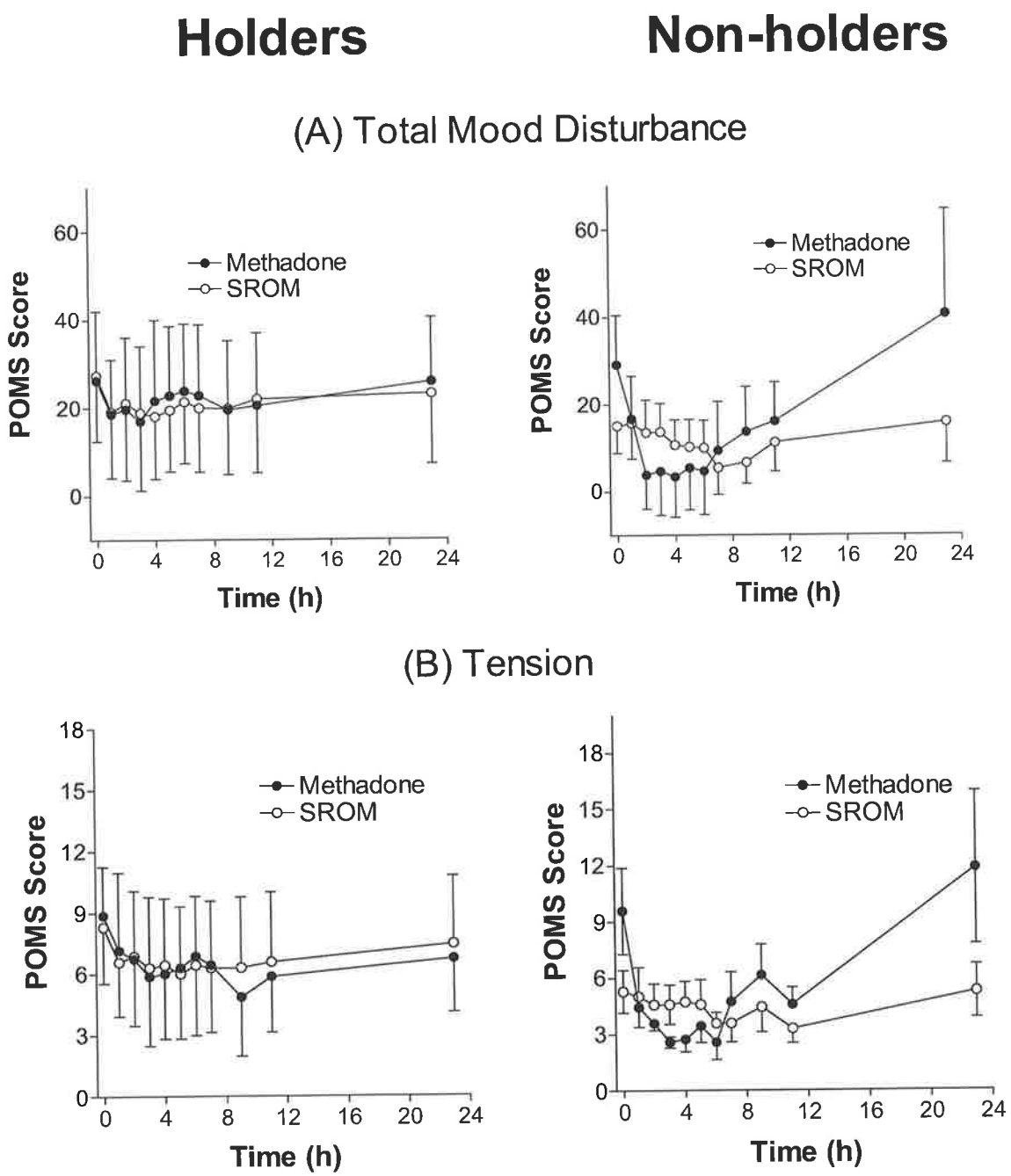

Figure 5-4. Total Mood Disturbance and Tension scores from the Profile of Mood States during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. p > 0.05 for all differences (methadone vs. SROM).

Repeated measure ANOVA used to determine differences in temporal patterns of mood states for methadone and SROM according to methadone holding status are presented in Table 5-2. Significant maintenance drug × holding status × time since dosing interactions were found for Total Mood Disturbance and Tension, as depicted in Figure 5-4. There were no main effects for holding status for either methadone or SROM, reflecting similar overall levels for each mood factor, and no other significant interaction effects according the maintenance drug or time since dosing.

Table 5-2. Repeated-measures ANOVA for the Profile of Mood States according to methadone holding status (n=14).

		POMS Scale						
	Df	TMD	Tension	Anger	Depress	Fatigue	Confus.	Vigour
Effect[a]	Within-drug conditions							
Hold								
Methadone	1,12	0.22	0.20	0.04	0.07	0.06	0.19	0.59
SROM	1,12	0.36	0.46	0.00	0.49	0.18	0.97	0.92
Time × Hold								
Methadone	12,120	1.34	2.90	1.00	0.90	1.11	0.71	1.70
SROM	12,120	0.69	0.39	0.78	1.29	0.20	0.95	0.35
	Between-drug conditions							
Drug × Hold	1,12	0.06	1.48	0.21	0.73	3.22	0.57	0.00
Drug × Time × Hold	10,120	*2.00	**2.89	1.29	1.44	1.14	0.46	1.64

Values are F ratios. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] ANOVA effects were time since dosing (Time), the maintenance drug (Drug) and methadone holding status (Hold). TMD = Total Mood Disturbance. Conf. = Confusion.

5.3.2. Determinants of mood responses

5.3.2.1. Dose, plasma drug concentrations and opioid withdrawal

Correlations used to determine the extent to which mood responses for methadone and SROM were linearly related to the maintenance dose, plasma concentrations and severity of opioid withdrawal are presented in Table 5-3. A consistent pattern of relationships was evident such

that the intensity of negative mood states was inversely related to dose and plasma concentrations of the maintenance drug and positively related to the number of self-reported opioid withdrawal symptoms. Correlation coefficients indicated that withdrawal severity showed the strongest pattern of relationships with mood responses, with significant relationships evident for all negative mood states for both methadone and SROM.

Table 5-3. Correlation coefficients for relationships between Profile of Mood States scores and dose, plasma drug concentrations, and the severity of opioid withdrawal (n=14).

	Mood covariate					
	Dose		Plasma concentration		Withdrawal symptoms	
POMS scale	Methadone	SROM	(R)-meth	morphine	Methadone	SROM
TMD	*-0.55	*-0.57	-0.42	-0.42	*0.63	*0.88
Tension	-0.45	-0.52	-0.37	-0.38	*0.67	*0.87
Anger	-0.46	*-0.57	-0.34	-0.38	*0.65	*0.82
Depression	-0.47	-0.49	-0.36	-0.33	*0.63	*0.84
Fatigue	-0.45	*-0.58	-0.40	-0.38	*0.67	*0.75
Confusion	*-0.53	-0.37	-0.41	-0.24	*0.60	*0.91
Vigour	0.13	0.12	0.07	0.32	0.49	0.10

Values represent Pearson r. * $p < 0.05$. Correlations used average values for each subject for all variables except dose. Plasma concentrations were for (R)-methadone and morphine.

The patterns of mood states observed for methadone holders and non-holders (Figure 5-4) suggests that the degree of mood change during the inter-dosing interval was strongly related to the severity of self-reported withdrawal (Chapter 4). To further characterise the importance of withdrawal in relation to mood responses, differences between methadone and SROM (SROM scores subtracted from methadone scores) in (a) the average number of withdrawal symptoms during the inter-dosing interval and (b) the degree of change in Total Mood Disturbance between baseline and the time of peak plasma concentration were correlated. A significant positive correlation was found ($r = 0.54$, $p = 0.047$) such that reductions in withdrawal severity for SROM compared to methadone were associated with reductions in the degree of peak to trough change in Total Mood Disturbance (Figure 5-5).

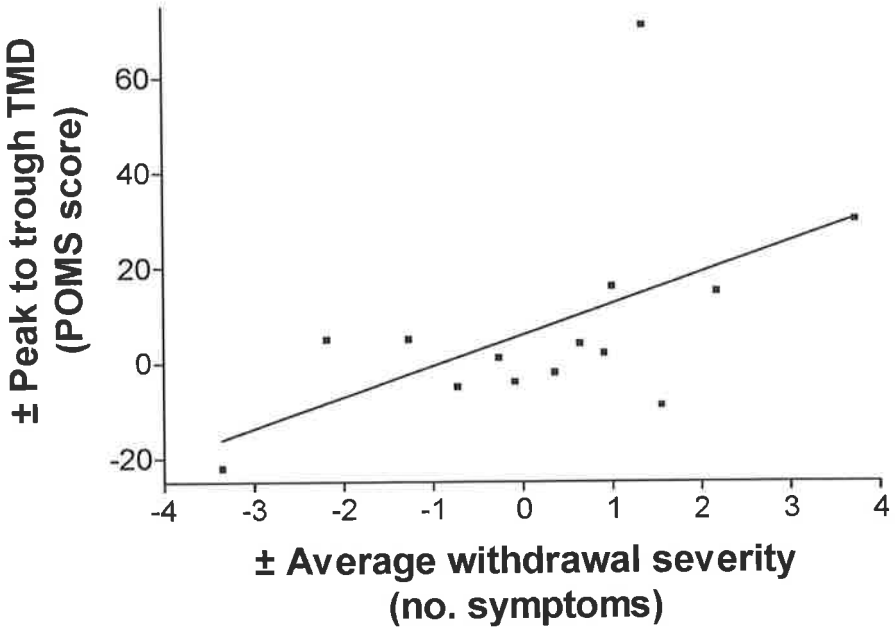

Figure 5-5. Relationship between changes in the average number of self-reported withdrawal symptoms and peak to trough variation in Total Mood Disturbance for SROM compared to methadone (n=14). Positive scores for X and Y axes indicate reduced withdrawal severity and mood change for SROM compared to methadone.

Temporal patterns for Total Mood Disturbance (Figure 5-1) and MBG scores (Figure 5-3) suggest that fluctuations in plasma concentrations for (R)-methadone and morphine resulted in a greater degree of change in negative compared to positive mood states. To achieve a more sensitive assessment of this difference, changes in Total Mood Disturbance and MBG between baseline and the time of peak plasma (R)-methadone and morphine concentrations for each subject were contrasted (Figure 5-6). For both methadone and SROM, peak plasma concentrations were associated with significant reductions in Total Mood Disturbance relative to baseline. The degree of change was greater for methadone compared to SROM (16 ± 25 vs. 8.0 ± 7.8), but this difference was not significant ($t(13) = 1.30$, $p = 0.22$). By comparison, peak plasma concentrations were associated with only a negligible and non-significant degree of change in MBG scores for both methadone and SROM.

Figure 5-6. Change in Total Mood Disturbance and Morphine Benzedrine Group scale scores between assessments prior to dosing and at the time of peak plasma (R)-methadone and morphine concentrations for methadone and SROM (n=14). Data are presented as mean ± SE. * $p < 0.05$ (prior to dosing vs. time of peak concentration).

5.3.2.2. Ratio of (S)- to (R)-methadone

To investigate whether relative exposure to the (S)- and (R)-methadone enantiomers explains variability in mood responses during methadone maintenance, relationships between mood states and the ratio of the area under the plasma concentration versus time curve (AUC) for (S)- compared to (R)-methadone were investigated using scatter plots and correlation analyses. Inspection of scatter plots indicated a positive association between negative mood states and the (S)-/(R)-methadone AUC ratio. These plots further indicated the presence of a single multivariate outlier for each of the mood states except vigour, which in all cases was due to the same subject (id. no. 6: female, holder). This subject showed average Total Mood Disturbance scores in excess of 100 for both methadone and SROM, and a very low methadone dose (25 mg) compared to the group mean (78 mg). In spite of this outlier, non-parametric Spearman correlations indicated that during methadone maintenance the (S)-/(R)-methadone AUC ratio was positively associated with Total Mood Disturbance (0.57), Tension (0.57), Anger (0.54), Depression (0.47, $p = 0.09$), Fatigue (0.58) and Confusion ($p = 0.06$) ($p < 0.05$ unless indicated), but no relationship was observed for Vigour (-0.24) or MBG (-0.08). The relationships for Total Mood Disturbance, Tension, Fatigue and Confusion were linear when the above-mentioned outlier was removed, yielding Pearson r values of 0.83, 0.78, 0.76

and 0.80, respectively ($p \leq 0.003$). These relationships are shown in Figure 5-7. For these subjects, there was also a marginally non-significant correlation between withdrawal severity and the (S)-/(R)-methadone AUC ratio ($r = 0.52$, $p = 0.07$). Partial correlations indicated that, when controlling for withdrawal severity and the AUC for (R)-methadone (respective r values in parentheses), the positive associations between the (S)-/(R)-methadone AUC ratio and Total Mood Disturbance (0.81, 0.83), Tension (0.69, 0.78), Fatigue (0.68, 0.76), and Confusion (0.78, 0.79) remained highly significant ($p \leq 0.014$).

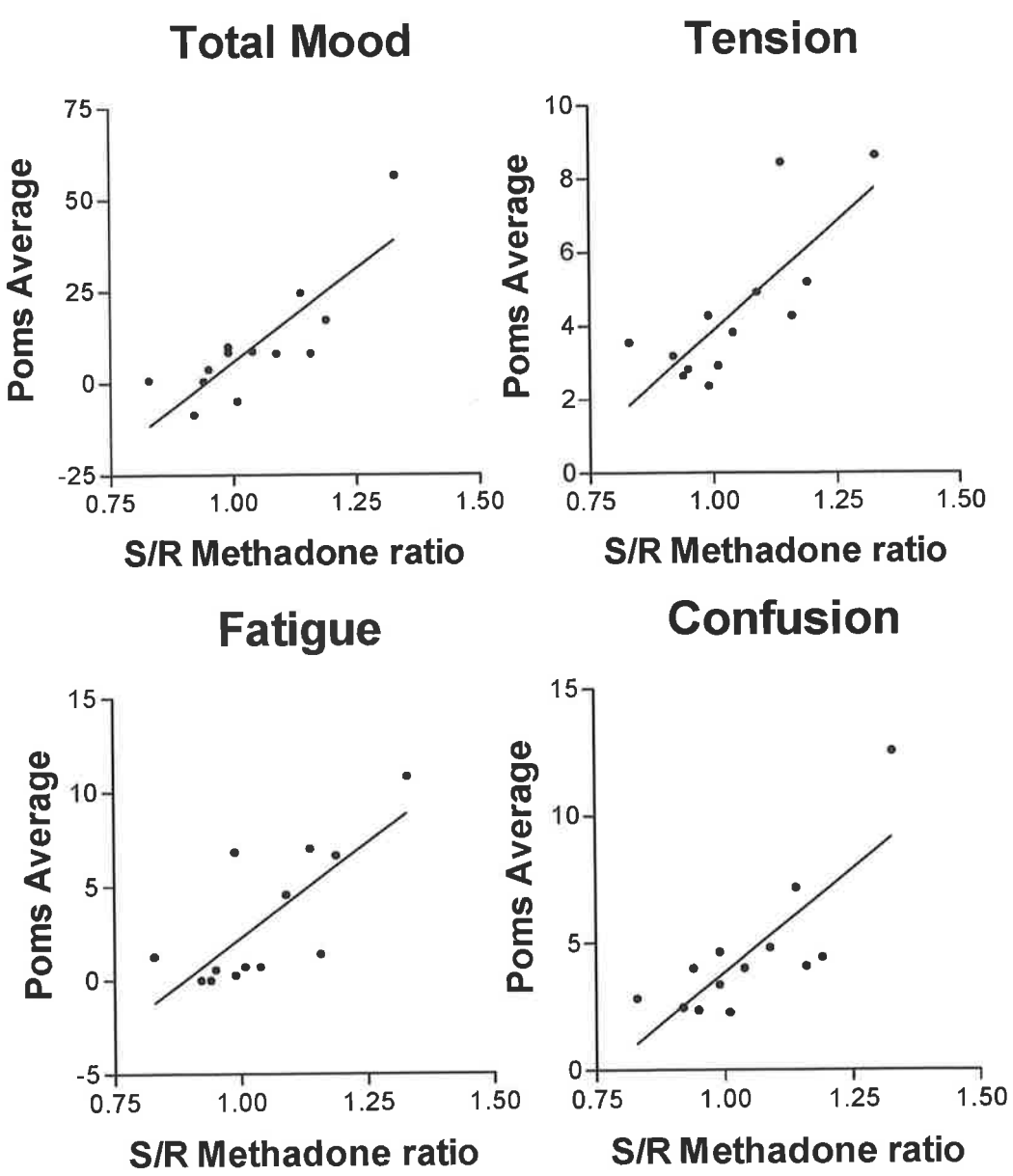

Figure 5-7. Relationship between the ratio of the area under the plasma-concentration time curves for (S)- compared to (R)-methadone and average Profile of Mood States scores during a 24-hour inter-dosing interval for methadone (n=13).

To investigate whether relative exposure to (S)- and (R)-methadone during methadone maintenance predicted different mood responses during SROM maintenance, relationships between the (S)-/(R)-methadone AUC ratio and the change in average POMS scores for SROM compared to methadone (SROM subtracted from methadone) were initially investigated using scatter plots and correlation analyses. Scatter plots revealed no evidence of strong linear association. Spearman correlations further showed no significant correlations between the (S)-/(R)-methadone AUC ratio and Total Mood Disturbance (-0.24), Tension (-0.43) Anger (-0.14), Depression (-0.10), Fatigue (-0.27), Confusion (-0.36), Vigour (-0.03) or

MBG (0.08). To explore these relationships further, repeated-measures ANOVA of POMS, MBG and MG scores were conducted using the (S)-/(R)-methadone AUC ratio as a covariate. These analyses indicated significant effects for the maintenance drug and maintenance drug × (S)-/(R)-methadone AUC ratio interaction term for Depression ($F(1, 11) = 9.24$, $p = 0.01$; $F(1, 11) = 9.85$, $p = 0.009$) and Confusion ($F(1, 11) = 5.73$, $p = 0.04$; $F(1, 11) = 6.72$, $p = 0.03$), such that SROM was associated with less Depression and Confusion than methadone and higher ratios of (S)- to (R)-methadone were associated with a greater degree of such improvement.

5.3.3. Reliability of the Profile of Mood States

Cronbach alpha values were high for Total Mood Disturbance (0.98), Tension (0.94), Anger (0.96), Depression (0.99), Vigour (0.91), Fatigue (0.95) and Confusion (0.87), indicating good internal scale consistency. Pearson correlations between methadone and SROM scores for Total Mood Disturbance (0.94) Tension (0.94), Anger (0.94), Depression (0.90), Vigour (0.28), Fatigue (0.84) and Confusion (0.54) suggested good overall test-retest reliability, although these relationships may also reflect the effects of each maintenance drug on mood responses.

5.4.Discussion

The purpose of the present study was to compare the intensity, temporal patterns and determinants of mood states for methadone and SROM. Positive and negative mood states were measured throughout a 24-hour inter-dosing interval on one occasion for each drug after at least 4 weeks on a stable dose in 14 methadone maintenance patients. Results indicated that SROM was associated with a more stable overall pattern of mood states during the inter-dosing interval in comparison to methadone. This difference was evident for the Total Mood Disturbance, Tension and Vigour subscales of the POMS, which showed a greater degree of variation during the inter-dosing interval for methadone compared to SROM. The intensity of negative mood states was positively associated with the severity of self-reported opioid withdrawal and also showed an inverse pattern of relationships with doses and plasma drug concentrations for both drugs. The important of withdrawal severity as a determinant of mood responses was evident in comparisons of Total Mood Disturbance and Tension between subjects self-identifying as methadone holders and non-holders prior to commencing the study. The holders, who experienced satisfactory and equivalent withdrawal for both methadone and SROM, showed relatively stable mood patterns between doses for both drugs. The non-holders, who experienced adequate withdrawal suppression for SROM but not methadone, showed pronounced fluctuations in mood for methadone and comparatively more stable mood patterns for SROM. Additional analyses showed that high ratios of (S)- to (R)-methadone in plasma were associated with a greater intensity of negative mood states during methadone maintenance and reductions in Depression and Confusion for SROM compared to methadone.

Consistent with hypothesis 1 and previous investigations (Dyer et al., 2001; Hiltunen et al., 1999), the present study has demonstrated that patients undergoing maintenance treatment for opioid dependence experience significant mood changes between doses in response to fluctuations in plasma concentrations of the maintenance drug and that the amplitude of these mood changes is inversely proportional to the adequacy of withdrawal suppression achieved.

In Chapter 4, it was demonstrated that the degree of withdrawal suppression achieved with SROM in comparison to methadone was comparable for methadone holders and superior for non-holders. The present study has shown that these reductions in withdrawal severity amongst the non-holders also resulted in a more stable pattern of mood states between doses for SROM compared to methadone. Given the likelihood that inconsistent mood patterns may compromise treatment outcomes, for example, by making patients more vulnerable to heroin cravings (Calsyn et al., 2000; Kanof et al., 1993; Krueger, 1981; Powell et al., 1992; Unnithan et al., 1992) and less amenable to counselling (Woody et al., 1984), the identification of alternative means of achieving mood stability is important. The results of this investigation suggest that the provision of SROM as a supplementary once-daily agonist option to methadone may facilitate greater mood stability in some methadone maintenance patients and hence increase the likelihood of positive outcomes eventuating from treatment.

The present study also highlights the high degree of mood disturbance associated with methadone maintenance patients. In a study by Dyer et al. (2001), healthy control subjects showed mean Total Mood Disturbance scores ranging from approximately –5 to –15. In the present study, methadone maintenance patients assessed using the same experimental protocol as Dyer et al. showed mean Total Mood Disturbance scores ranging from 10 to 30. Notably, in contrast to the findings of Dyer et al., the present study found no evidence that non-holders exhibited a greater overall level of mood disturbance compared to holders, despite showing more pronounced temporal changes in mood states during the inter-dosing interval. In addition, it was evident that increases in plasma concentrations of (R)-methadone and morphine produced significant reductions in mood disturbance, but did not elicit any significant degree of positive opioid effects. These findings are consistent with evidence that chronic opioid exposure is associated with a shift towards dysphoric and depressed mood patterns (Fraser et al., 1963; Martin & Jasinski, 1970; Martin et al., 1973; McNamee et al., 1976; Mirin et al., 1976a; Mirin et al., 1976b). Consequently, even patients reporting adequate

withdrawal suppression between doses may be at significant risk of relapse due to persistent negative mood states. This suggests that assessments of relapse risk in clinical settings could benefit from including measures of mood states in addition to considering the physical signs of opioid withdrawal.

Another major finding of the present study is the demonstration of a relationship between the AUC ratio of (S)- to (R)-methadone and the intensity of negative mood states including Total Mood Disturbance, Tension, Fatigue and Confusion. This pattern of relationships was not explained by variance in the severity of opioid withdrawal. It is also notable that there was no relationship between the ratio of (S)- to (R)-methadone and AUC for (R)-methadone. Although further studies are needed to establish causation, these findings suggest the possibility of different affective profiles for (R)- and (S)-methadone. This possibility is consistent with a number of previous research findings.

In one study, opioid dependent subjects administered high-doses of (S)-methadone (650-1000 mg/day) disliked the subjective effects and denied they were opioid-like in nature, despite showing partial suppression of the opioid abstinence syndrome and mild physical dependence (Fraser & Isbell, 1962). Other studies have reported the need for increases in daily racemic methadone doses following the transfer of maintenance patients from (R)-methadone to racemic methadone, despite patients showing no signs of increased withdrawal after the transfer (de Vos et al., 1998; Eap et al., 1996; Scherbaum, Finkbeiner, Leifert, & Gastpar, 1996). It is possible that requests for dose increases may have been caused by affective changes relating to effects of (S)-methadone. If these effects were mediated by non-opioid mechanisms (e.g., NMDA antagonism; see below) this could explain the absence of changes in opioid withdrawal severity. Whilst a double-blind study in the 1960s found no differences in efficacy for (R)- and (R, S)-methadone as maintenance treatments (Judson, Horns, & Goldstein, 1976), this does not preclude the possibility of important affective changes that

may not be detectable using standard indicators designed to measure opioid-specific effets and which may only apply to a sub-population of patients.

Differences in the affective profiles of (R)- and (S)-methadone may arise from differences in the pharmacological actions of each enantiomer. Despite showing negligible potency as an opioid agonist (Kristensen, Christensen, & Christrup, 1995; Scott et al., 1948) and as an inhibitor of serotonin and noradrenaline re-uptake (Codd et al., 1995), (S)-methadone has been demonstrated to possess significant NMDA antagonist characteristics in both *in vitro* and *in vivo* animal studies (Davis & Inturrisi, 1999; Gorman et al., 1997; Shimoyama et al., 1997). Indeed, the affinity of both (R)- and (S)-methadone for the NMDA receptor is similar to that of other well-documented NMDA antagonists such as ketamine and dextromethorphan (Gorman et al., 1997), use of which has been associated with negative affective reactions including confusion and schizophrenic-like mood disturbances (Abi-Saab et al., 1998; Adler et al., 1999; Curran & Monaghan, 2001; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996). NMDA antagonism is one mechanism that may account for a more negative profile of mood responses to (S)- comparison to (R)-methadone, as suggested by the findings of both the present and previous studies (Fraser & Isbell, 1962; Olsen et al., 1977; Scott et al., 1948).

In summary, the present study has shown that transfer from methadone to SROM may facilitate greater consistency of mood states during the inter-dosing interval, particularly for patients experiencing inadequate withdrawal suppression between doses. This is likely to facilitate the achievement of treatment goals, for example, by making patients less vulnerable to heroin cravings and more amenable to counselling and other psychosocial interventions. In addition, the present study found that high ratios of (S)- to (R)-methadone in plasma were associated with a greater intensity of negative mood states during methadone maintenance and, conversely, greater reductions in Confusion and Depression for SROM compared to

methadone. Variation in the enantiomeric ratio between-individuals and within-individuals during the inter-dosing interval, which was shown to be significant in Chapter 3, may thus be an important determinant of affective responses during methadone maintenance. Further research is required to confirm this relationship and to establish whether the non-opioid mechanisms of methadone may have a causal role in this regard. To the extent that (S)-methadone is associated with negative mood states, the enantiomeric ratio may have clinical utility as a means of identifying patients that may show improved mood responses following transfer from methadone to another maintenance pharmacotherapy.

6. SENSITIVITY TO PAIN DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SROM

6.1. Introduction

Chronic exposure to methadone and other opioids is associated with the development of an increased sensitivity to pain, or hyperalgesia. This is of concern for two major reasons. Firstly, persistent pain is associated with the development of negative affective states such as depression and anxiety and a general reduction in quality of life (Hunt & Mantyh, 2001). These factors may promote compensatory use of illicit opioids (Calsyn et al., 2000; Kanof et al., 1993; Krueger, 1981; Powell et al., 1992; Unnithan et al., 1992) and thus reduce the likelihood of positive outcomes from treatment. Second, hyperalgesia contributes to the numerous challenges associated with acute pain management in methadone maintenance patients (e.g., opioid tolerance, prejudices against opioid users) (Doverty et al., 2001b). To this extent, pain sensitivity may be a useful marker of patient outcomes during maintenance treatment for opioid dependence and is thus an important consideration in the evaluation of prospective maintenance pharmacotherapies such as SROM. Methadone and morphine have different effects on the physiological systems involved in the perception of pain and the development of hyperalgesia that could result in different patterns of pain sensitivity for each drug (Codd et al., 1995; Ebert et al., 1998; Gorman et al., 1997). The purpose of the present study was to compare sensitivity to pain for methadone and SROM. This necessitates a review of the literature regarding the relationship between pain sensitivity and chronic opioid exposure, the clinical implications of hyperalgesia during maintenance treatment for opioid dependence, and the physiological mechanisms of pain perception that may influence sensitivity to different pain induction methods for methadone and SROM.

6.1.1. Relationship between sensitivity to pain and chronic exposure to opioids

Studies investigating the relationship between chronic opioid exposure and alterations in pain sensitivity have produced variable results. Individuals with a past or present dependence on

opioids have been reported to be less tolerant (Compton, 1994; Compton et al., 2000; Ho & Dole, 1979; Martin & Inglis, 1965), similarly tolerant (Dyer et al., 1999; Schall, Katta, Pries, Kloppel, & Gastpar, 1996a) and more tolerant (Lehofer et al., 1997; Liebman et al., 1994; Liebmann et al., 1997) of pain in comparison to opioid-naïve populations. These discrepancies partly reflect the inherent challenges associated with attempts to assess pain in clinical and scientific contexts. Pain does not derive from a single, individualised physiological system but rather from a collection of subsystems (e.g., sensory, motor, emotional, motivational) operating in unison (Hunt & Mantyh, 2001; Le Bars, Gozariu, & Cadden, 2001). Incongruities in the research literature may thus result from the different pain induction methods used by different researchers, which often involve distinct neural and physiological mechanisms (Le Bars et al., 2001). More generally, the capacity to experimentally induce pain that is qualitatively similar to real life pain associated with injury or disease has been questioned (Beecher, 1962). To overcome the uncertainties that arise from methodological variations, it is preferable that studies investigating pain sensitivity use more than one method of pain induction. However, this approach has rarely been employed in studies examining pain responses in chronic opioid users.

A method commonly used to model pain in experimental settings is the cold pressor test. Although numerous variations of this technique have been reported, its defining characteristic involves the immersion of a limb (usually the forearm) into an ice water bath. Subjects are typically instructed to indicate verbally when the cold water first becomes painful (pain detection) and subsequently to keep their limb immersed for as long as they can reasonably tolerate the pain (pain tolerance). The following studies investigated pain sensitivity in relation to chronic opioid use using the cold pressor test as the sole method of pain induction.

In an early study, Martin and Inglis (1965) compared cold pressor pain responses in two groups, each of 24 female prisoners; one group comprised former opioid addicts, the other

non-addicts. Using a cold water temperature of 5 °C, pain tolerance was found to be significantly reduced in the former opiate-addicts compared to a never-addicted group (73 s vs. 404 s). Pain detection was not assessed in this study

Subsequently, Ho and Dole (1979) compared cold pressor pain detection and tolerance in three groups, each of 10 individuals, comprising drug-free ex-addicts, methadone maintenance patients (mean dose 80 mg) and a control group of non-addict siblings of heroin users. The cold pressor method involved immersion of subjects' hands first in a warm water "adaptation bath" (30°C) for two minutes prior to immersion in the cold water bath (1°C) and was averaged over three repeated trials for both the left and right hand in each subject. Pain detection was significantly lower for both the drug-free ex-addicts (14 s) and the methadone maintenance patients (16 s) in comparison to the non-addict siblings of heroin users (20 s), although there were no differences between these groups in pain tolerance (27, 28 and 32 s, respectively).

A series of studies investigating the relationship between opioid use and pain responses were reported by Compton and colleagues (Compton, 1994; Compton et al., 2000; Compton et al., 2001). In the first of these investigations, Compton (1994), using a cold water bath temperature of 0-2 °C, found no differences in mean pain tolerance between abstinent heroin users (n = 26; 72 s) and methadone maintenance patients (n = 43; 65 s). However, both of these groups showed significantly reduced mean pain tolerance in comparison to abstinent cocaine users (n = 32; 167 s). This suggests that the observed alterations in pain response were specific to opioids and not merely a function of long-term illicit drug exposure.

In a second study, Compton et al. (2000) compared tolerance to cold pressor pain (cold water temperature 0-2°C) in methadone maintenance patients (n = 60) and a group of matched opioid-naive control subjects (n = 60) both before and after oral administration of therapeutic

doses of opioid (hydromorphone 2 mg) and nonsteroidal anti-inflammatory (ketorolac 10 mg) analgesic agents. Pain tolerance was significantly less in the methadone maintenance patients (44 s) compared to the control subjects (94 s), but was not significantly affected by the analgesic agents. Compton et al. concluded that "opioid abusers represent a pain-intolerant subset of clinical patients" and that "their complaints of pain should be evaluated seriously and managed aggressively".

In a third study, also using cold pressor pain induction method (cold water temperature 0-2°C), Compton et al. (2001) reported no significant difference in mean pain tolerance for buprenorphine (n = 18; 61 s) and methadone (n = 18; 59 s) maintenance patients. However, both groups were significantly less pain tolerant compared to a group of opioid-naïve control subjects matched according to age, sex and race controls (n = 18; 138 s). For the small number of maintenance patients who returned opioid-free urine samples throughout the study, withdrawal latencies were significantly shorter in the methadone group (n = 5, 32 s) compared to the buprenorphine group (n = 7, 87 s).

The studies reviewed above demonstrate a relationship between chronic exposure to opioids and responses to pain induced using the cold pressor test. Specifically, these studies suggest that chronic opioid exposure is associated with an increased sensitivity to pain. Moreover, it is apparent that this relationship applies even to individuals reporting past but not current opioid use.

In contrast to these results, Liebmann et al. (1997) found that cold pressor pain tolerance thresholds were greater for a group of detoxified opioid users undergoing rehabilitation (n = 31) compared to a group of drug-free volunteers (n = 31). A similar trend was observed for pain tolerance, but did not reach statistical significance. In explaining the discrepancies between these results and those of previous studies, a number of methodological features are

notable. Firstly, pain tolerance was determined for approximately 50% of both groups only, because the remainder failed to report an intolerable degree of pain prior to the 7-minute cut-off employed in the study. This suggests that the temperature of the ice-water bath (4-6 °C) may have been insufficiently cold to produce a pain-specific response, which may explain the wide distribution of observed pain scores and hence the authors' use of log-transformations to analyse pain response. Second, an uneven gender distribution was apparent, such that 68% of the detoxified opioid users but only 41% of the control group were male. In spite of these methodological shortcomings, and the lack of congruence with previous results (which were not reviewed by the authors), the authors speculated that their results may represent evidence of a lasting up-regulation of pain responses in chronic opioid users, which may contribute to the high relapse rate seen amongst this population.

In a related survey by this research group (Lehofer et al., 1997), 63 successfully detoxified opioid users were asked to retrospectively rate their sensitivity to pain, cold and warmth before and during their addiction to opioids, during the detoxification period, and for the present day. Compared to 63 matched controls, detoxified opioid users self-reported less sensitivity to pain and cold, but not warmth, for every period of assessment except during detoxification. The authors suggest that pre-existing differences involving a reduced sensitivity to pain in the opioid using group may be indicative of a physiological pre-disposition to addiction. As an alternative explanation for these results, it has been proposed that the higher pain tolerance observed for the detoxified heroin users may be a factor that predisposes individuals to a greater chance of successfully detoxifying from opioids (Hajek, 1998).

Other studies have used different pain induction methods to investigate pain sensitivity in methadone maintenance patients. Schall (1996a) compared pain tolerance for methadone maintenance patients (n=42) and drug free controls (n=16) by applying mechanical pressure

to subjects' hands. Subjects in the methadone group were assessed pre-dose, and then randomly allocated to be re-assessed at 1, 2 or 4 hours post-dose. There were no differences between the methadone (pre-dose) and control groups, but pain tolerance was increased following administration of the methadone dose in the methadone-maintained group.

Dyer et al. (1999) similarly demonstrated temporal changes in pain responses following administration of methadone in a maintenance population (n = 18) using subcutaneous electrical stimulation of the ear lobe as the pain stimulus. Pain threshold (operationally defined as the voltage at which the stimuli became painful) was measured on 11 occasions over a single 24-hour dosing interval. Compared to a drug-free control group (n = 10), the methadone maintenance patients showed a significantly greater mean pain threshold compared to the control group at all measurement times except immediately prior to dosing, for which no difference was observed. Moreover, results indicated changes in pain threshold in the methadone maintenance subjects during the inter-dosing interval that were consistent with concurrently determined plasma racemic methadone concentrations.

Noting methodological inconsistencies in the literature, Doverty et al. (2001a, 2001b) conducted two studies of pain sensitivity in methadone maintenance patients that featured the use of multiple pain induction methods and the concurrent determination of plasma methadone concentrations. In the first study (Doverty et al., 2001b), methadone maintenance patients (n = 16) were tested for pain sensitivity at times corresponding to putative trough and peak plasma concentrations (30 minutes prior to and 3 hours following methadone dosing, respectively). Matched controls (n = 16) were similarly assessed twice, three hours apart. Pain sensitivity was assessed using the cold pressor (ice water 0.5-1.0 °C) and electrical stimulation pain induction techniques. For both measures, subjects were asked to indicate when they first detected pain (pain detection) and when the pain became intolerable (pain tolerance). Results indicate that for electrical stimulation, pain tolerance in methadone

maintenance patients was lower at 0 hours but higher at 3 hours in comparison to normal controls, although no differences in pain detection were observed. For the cold pressor test, methadone maintenance patients showed reduced pain detection at 0 hours and reduced pain tolerance at both 0 hours and 3 hours in comparison to the controls. For both nociceptive stimuli, trough to peak (i.e., 0 to 3 hour) increases in plasma methadone concentrations predicted increased pain detection and tolerance amongst the methadone maintenance patients.

In their second study, Doverty et al. (2001a) investigated the antinociceptive effects of morphine on cold pressor and electrical stimulation pain responses in methadone maintenance patients (n = 4) and matched controls (n = 4). Nociceptive responses were recorded at baseline and subsequently on another 10 occasions in the following 7 hours. An intravenous morphine infusion was used to achieve two pseudo-steady-state plasma morphine concentrations (Css) during the first and second hours in the control (target Css = 20 and 60 ng/mL, observed Css = 11 and 33 ng/mL, for first and second hours, respectively) and methadone (target Css = 20 and 80 ng/mL, observed Css = 16 and 55 ng/mL, for first and second hours, respectively) groups. Control subjects were given less morphine in the second hour to minimise adverse effects. Methadone maintenance patients were tested on two occasions such that the study commenced at the time of putative trough (23.5 h) and peak (2 h) plasma methadone concentrations in relation to the previous dose. Results indicated that methadone maintenance patients were hyperalgesic relative to the controls for pain induced by the cold pressor test (e.g., at baseline, tolerance approximately 55 s and 25 s for control and methadone groups, respectively; data estimated from graphs), but not for electrical stimulation (e.g., at baseline, tolerance approximately 51 V and 48 V for control and methadone groups, respectively; data estimated from graphs). Despite significantly higher plasma morphine concentrations, methadone maintenance patients experienced very little ăntinociceptive effect from morphine in comparison to the controls (e.g., difference in cold pressor pain tolerance for 2 h vs.

baseline = 115 s vs. 55 s and 30 s vs. 25 s for control and methadone groups, respectively; data estimated from graphs).

Ongoing studies by these researchers have similarly demonstrated that methadone maintenance patients are highly tolerant to the antinociceptive effects of morphine, even at very high plasma morphine concentrations (>200ng/mL) (Athanasos et al., 2002). These studies indicate that differences in pain sensitivity between methadone maintenance patients and other opioid users in contrast to normal populations are dependent on the nature of the nociceptive stimulus (e.g., electrical stimulation), the plasma methadone concentration, and whether thresholds are determined for pain detection or pain tolerance (Doverty et al., 2001a; Doverty et al., 2001b).

In summary, many studies suggest that chronic opioid use and methadone maintenance are associated with an increased sensitivity to pain, or hyperalgesia. Although some authors have reported conflicting results, these are probably attributable to methodological factors including the utilisation of different pain induction and measurement techniques. Investigations of pain sensitivity in patients undergoing maintenance treatment for opioid dependence should employ multiple pain induction (e.g., cold pressor and electrical stimulation) and measurement (e.g., detection and threshold) methods and take account of daily fluctuations in plasma concentrations of the maintenance drug. Since the subjective experience of pain derives from multiple physiological systems, interpretation of such studies necessitates an understanding of the physiological mechanisms of pain and how different nociceptive stimuli and maintenance drugs may influence those mechanisms (discussed below in section 6.1.3).

6.1.2. Clinical implications of opioid-induced hyperalgesia

The association between hyperalgesia and chronic opioid exposure has a number of clinical implications. Firstly, to the extent that the mechanisms responsible for the development of

hyperalgesia and opioid tolerance dependence appear similar (Mayer, Mao, Holt, & Price, 1999), the former may be an important consideration in the aetiology and treatment of opioid dependence. As suggested by Mayer et al. (1999), it is conceivable that the reduced analgesic effects of opioids during chronic treatment for pain could result from both pharmacological tolerance and from tolerance-associated hyperalgesia. Persistent pain is associated with secondary symptoms including anxiety and other negative mood states (Hunt & Mantyh, 2001). In the context of illicit opioid use, it is similarly possible that compulsive opioid use may partially derive from attempts to overcome hyperalgesia and associated affective states (e.g., dysphoria, anxiety), resulting in a dependence-perpetuating cycle involving increasing opioid use, tolerance, hyperalgesia, and associated dysphoric mood shifts.

A second major clinical implication of opioid-induced hyperalgesia concerns the challenges of acute pain management in patients undergoing maintenance treatment for opioid dependence (Compton & McCaffery, 2001; Doverty et al., 2001b). Despite being more sensitive to pain and as likely, if not more likely, to require acute pain relief compared to normal populations, methadone maintenance patients show extreme tolerance to plasma concentrations of morphine that are normally associated with adequate postoperative pain relief (Doverty et al., 2001b). Additionally, effective management of acute pain in these individuals may be impeded by misunderstandings and prejudices amongst medical professionals, including the belief that the maintenance dose will contribute significantly to analgesia, fears of exacerbating opioid addiction, social prejudices against opioid users, and a reluctance to prescribe adequate doses of opioids to patients with a history of opioid abuse (Cleeland, 1987; Doverty et al., 2001b; Hicks, 1989).

6.1.3. Mechanisms of pain, nociception and hyperalgesia

In understanding the physiological determinants of pain sensitivity, it is important to distinguish between nociception and pain. Nociception involves the transmission of information about potentially noxious stimuli to the central nervous system. In contrast, pain

is the subjective experience that occurs in response to certain nociceptive stimuli, and is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merksey et al., 1979). Nociception can occur independently of pain and vice versa (Loeser & Cousins, 1990). Thus, whilst acute pain normally derives from nociceptive stimuli, involving an intense noxious stimulation, chronic pain states such as hyperalgesia result from adaptations of the physiological systems involved in the transmission of nociceptive information (Hunt & Mantyh, 2001; Mayer et al., 1999). In describing the physiological mechanisms responsible for nociception, pain and hyperalgesia, focus will be restricted to those mechanisms that are influenced differently by nociceptive stimuli (i.e., cold pressor and electrical stimulation) and maintenance drugs (i.e., methadone and morphine) under consideration in the present study.

The transmission of nociceptive information is associated with electrical conductivity along small diameter afferent fibres whose sensory nerve endings are located in peripheral tissues (Belemont & Cervero, 1996; Le Bars et al., 2001; Markenson, 1996; Mayer et al., 1999; Millan, 1999). Two classes of afferent fibres are involved in the transmission of nociceptive impulses. C fibres are non-myelinated and hence slow-conducting fibres that are generally associated with the experience of dull, burning and aching pain. Less abundant are A-delta fibres, which are myelinated and are associated with greater conductance velocities and the experience of sharp, well-localised pain.

Nociceptors associated with C and A-delta fibres are activated by similar types of stimuli, but differ from non-nociceptors in a number of ways. Firstly, nociceptors are polymodal, meaning that they respond to a number of different forms of noxious stimulation including that of thermal, mechanical and chemical origin. Second, the activation threshold of nociceptors is greater, such that generally only stimuli of intensity sufficient to indicate likely tissue damage

will result in activation of the cell. Third, whereas the activation threshold of non-nociceptors is not significantly activity-dependent, nociceptors become more sensitive when tissue damage occurs.

An understanding of the characteristics of peripheral fibres is important in understanding the types of subjective experience associated with different nociceptive stimuli. The two methods of pain induction most frequently used in previous studies of pain responses in opioid users, which will also be employed in the present study, are electrical stimulation and the cold pressor test. Electrical stimulation is considered a relatively non-selective and hence unnatural stimulus, in that it activates many peripheral fibres in a non-differential fashion (including those not directly involved in nociception) and by its very nature involves a short-circuiting of peripheral nociceptors that would otherwise initiate electrical conductance to the central nervous system (Le Bars et al., 2001). In contrast, thermal stimuli, such as those involved in the cold pressor test, are considered more selective in the way they activate cutaneous receptors (Le Bars et al., 2001). The immersion of limbs in thermostatic baths provides a rapid, though not instantaneous, change in skin temperature that in the case of the cold pressor produces dull, burning pain of the type associated with C-fibre transmission (Handwerker & Kobal, 1993). Opioid analgesics are considered more effective in relieving pain associated with slow-conducting C-fibres in comparison to the fast-conducting A-delta fibres (Le Bars et al., 2001). The different conductance velocities of these fibres sometimes gives rise to a phenomenon of "double-pain" involving an initial reaction to A-delta related pain, which sometimes disappears before the onset of pain related to C-fibre activity (Handwerker & Kobal, 1993). Nociceptive stimuli such as electrical stimulation are often terminated at the first sign of pain (i.e., attributable to A-delta transmission), and hence may be less sensitive to the effects of opioids in comparison to cold pressor-induced pain (Le Bars et al., 2001).

A number of chemical mediators are involved in the transmission of nociceptive impulses. Of particular importance to the present discussion are the roles of opioid peptides, serotonin, noradrenaline and glutamate (acting via NMDA receptors) on transmission of nociceptive impulses. Animal studies indicate that systemically administered opioid agonists, serotonin and noradrenaline inhibit the transmission of nociceptive impulses via centrally mediated mechanisms (Codd et al., 1995). NMDA receptors mediate glutamate-facilitated nociceptive transmission in the dorsal horn and also play a major role in the development of both hyperalgesia and opioid tolerance (Mayer et al., 1999). Compelling evidence has accumulated to suggest that tonic activation of the neural pathways involved in nociceptive transmission results in neuroplastic changes in the spinal cord (i.e., sensitisation of nociceptive pathways) and the development of hyperalgesia (Mayer et al., 1999). Animal models of neuropathic pain (e.g., chronic constrictive injury of the sciatic nerve in rats) have been shown to involve similar cellular mechanisms to those involved in the development of opioid tolerance (Mao & Mayer, 2001; Mayer et al., 1999), which were described in Chapter 1. Tonic activation of excitatory amino acid receptors such as the NMDA receptor results in activation of second messenger systems that in turn leads to phosphorylation and sensitisation of the receptor (Mao & Mayer, 2001; Mayer et al., 1999). Thus, a common substrate of both hyperalgesia and morphine tolerance may involve hyperactivation of nociceptive pathways in the spinal cord dorsal horn.

An understanding of the roles of opioid, serotonergic, noradrenergic and NMDA systems in the transmission of nociceptive impulses is important because these systems are differentially influenced by methadone and morphine. Methadone differs from morphine by showing greater intrinsic efficacy for the mu opioid receptor (Adams et al., 1990), greater selectivity for mu over delta and kappa opioid receptors (Codd et al., 1995), NMDA antagonist characteristics (Ebert, Andersen, & Krogsgaard-Larsen, 1995; Ebert et al., 1998; Gorman et al., 1997), and the capacity to block the neuronal uptake of both serotonin and noradrenaline

(Codd et al., 1995). Although both opioids share a common analgesic action that is primarily considered a mu opioid receptor-mediated effect, differential modulation of the above neurotransmitter systems may nonetheless influence the level of pain sensitivity associated with each drug. Furthermore, to the extent that changes in pain sensitivity occur in response to fluctuating plasma methadone concentrations (Doverty et al., 2001a; Doverty et al., 2001b; Dyer et al., 1999), differences in the plasma concentration-time profiles for methadone and SROM may contribute to a different pattern of pain sensitivity for each drug over the 24-hour inter-dosing interval. An assessment of these differences is necessary given the potential clinical implications of changes in hyperalgesic and pain responses during maintenance treatment for opioid dependence.

6.1.4. The present study

Chronic administration of opioid agonists is associated with an altered sensitivity to certain nociceptive stimuli (Mao, 2002). Methadone maintenance patients are hyperalgesic to cold pressor pain and demonstrate significant changes in responses to both cold pressor and electrical stimulation pain due to fluctuations in plasma methadone concentrations following dosing (Doverty et al., 2001a; Doverty et al., 2001b; Dyer et al., 1999). Since the mechanisms responsible for nociceptive transmission and the development of hyperalgesia include systems that are differentially affected by methadone and morphine, it is possible that methadone and SROM may entail different responses to pain when used as maintenance pharmacotherapies. Moreover, differences in the plasma concentration-time profiles of each drug may also entail a different pattern of responses to pain during the 24-hour inter-dosing interval. The clinical significance of these potential differences in pain function and response has yet to be determined. In addition, it is notable that no previous studies have examined pain responses in opioid dependent maintenance patients to more than one maintenance drug using a within-subjects design. The present study compared methadone and SROM in terms of nociceptive responses to (a) electrical stimulation pain measured on 11 occasions across a 24-hour inter-

dosing interval and (b) cold-pressor pain measured at times corresponding to trough plasma drug concentrations on one occasion at steady-state for each drug.

6.1.4.1. Aims

Aims of the present study were:

- To determine whether responses to pain induced by electrical stimulation of the earlobe and the cold pressor test differ for methadone and SROM and to characterise the pharmacological basis of any such difference.

6.1.4.2. Hypotheses

1. Temporal patterns for detection and tolerance of electrical stimulation-induced pain will be related to plasma concentrations of (R)-methadone and morphine during the inter-dosing interval for methadone and SROM.

6.2.Methods

6.2.1. Subjects and procedures

The subjects and general procedures for this aspect of the study were as described in Chapter 2. Responses to painful stimuli for methadone and SROM maintenance were determined during a single 24-hour inter-dosing interval in fourteen opioid-dependent volunteers undergoing maintenance treatment after at least 4 weeks on a stable dose of each drug in an open-label, randomly-ordered, crossover design. Two method of pain induction were used: electrical stimulation and the cold pressor test (described below). Responses to electrical stimulation were recorded on 11 occasions at 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, and 23 hours following administration of the maintenance drug. The cold pressor test was administered only once immediately prior to the next dose at the completion of each 24-hour assessment. More frequent assessments of cold pressor responses may have confounded other pharmacodynamic data collected during the study and were considered impractical given the time constrains of the experimental protocol.

6.2.2. Measures

The methods for inducing electrical stimulation were based on those of Dyer et al. (1999) and Doverty et al. (2001a; 2001b). Cutaneous electrodes were attached to one earlobe using a clip and linked to an electrical stimulator (Grass model S6C, Grass Instruments, Quincey, MA, USA). Electrode gel (Spectra 360, Parker Laboratories, Orange, NJ, USA) was applied to the earlobe prior to attachment of the ear clip in order to facilitate conductance between the electrodes and the skin. The electrical stimulator was used to apply square wave electrical pulses (14 ms duration, 0.7 pulses per second) of increasing intensity, whereby the voltage was raised in increments of 2 V every 1.4 seconds. Subjects were asked to verbally indicate when they first detected the stimulus (stimulus detection threshold) and when the stimulus first became painful (pain detection threshold), at which point the stimulus was terminated.

The cold pressor method was based on that of Doverty et al (2001a; 2001b). Two cylindrical containers (38cm in depth, 30 cm in diameter) were used. The first contained warm water (34.5 to 35.5 °C). The second container was filled with crushed ice and cold water (0.5 to 1.0 °C). An aquatic pump (Brolga MV 1500, Brolga Australia Pty. Ltd., Haberfield, NSW, Australia) was used to circulate the cold water during the test to prevent laminar warming from the subject's immersed limb. Prior to testing, the test procedures were described and subjects were instructed to verbally indicate when, upon immersion of their limb in the cold water, they first felt pain (pain detection) and when they could no longer tolerate that pain (pain tolerance). Subsequently, subjects knelt beside the water containers and were blindfolded to exclude temporal cues and visual distractions. With a blood-pressure cuff attached, subjects were assisted in immersing their non-dominant forearm, with fingers spread and without touching the sides of the containers, in the warm water bath for 2 minutes. At 1 minute and 45 seconds, the blood pressure cuff was inflated to 20 mmHg below diastolic blood pressure to minimise the role of vascular flow in determining pain responses. Fifteen seconds later, subjects were assisted in removing their arm from the warm to the cold water container (with fingers spread without touching sides of the container). Pain detection was recorded from the time of full immersion in the cold water until verbal indication of pain; pain tolerance was recorded as the time from immersion until complete removal of the arm from the cold water. At this point, the blood pressure cuff was deflated, the eye patch removed, and a towel provided for the subject to dry their arm.

6.2.3. Statistical analyses

Repeated-measures ANOVA was used to examine the effects of the maintenance dose, the time since dosing and methadone holding status on pain responses. Additional comparisons of pain responses according to the maintenance drug and the time since dosing (peak vs. trough comparisons) were made using paired t-tests. The degree of association between paired variables was examined using scatter plots and Pearson correlation coefficients. Cronbach's

alpha was used to assess the degree of inter-correlation in electrical stimulation responses across the inter-dosing interval for methadone and SROM. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). An alpha level of 0.05 was used for all analyses. Data are presented as mean ± SD (range) unless otherwise indicated.

6.3.Results

6.3.1. Electrical stimulation

Comparisons of the stimulus detection (i.e., the voltage at which subjects first perceived the electrical stimulus) and pain detection (i.e., the voltage at which subjects first perceived the electrical stimulus as painful) thresholds during the 24-hour inter-dosing interval for methadone and SROM are presented in Figure 6-1. These data indicate that temporal patterns of sensitivity to pain induced by electrical stimulation of the earlobe, as measured by the stimulus detection and pain detection thresholds, were similar for methadone and SROM. For both methadone and SROM, mean stimulus detection was maximal prior to dosing (25 ± 8 V and 26 ± 9 V) and showed a gradual decline until reaching nadir levels (15 ± 7 V and 17 ± 6 V) at 9 and 11 hours after dosing, respectively. Slight increases were observed for methadone and SROM at the end of the inter-dosing interval the following morning (17 ± 6 V and 22 ± 7 V) but responses did not return to pre-dose levels for either drug. One-way ANOVA indicated that these changes in response during the inter-dosing interval were significant for both methadone ($F(10, 130) = 6.65$, $p < 0.001$) and SROM ($F(10, 130) = 5.05$, $p < 0.001$). Although mean responses were slightly greater for SROM compared to methadone at every time point, two-way repeated-measures ANOVA indicated no significant main effect for maintenance drug ($F(1, 13) = 2.43$, $p = 0.14$). The interaction effect for maintenance drug × time since dosing was also non-significant ($F(10, 130) = 1.05$, $p = 0.41$).

The pattern of responses for pain detection was similar for both drugs and to that described above for stimulus detection. For methadone and SROM, the mean pain detection threshold was maximal prior to dosing (44 ± 9 V and 47 ± 11 V), gradually declined before reaching nadir levels (32 ± 11 V and 35 ± 9 V) at 9 and 11 hours after dosing, respectively, and increased slightly the following morning prior to the next dose (35 ± 9 V and 37 ± 10 V). Repeated-measures ANOVA indicated significant changes in mean pain detection during the

inter-dosing interval for both methadone ($F(10, 130) = 3.74$, $p < 0.001$) and SROM ($F(10, 130) = 7.78$, $p < 0.001$), but no significant main effects for the maintenance drug ($F(1, 13) = 0.93$, $p = 0.35$) or the maintenance drug × time since dosing interaction ($F(10, 130) = 1.08$, $p = 0.38$) were found. When analysed using methadone holding status as a between-subjects variable, there were no significant effects for holding status, holding status × maintenance drug, or holding status × maintenance drug × time since dosing ($p \geq 0.62$).

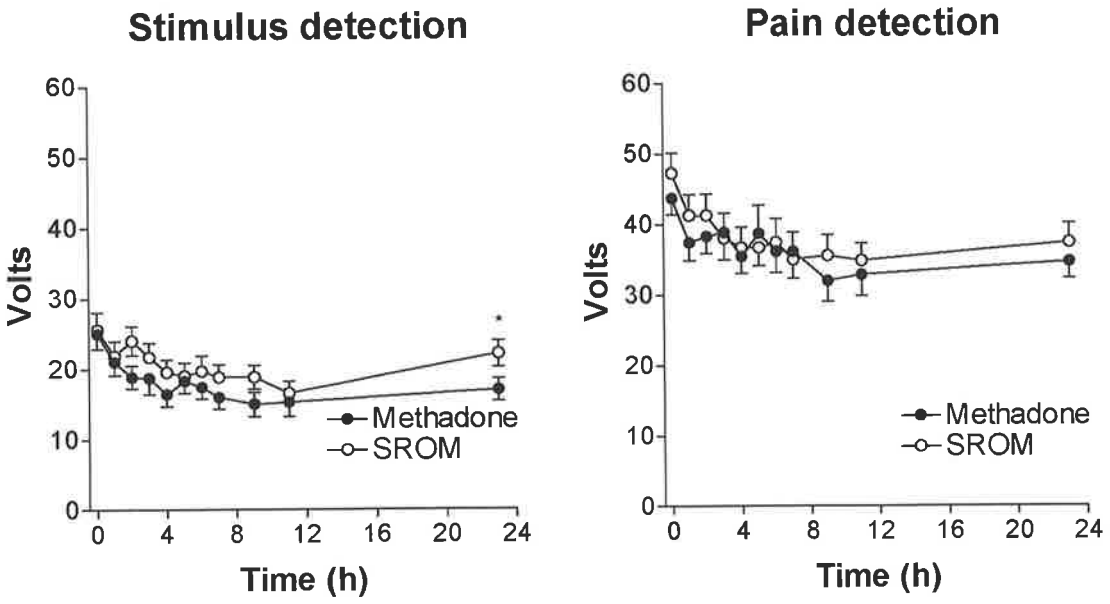

Figure 6-1. Stimulus detection and pain detection thresholds following electrical stimulation of the earlobe during a 24-our inter-dosing interval for methadone and SROM (n=14). Data are presented as mean ± SE. * $p < 0.05$ (methadone vs. SROM).

Notably, neither stimulus detection nor pain detection showed a temporal pattern consistent with changes in plasma drug concentrations presented in Chapter 3. Indeed, examination of scatter-plots and correlation coefficients revealed no significant linear relationship between stimulus and pain detection scores and dose, weight-controlled plasma drug concentrations, opioid withdrawal (MSC), mood states (POMS) or any physiological parameter. To provide a more sensitive assessment of whether changes in plasma concentrations following dosing were associated with changes in responses to electrical stimulation-induced pain, changes in stimulus detection and pain detection between baseline and the time of peak plasma drug concentration for each subject were determined for methadone and SROM. For methadone

maintenance, the mean increase in plasma (R)-methadone concentration of 104 ± 58 ng/mL (range 24-241 ng/mL) from baseline to peak was associated with a significant decrease in stimulus detection (25.0 ± 7.9 V vs. 20.4 ± 6.5 V, $t(13) = 2.32$, $p = 0.04$) and a non-significant decrease in pain detection (43.7 ± 8.6 V vs. 40.9 ± 12.5 V, $t(13) = 1.08$, $p = 0.30$). For SROM maintenance, the mean increase in plasma morphine concentration of 80 ± 49 ng/mL (range 43-358 ng/mL) from baseline to peak was associated with significant decreases in both stimulus detection (25.6 ± 9.2 V vs. 19.7 ± 7.2 V, $t(13) = 2.37$, $p = 0.03$) and pain detection (47.3 ± 10.9 V vs. 35.3 ± 11.1 V, $t(13) = 4.40$, $p = 0.001$).

Assessments of Cronbach's alpha indicated a very high level of consistency in subjects' stimulus detection (methadone 0.95; SROM 0.95) and pain detection (methadone 0.95; SROM 0.98) thresholds across the 11 repetitions of the electrical stimulation procedure conducted for both methadone and SROM. Significant correlations were also found between subjects' mean stimulus detection and pain detection thresholds (methadone $r = 0.53$, $p = 0.05$; SROM $r = 0.89$, $p = 0.001$), such that subjects perceiving the stimulus earlier also perceived the stimulus as painful earlier and vice versa. Based on subjects' mean responses for the methadone and SROM assessments, test-retest correlations indicated only a moderate degree of consistency for stimulus detection ($r = 0.42$, $p = 0.14$) but a strong degree of consistency for pain detection ($r = 0.79$, $p = 0.001$; see Figure 6-2). Collectively, these results suggest that the electrical stimulation pain induction method produced reliable and consistent results. The apparent insensitivity of this pain induction method to changes in plasma (R)-methadone and morphine concentrations during the inter-dosing interval is therefore not readily attributable to measurement error.

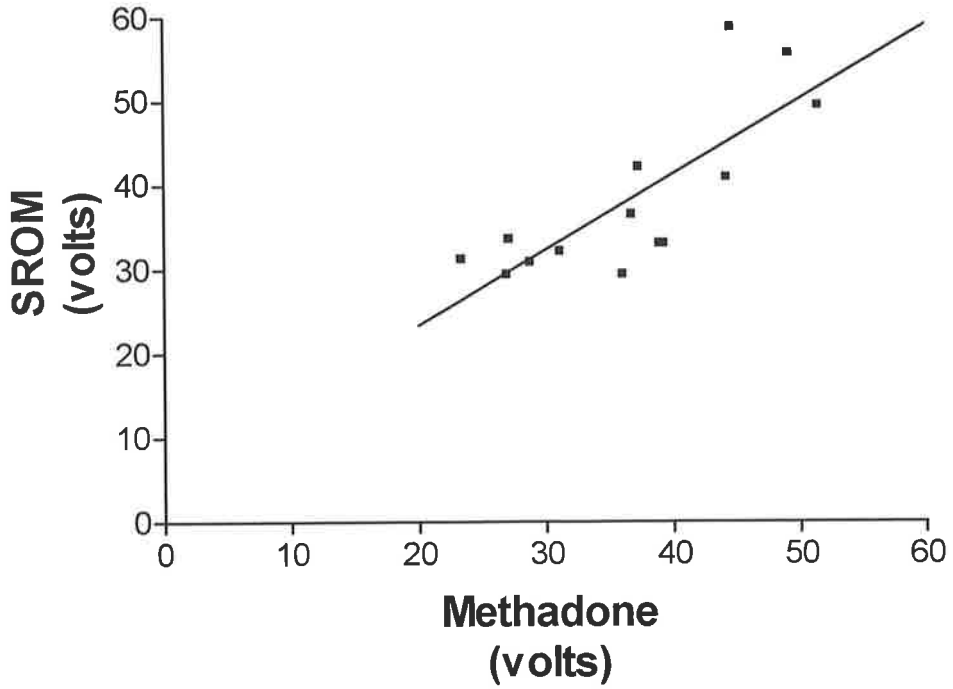

Figure 6-2. Scatter plot of average electrical stimulation pain detection scores obtained approximately 6 weeks apart for methadone and SROM (n=14).

Linear regression analyses indicated that mean responses for both stimulus detection (methadone $r^2 = 0.67$, $p = 0.002$; SROM $r^2 = 0.47$, $p = 0.02$) and pain detection (methadone $r^2 = 0.66$, $p = 0.002$; SROM $r^2 = 0.64$, $p = 0.032$) tended to increase with each assessment. This result is consistent with an order effect, such that repetitions of the electrical stimulation procedure were associated with predictable declines in mean pain responses.

6.3.2. Cold pressor test

Comparisons of cold pressor pain detection and tolerance scores for methadone and SROM are presented in Figure 6-3. There were no significant mean differences between methadone and SROM for either pain detection (4.6 ± 1.8 s vs. 4.6 ± 2.3 s, $t(13) = -0.15$, $p = 0.89$) or pain tolerance (15.0 ± 7.8 s vs. 16.1 ± 8.9 s, $t(13) = -0.86$, $p = 0.41$). Repeated-measures ANOVA indicated no significant effects for methadone holding status or holding status × maintenance drug for either pain detection ($p \geq 0.55$) or tolerance ($p \geq 0.25$). Inspection of scatter plots and correlation coefficients indicated no significant relationships between cold pressor detection and pain tolerance scores for methadone and SROM and indices of opioid effect including

plasma (R)-methadone or morphine concentrations, the ratio of (S)- to (R)-methadone (applicable to methadone only), POMS mood scores, or the number of self-reported opioid withdrawal symptoms ($p \geq 0.19$).

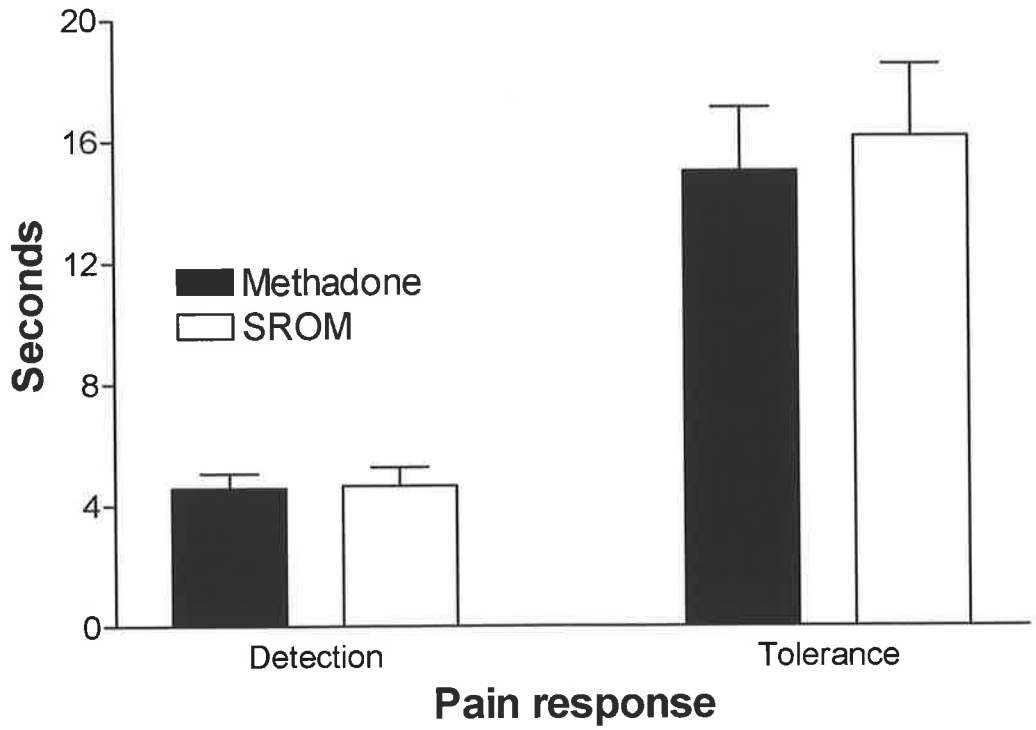

Figure 6-3. Pain detection and tolerance for the cold pressor test prior to dosing for methadone and SROM (n=14). Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone vs. SROM).

Test-retest correlation coefficients using scores for methadone and SROM were moderate for pain detection ($r = 0.65$, $p = 0.01$) and strong for pain tolerance ($r = 0.83$, $p < 0.001$). A scatter plot of cold pressor pain tolerance scores for methadone and SROM is shown in Figure 6-4. The level of consistency and similarity evident in subjects' responses to the cold pressor test is highly notable, given that the two tests involved a change of maintenance medication and were separated by 6 weeks. Moderate to strong correlations between pain detection and tolerance scores were observed for methadone ($r = 0.79$, $p = 0.001$) and SROM ($r = 0.51$, $p = 0.07$), suggesting good within-subject consistency in responses to cold pressor induced pain.

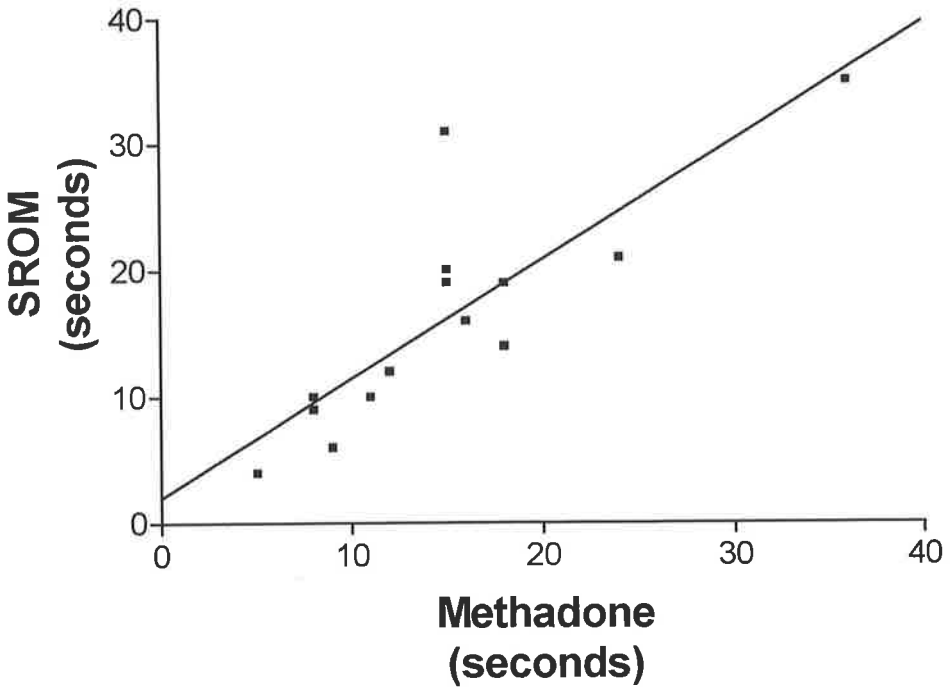

Figure 6-4. Scatter plot of cold pressor pain tolerance scores obtained approximately 6 weeks apart for methadone and SROM (n=14).

6.3.3. Relatedness of pain induction methods

As the results presented above suggest that both the electrical stimulation and cold pressor tests produced consistent and reliable results, it is of interest to examine whether subjects' responses to these two different forms of nociceptive stimuli are related. Inspection of scatter plots and correlation coefficients indicated no significant correlations between stimulus and pain detection thresholds for the electrical stimulation procedure and pain detection and tolerance thresholds for the cold pressor test ($-0.23 \geq r \leq 0.40$; $p \geq 0.16$).

6.4.Discussion

The purpose of the present study was to compare sensitivity to pain for methadone and SROM as maintenance pharmacotherapies for opioid dependence. Sensitivity to pain induced by electrical stimulation of the earlobe (measured on 11 occasions throughout a 24-hour inter-dosing interval) and the cold pressor test (measured on one occasion prior to dosing) was assessed in 14 methadone maintenance patients after at least 4 weeks on a stable dose of each drug. Results indicated that responses to both electrical stimulation- and cold pressor-induced pain remained highly stable between assessments for methadone and SROM and did not differ significantly for each drug. The high degree of consistency in subjects' responses to pain for methadone and SROM was notable given the subjective nature of pain measurement, the approximately 6-week interval separating each assessment, and the differential interaction of methadone and morphine with multiple neurotransmitter systems (e.g., opioid, NMDA, serotonergic, noradrenergic) involved in the perception of pain. Although both the electrical stimulation and cold pressor pain induction methods yielded consistent results, responses to each measure were not significantly correlated. These results have a number of important implications for both the delivery of maintenance treatment and the measurement of pain in experimental settings.

Results obtained for electrical stimulation-induced pain in the present study are only partly consistent with three previous studies that have assessed pain responses in methadone maintenance patients using this method (Doverty et al., 2001a; Doverty et al., 2001b; Dyer et al., 1999). In the present study, the mean voltage at which subjects first perceived the stimulus as painful (pain detection threshold) whilst maintained on methadone was 44 V prior to dosing and subsequently showed a steady and significant decline to reach a nadir of 32 V at 9 hours post-dose. In studies by Dyer et al. (1999) and Doverty et al. (2001a; 2001b), the pain detection threshold was directly related to plasma methadone concentrations, with each study similarly showing an increase from approximately 29-31 V to 37-38 V from pre-dose levels to the time of putative peak plasma methadone concentrations (3 h). Thus, whilst consistent in

finding a similar range of values for pain detection during the methadone inter-dosing interval, results of the present study differed by showing a slightly higher level of pain detection prior to dosing and a pattern of pain detection post-dose that, contrary to hypothesis 1, was not consistent with fluctuations in plasma methadone concentrations. The absence of such a relationship also applied to patterns of pain detection for SROM.

In attempting to reconcile the discrepancies between the result of the present study and those of earlier investigations that examined nociceptive responses to electrical stimulation, a number of issues warrant attention. Firstly, the possibility that the absence of apparent opioid effect on pain detection in the present study was due to measurement error seems highly unlikely, given the high degree of consistency in responses within- and between- sessions. The significant correlation between stimulus detection and pain detection values similarly suggests that subjects' responses to the stimulus were internally consistent. It is similarly unlikely that there were any major methodological variations between the three studies, since the equipment and procedures used (e.g., rate and magnitude of incremental voltage increases) were the same in each case.

To this extent, possible variations in the patient populations under investigation must be considered. In this respect, it is notable that the mean methadone dose in the present study (78 mg) was higher than that reported by Dyer et al. (1999) (65 mg) and Doverty et al. (2001b) (62 mg). It is possible that the higher doses shown by subjects in the present study were associated with greater tolerance and cross-tolerance to the analgesic effects of methadone and morphine, respectively. Doverty et al.'s (2001a) other study showed a mean methadone dose of 81 mg, but sampled only 4 patients. It is also notable that subjects in Dyer's (1999) study, but not the present study, showed significant increases in MBG (positive opioid effect) scores during the methadone inter-dosing interval, providing further indication of a possible difference in the magnitude of direct opioid effects experienced by the two samples. Other

than methadone dose, there were no readily discernible differences in the patient populations sampled in each study.

Since nociceptive responses to the electrical stimulation procedure were highly consistent, but insensitive to large peak to trough changes in plasma (R)-methadone (mean 104 ng/mL) and morphine (mean 80 ng/mL) concentrations, the external validity of this pain induction method must be addressed. As described in the introduction, electrical stimulation is a relatively non-selective stimulus (i.e., it activates many peripheral fibres not involved in nociception), involves a short-circuiting of the peripheral nociceptors that would otherwise initiate electrical conductance, and produces an unnatural sensation not readily comparable to anything normally encountered in day to day life (Le Bars et al., 2001). Anecdotally, comments of subjects indicated that many perceived the stimulus as "annoying" and "irritating" more so than painful. Curiously, some subjects described the electrical stimulation stimulus as more unpleasant, yet less painful, in comparison to the cold pressor test. It should also be noted that opioids are considered more effective in relieving the dull, burning pain associated with slower conducting C-fibres in comparison to the sharp, well-localised pain associated with rapidly-conducting A-delta fibres (Le Bars et al., 2001). Since electrical stimulation produces a sharp, intense stimulus more representative of A-delta than C-fibre activity (Le Bars et al., 2001), this may also partially explain the lack of analgesic effect observed for methadone and morphine on the electrical stimulation measures in the present study.

In comparison to results for the electrical stimulation procedure, results for the cold pressor test in the present study were highly consistent with previous studies in methadone maintenance patients that used the same method (Doverty et al., 2001a; Doverty et al., 2001b). The mean times associated with the detection of pain (pain detection) and the point at which the pain became intolerable (pain tolerance) for methadone in the present study (5 and

15 s) were very similar to those reported in two studies by Doverty and colleagues: (1) 5 and 13 s (Doverty et al., 2001a) and (2) 5 and 16s (Doverty et al., 2001b) for pain detection and tolerance, respectively (data estimated from graphs). Whilst maintained on methadone, only 1 subject in the present study tolerated the ice water bath for longer than 24 seconds (35 s). Notably, this subject (id. no. 9: male, age 34 years) had been maintained on methadone for only 6 weeks and reported consistent use of heroin (no interruptions greater than one week) for just two months prior to entry, despite first using heroin at the age of 17. These results support earlier studies suggesting methadone maintenance patients are hyperalgesic to cold pressor pain, in which healthy control subjects have been shown to tolerate the ice water bath for more than 50 seconds on average (Doverty et al., 2001a; Doverty et al., 2001b).

Extending these earlier findings, the results of the present study indicate that hyperalgesia may also apply when morphine, instead or methadone, is used for maintenance treatment of opioid dependence. The cold pressor test yielded almost identical values for methadone and SROM for both pain detection (4.6 s vs. 4.6 s) and pain tolerance (15.0 s vs. 16.1 s). Only 1 subject showed a difference of greater than 5 seconds in pain tolerance for SROM compared to methadone, with correlation coefficients indicating a very strong relationship ($r = 0.89$) between scores obtained for each drug. This degree of consistency in pain responses is noteworthy for a number of reasons, including the subjective nature of pain measurement, the time interval separating assessments for each drug (approximately 6 weeks), and, in particular, the distinct actions of methadone and morphine on neurological systems involved in the perception of pain. It is apparent that these differences did not have any clinically significant impact on subjects' nociceptive responses to pain induced by the cold pressor test over the time-course considered in the present study. Despite the high degree of similarity in cold pressor responses for methadone and SROM, it must be noted that the total duration of prior maintenance treatment was significantly greater for the former drug. To conclusively demonstrate that methadone and SROM exhibit an equivalent capacity to produce

hyperalgesia, as assessment of nociceptive responses in individuals who have been maintained on SROM without prior exposure to methadone is necessary.

The findings of the present study support earlier work indicating that chronic opioid exposure is associated with an enduring and marked reduction in pain tolerance (Compton et al., 2000; Compton et al., 2001; Doverty et al., 2001b). The apparent specificity of this effect and its stability over time, despite a change in the maintenance medication, is consistent with a previous conceptualisation of opioid tolerance as resembling an immune response (i.e., all or none), rather than a dose-response curve (Aylett, 1982). This has important implications for the aetiology and treatment of opioid dependence. Foremost, it is evident that irrespective of whether maintenance patients report normalisation of the opioid withdrawal and other physical signs of opioid dependence, chronic opioid treatment is likely to be ineffective in normalising perception of pain and may even make the problem worse. To the extent that chronic pain is associated with negative affective states (Hunt & Mantyh, 2001) that may precipitate compensatory use of illicit opioids (Unnithan et al., 1992), it is possible that maintenance treatment may inherently contribute to a continuation of opioid-seeking behaviour. Further research is required to establish the legitimacy of these potential threats to treatment outcome and to investigate possible interventions for the problems of hyperalgesia during chronic opioid treatment. For reasons outlined in the introduction, these efforts will also markedly influence the capacity to deliver effective pain management in this population, given the numerous barriers to that currently impede this process (Compton & McCaffery, 2001; Doverty et al., 2001b).

Results of the present investigation also have implications for the assessment of pain in experimental settings. Previous authors have highlighted how variations in the methods used to induce pain in experimental settings can produce variability in results and hence the need to use more than one pain induction procedure (Compton & McCaffery, 2001; Doverty et al.,

2001b). However, to the best of my knowledge, no previous studies investigating pain responses in chronic opioid users have examined the relationship between responses obtained for two or more different pain induction tests. Although pain tolerance was measured only for the cold pressor test, and stimulus detection applied only to the electrical stimulation procedure, both tests featured the determination of pain detection thresholds. The present study found no relationship between responses to cold pressor and electrical stimulation pain.

In addition to highlighting the need for multiple pain induction methods, the lack of relationship between responses to the electrical stimulation and cold pressor methods suggests that one or both of these tests lacks external validity. In this respect, it is generally considered that the cold pressor test produces a pain that more closely resembles clinically encountered pain conditions in comparison to electrical stimulation (Le Bars et al., 2001). The insensitivity of electrical stimulation responses to large increases in plasma (R)-methadone and morphine concentrations in the present study, and evidence that methadone maintenance patients show hyperalgesic responses to the cold pressor but not the electrical stimulation test (Doverty et al., 2001a; Doverty et al., 2001b), further suggest that the latter lacks external validity. To the extent that previous studies have found changes in response to electrical stimulation during the methadone inter-dosing interval (Doverty et al., 2001a; Doverty et al., 2001b; Dyer et al., 1999), this procedure may nonetheless have some experimental utility as a means of tracking the time-course and magnitude of opioid effects between doses in some patients.

In conclusion, the present study has shown that pain responses amongst opioid dependent individuals undergoing maintenance treatment did not differ for methadone and SROM. In the case of the cold pressor test, both drugs were associated with markedly reduced pain tolerance relative to that which has been previously reported for healthy controls using the same experimental procedure. The persistence and stability of hyperalgesic responses to cold pressor pain despite the subjective nature of pain measurement, the time interval between

assessments for each drug, and the differences in the effects of methadone and morphine on physiological mechanisms involved in pain perception, is notable. The invulnerability of pain responses to each of these factors suggests, in agreement with previous findings, that chronic opioid exposure is associated with an enduring change in pain perception. This change persists irrespective of whether opioid withdrawal and other physical signs of opioid dependence show normalisation during maintenance treatment. To the extent that a heightened sensitivity to pain may directly or indirectly precipitate compensatory use of illicit opioids, further research is required to understand the potential ramifications of hyperalgesia for treatment outcome and the mechanisms by which effective interventions may operate.

7. CLINICAL EFFICACY AND ACCEPTABILITY OF METHADONE AND SROM

7.1. Introduction

Although preliminary reports indicate that SROM may have clinical utility as an alternative maintenance pharmacotherapy to methadone for the treatment of opioid dependence (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), quantitative comparisons of the clinical efficacy and acceptability of these two treatment modalities are presently lacking. Of the available reports in which use of SROM as a maintenance option has been documented, most have either comprised anecdotal reports or case studies (Brewer, 1995; Sherman, 1996), used SROM formulations requiring multiple doses per day (Fischer et al., 1999b; Fischer et al., 1996; Schneider, 1995), provided few quantitative descriptions of outcomes (Fischer et al., 1999b; Fischer et al., 1996; Schneider, 1995), not included a comparison group (e.g., methadone maintenance) (Kraigher et al., 2002), or focused on the use of SROM as a treatment option for opioid dependent, pregnant women (Fischer et al., 1998; Fischer et al., 1999b; Kraigher et al., 2002; Schneider et al., 1996). There have been just three controlled evaluations of once-daily SROM maintenance (Eder et al., 2002; Giacomuzzi et al., 2001; Kraigher et al., 2002), each of which sampled heroin users commencing treatment. Given the abundance of evidence supporting the use of methadone in maintenance programs, initial clinical implementation of SROM is most likely to involve its use as an alternative for patients responding poorly to methadone rather than as a first-choice treatment option. Moreover, although many studies suggest that SROM is well accepted and possibly preferable to methadone for many patients, it is unclear whether that preference is related to treatment outcome and thus whether the provision of a choice between methadone and SROM would facilitate better retention in maintenance programs. The present study compared the clinical efficacy and acceptability of methadone and SROM and attempted to address key areas of uncertainty that have yet to be adequately addressed by previous investigations of SROM maintenance.

7.1.1. Limitations of the existing evidence-base

As a detailed description of previous evaluations of SROM maintenance was provided in Chapter 1, the focus of the present discussion will be the major shortcomings of those studies and the areas of knowledge for which further investigation is required. Many of the limitations associated with the existing evidence base for SROM maintenance concern the applicability of previous findings to the clinical problems and issues being addressed in the present study. At the most general level, it is notable that nearly all of the publications reviewed earlier that describe the use of SROM for maintenance of opioid dependence, including all of the clinical trials, were conducted in Austria (Eder et al., 2002; Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Fischer et al., 1996; Giacomuzzi et al., 2001; Kraigher et al., 2002; Schneider, 1995; Schneider et al., 1996). Since there may be important contextual differences between Austria and other countries, including differences in treatment delivery and patient characteristics, it is important that controlled clinical evaluations of SROM maintenance are carried out in other treatment contexts.

Additionally, as noted earlier, most of these previous reports comprised anecdotal or case study reports (Brewer, 1995; Roberts & Crofts, 2000; Sherman, 1996), used short-acting SROM formulations requiring multiple doses per day (Brewer, 1995; Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Fischer et al., 1996; Schneider, 1995; Schneider et al., 1996) or involved the use of SROM for maintenance of opioid dependent, pregnant women (Fischer et al., 1999a; Fischer et al., 1998; Fischer et al., 1999b; Schneider, 1995; Schneider et al., 1996). Hence, although these reports implied that SROM is safe, efficacious and acceptable to patients, the extent to which these findings are informative regarding the clinical utility of once-daily SROM formulations in the wider opioid dependent and methadone maintenance population is somewhat limited.

Evaluations of once-daily SROM maintenance reported by Eder et al. (2002), Kraigher et al. (2002), and Giacomuzzi et al. (2001) are more informative. However, all of these studies sampled heroin users entering treatment and exhibited at least one major methodological limitation including the use of dextromethorphan as a placebo medication (Eder et al., 2002), the failure to include a control group (Kraigher et al., 2002), and the use of a cross-sectional comparison of seemingly non-comparable groups (Giacomuzzi et al., 2001). Given the abundance of evidence supporting methadone maintenance, initial use of SROM in Australia is most likely to involve its selective use as an alternative for patients already maintained on methadone but who report unfavourable responses. This includes the high proportion of methadone maintenance patients who experience inadequate withdrawal suppression and adverse effects whilst maintained on methadone (Dyer & White, 1997; Judson & Goldstein, 1982; Judson et al., 1976). As yet, there have been no controlled evaluations of once-daily SROM as an alternative for patients responding poorly to methadone.

Other limitations of the existing evidence base for SROM maintenance pertain to the selection of outcome measures in previous studies. In particular, the absence of studies in which the use of objective, biological markers specific for heroin (diacetylmorphine) use is notable. Although the standard clinical practice of assaying for urinary morphine levels cannot be used for SROM maintained patients, this does not preclude measurement of heroin (diacetylmorphine, DAM) and its specific metabolite 6-mono-acetylmorphine (6MAM). Since DAM and 6MAM both have short urinary detection windows (Reiter et al., 2001), it is preferable that other cumulative indices of heroin use (e.g., analyses of hair samples and sweat patches) are also employed (Kintz, Bundeli, Brenneisen, & Ludes, 1998; Taylor, Watson, Tames, & Lowe, 1998). The determination of DAM and 6MAM concentrations in hair samples is one such method that has been successfully utilised in evaluations of other maintenance pharmacotherapies such as LAAM and methadone (White et al., 2002).

Another major limitation of the existing evidence base for SROM maintenance is that several authors have reported a number of positive patient outcomes in comparison to methadone (e.g., improved sleep, weight loss, increased drive and concentration) (Fischer et al., 1996; Schneider, 1995) without providing quantitative data in support of such findings. Moreover, although the results of many studies imply that SROM has high efficacy and patient acceptability among maintenance patients, no studies have quantified patient preference for methadone or SROM, examined the reasons for preferring either drug, or related treatment preference to patient outcomes. Additional issues pertaining to the selection of appropriate outcome indicators are discussed below.

7.1.2. Selecting appropriate outcome indicators

The comparison of patient outcomes and preference for methadone- and SROM maintenance in the current study presents a number of challenges that warrant discussion. Foremost among these is the need to select an appropriate battery of outcome indicators given the resource and methodological constraints of the study. The goals of maintenance treatment are multifaceted and often require long periods of treatment and large numbers of subjects in order for the observed consequences of treatment to become apparent (e.g., protection against HIV infection). There are nonetheless a number of important treatment outcome indicators for which clinically significant differences, if present, may be expected to become apparent within the confines of a six week crossover comparison of methadone and SROM.

In selecting the clinical endpoints for which comparisons for methadone and SROM should be made in the present study, three categories of important treatment outcome indicators are readily discernible. The first category comprises standard clinical outcome indicators that are commonly used to assess treatment progress and which are likely to be sensitive to changes in opioid withdrawal and other foci of the present investigation. Among this category are subjective and objective (e.g., hair analysis) measures of additional drug use and indices of depression and health. Although drug use is often emphasised as the primary endpoint of

treatment, it is noteworthy that some studies have found that outcomes pertaining to health and social functioning, rather than drug use per se, are more important determinants of outcomes and retention in treatment (Rounsaville & Kleber, 1985). These outcomes were assessed using the Beck Depression Inventory and SF-36 Health Survey, for which comparative data in opioid dependent populations are available (Ryan & White, 1996; Steer, Emery, & Beck, 1980; White et al., 2002).

A second category of outcome indicators involves the measurement of patient outcomes for which the existing evidence base has suggested possible differences between methadone and SROM, but for which no quantitative data have yet been presented. Among this category are changes in body weight, sleep patterns and both self-esteem and social functioning (Fischer et al., 1996; Schneider, 1995).

A third category of outcome measures involves the quantification of patient preference for methadone and SROM and, moreover, the relationship between treatment preference and outcomes. The clinical utility of SROM as an alternative maintenance pharmacotherapy to methadone is subject not only to its efficacy but also to the likelihood that patients will choose to remain in treatment and that retention will result in positive treatment outcomes (White et al., 2002). In addressing these issues, it is important to also incorporate qualitative assessments (e.g., semi-structured interviews) of patient outcomes and preference, as it is unreasonable to expect that the selected quantitative outcome indicators will encompass all clinically significant differences between the two medications. Qualitative information of this nature is likely to be particularly beneficial in informing the selection of outcome measures in further, large-scale comparisons of methadone and SROM maintenance.

7.1.3. The present study

In spite of preliminary evidence suggesting that once-daily SROM is an effective alternative to methadone for maintenance treatment of opioid dependence, quantitative comparisons of

these two treatments are lacking and a number of questions remained unanswered. The present study compared the clinical efficacy (objective and subjective indices of heroin and other drug use, depression, health, social functioning, self-esteem, sleep quality, body weight) and acceptability (treatment preference and satisfaction) of methadone and SROM in methadone maintenance patients reporting adequate (holders) or inadequate (non-holders) withdrawal suppression between doses. On the basis of the studies reviewed above (and in detail in Chapter 1), it is anticipated that the overall clinical efficacy and acceptability of SROM will be at least as good as for methadone. To this extent, it is expected that the clinical efficacy and acceptability of each drug will be similar in the methadone holder group but will improve for SROM compared to methadone in the methadone non-holder group.

7.1.3.1. Aims

Specific aims of the present study were:

- To determine whether SROM and methadone produce equivalent clinical outcomes.
- To determine whether comparative clinical outcomes for methadone and SROM differ for methadone holders and non-holders.
- To quantify patient preference for methadone and SROM in relation to treatment outcomes.
- To explore differences between methadone and SROM using qualitative research instruments.

7.1.3.2. Hypotheses

1. For the methadone holders, treatment efficacy and acceptability will be at least as good for SROM as for methadone.
2. For the methadone non-holders, treatment efficacy and acceptability will show significant improvements for SROM compared to methadone.

7.2.Methods

7.2.1. Subjects and procedures

The subjects and general procedures for this aspect of the study were described in Chapter 2. General clinical outcomes were compared for methadone and SROM in fifteen volunteers undergoing maintenance treatment for opioid dependence after at least 4 weeks on a stable dose of each drug in an open-label, randomly-ordered, crossover design. This included a subject who completed the two 24-hour inter-dosing interval assessments for methadone and SROM, respectively, but whose data were excluded following evidence of additional opioid use.

7.2.2. Measures

The following measures were collected during the 24-hour assessments conducted for methadone and SROM and were used to assess outcomes in the month prior to assessment for each drug. First, hair samples (1cm of most recent growth) were collected for later quantification of concentrations of the diacetylmorphine (heroin), 6-monoacetylmorphine, and morphine. Second, subjects were engaged in a structured interview regarding their employment, welfare benefits, drug use, criminal behaviour and legal pressures, contact with medical specialists, illnesses, and medication usage in the previous 4 weeks. For each of the following drug classes, subjects were also asked to state the number of days they had used the drug in the preceding month: heroin, "street" methadone, other opiates (excluding heroin and maintenance drug), alcohol, tobacco, amphetamines, cocaine, ecstasy, hallucinogens, marijuana, benzodiazepines, and inhalants. Body weight and height were recorded using standard scales and used to calculate the percentage change in body mass index (kg/m^2) for SROM compared to methadone. Subjects self-administered the following questionnaires pertaining to their physical and mental health.

The *SF-36 Health Status Questionnaire* (Ware et al., 1993) comprises 36 items that yield scores on eight health subscales: general health, mental health, physical functioning, bodily pain, vitality, social functioning, role limitations due to emotional problems, and role limitations due to physical problems. Scores for each scale are summed and transformed to a scale ranging from 0 (worst possible health state) to 100 (best possible health state).

The *Beck Depression Inventory (BDI-II revised)* (Beck et al., 1996) comprises 21 groups of 4 statements for which subjects indicate the statement that best describes how they are feeling. Each statement yields a score ranging from 0 to 3 that are summed to produce an overall depression score (range 0-63), with higher scores indicating poorer mental health.

The *Leeds Sleep Evaluation Questionnaire (LSEQ)* (Parrott & Hindmarch, 1980) includes 10 × 100 mm VAS ratings that measure subjectively perceived changes with respect to four aspects of sleep: getting to sleep, quality of sleep, awakening from sleep, and behaviour following wakefulness. The LSEQ is used to directly monitor sleep changes during psychopharmacological interventions and requires subjects to indicate the degree of sleep change they perceived during the intervention compared to 'normal', such that the mid point of each scale represents no change and the extremes (±50 mm) represent maximum change. Subjects in the present study completed the LSEQ on the day of assessment for SROM maintenance and were asked to compare their sleep in the previous month with their 'normal' sleep patterns during methadone maintenance. The 0-100 mm VAS items were anchored as follows: How would you compare getting to sleep on Kapanol™ with getting to sleep normally (i.e., on methadone? (1) harder than usual – easier than usual, (2) slower than usual – quicker than usual, (3) felt less drowsy than usual – felt more drowsy than usual; How would you compare your quality of sleep while on Kapanol™ with your quality of sleep normally (i.e., on methadone)? (4) more restless than usual – more restful than usual, (5) more periods of wakefulness than usual – fewer periods of wakefulness than usual; How did your

awakening on Kapanol™ compare with your usual pattern of awakening (i.e., on methadone)? (6) more difficult than usual – easier than usual, (7) took longer than usual – took shorter than usual; How did you feel on waking? (tired – alert); How do you feel now? (tired – alert); How was your sense of balance and coordination upon getting up? (more clumsy than usual – less clumsy than usual).

As a supplement to the LSEQ, subjects completed a questionnaire asking them to specify, for a typical night in the preceding month, the average time at which they started trying to get to sleep, the length of time it took to get to sleep, the number of hours slept, the number of night-time awakenings, and the time of morning awakening. In addition, subjects were asked to rate the frequency (0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = very often) with which they were satisfied with the amount of sleep they had, found it difficult getting up in the morning, remembered their dreams, dreamt about things to do with drugs, and had unpleasant dreams.

The Opiate Treatment Index (OTI) (Darke et al., 1992) is a multi-dimensional instrument that provides a quick, valid and reliable assessment of patients undergoing treatment for opioid dependence on six independently measured outcome domains: drug use; HIV risk-taking behaviour; social functioning; criminality; health; and psychological adjustment. For the present study, subjects were presented with a selection of eight multiple-responses questions from the OTI social functioning scale, as follows: How often in the last month have you had conflict with your (1) relatives, (2) partner(s), and (3) friends? (Very often, often, sometimes, rarely, never); (4) about how many close friends would you estimate that you have (include partner)? (none, one, two, three, four or more); (5) When you are having problems, are you satisfied with the support you get from your friends? (very satisfied, satisfied, reasonably OK, not satisfied, very unsatisfied); (6) About how often do you see your friends? (very often, often, sometimes, fairly often, never); (7) How much of the last month have you been living

with anyone who uses heroin? (all of the time, most of the time, half of the time, some of the time, none of the time); and (8) How many of the people you hang around with now are users? (none, less than half, about a half, more than half, all of them).

As a measure of self-esteem, subjects completed a validated and reliable self-evaluation questionnaire developed by Bachman and O'Malley (Bachman & O'Malley, 1977). The questionnaire comprises 10 statements for which subjects are asked to select one of five possible responses according to how often the statement truthfully applies to them: almost always true, often true, sometimes true, not often true, and never true. The ten statements are: (1) I feel that I'm a person of worth, at least on an equal plane with others; (2) I feel that I have a number of good qualities; (3) I am able to do things as well as most other people; (4) I feel I do not have much to be proud of; (5) I take a positive attitude towards myself; (6) I think I am no good at all; (7) I am a useful person to have around; (8) I feel that I can't do anything right; (9) when I do a job, I do it well; and (10) I feel that my life is not very useful. Responses for each item can be scored from 0 to 4 such that high scores represent the most positive self-evaluation possible, yielding a self-esteem scale ranging from 0 to 40.

Subjects completed 7 × 100 mm VAS ratings asking them to rate their current maintenance medication according to the following questions (0-100 mm scale anchoring is presented in parentheses): How well has this drug been holding you? (too low – too high); How much of a buzz does this drug give you? (none – a lot); How many side effects do you feel from this drug? (none – a lot); How much do side effects from this drug bother you? (not at all – a lot); How much do you like this drug? (not at all – a lot); Does this drug make you feel more "normal"? (definitely no – definitely yes); How much do you crave heroin while on this drug (not at all – a lot)? These scales have been previously used to compare methadone and LAAM as maintenance pharmacotherapies (White et al., 2002).

To characterise qualitative and quantitative aspects of subjects' preference for SROM or methadone, the following measures were used. Firstly, as part of the questionnaire material described above, subjects were presented with open-ended questions asking them to describe the best and worst things about each drug and were also provided space to make any additional comments regarding either drug or the conduct of the trial. Secondly, upon termination or completion of the study, subjects were asked to state a preference for SROM or methadone and indicate the strength of that preference on a 100 mm VAS ranging from 0 (definitely prefer methadone) to 100 (definitely prefer SROM). They were also asked to specify their reasons for preferring either drug and to indicate which reason was the main factor influencing their choice.

7.2.3. Analysis of hair samples

Analyses of hair samples were performed by Noel Sims (Department of Forensic Sciences, State Government of South Australia) using previously described methods (Kintz et al., 1998). Hair samples were washed with dichloromethane and 1cm of the most recent growth was cut into 1 – 2 mm segments. Approximately 1-5 mg of hair was taken for each sample, depending upon availability. Following addition of deuterated internal standard, the hair segments were incubated overnight at 45°C in 1 millilitre of methanol. The solvent was removed and carefully evaporated and the residue was derivatised with pentafluoropropionic anhydride. Diacetylmorphine and 6-mono-acetylmorphine were identified and quantified by gas chromatography/mass spectrometry/mass spectrometry. Results were considered positive if the concentration of the drug in hair exceeded 0.005 ng/mg.

7.2.4. Statistical analyses

Comparisons of continuous outcome variables for methadone and SROM were conducted using paired t-tests for parametric data and the Wilcoxon test for non-parametric data. Frequency data were analysed according to the maintenance drug and methadone holding status using McNemar and chi-square tests. One-sample t-tests were used to contrast VAS

data for the LSEQ and treatment preference in reference to the scale midpoint. Pearson correlation coefficients were used to examine the linear association between outcomes and preference data. Multiple response analysis was used to examine subjects' specified reasons for choosing methadone or SROM. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). All significance tests were two-tailed and used an alpha level of 0.05. Data are presented as mean ± SD (range) unless otherwise indicated.

7.3.Results

7.3.1. Drug use

The frequency with which diacetylmorphine (DAM) and 6-mono-acteylmorphine (6MAM) were detected in hair samples for methadone and SROM is shown in Table 7-1. The proportion of subjects for whom recent heroin use was indicated, as evidenced by the presence of either DAM or 6MAM in hair, was similar for methadone and SROM (6/15 vs. 4/15, p = 0.63). There were also no differences between methadone and SROM in the concentrations of diacetylmorphine (0.02 ± 0.04 ng/mg vs. 0.12 ± 0.41 ng/mg, Z = -0.16, p = 0.86) and 6-monoacetylmorphine (0.83 ± 2.17 ng/mg vs. 0.81 ± 2.56 ng/mg, Z = -0.95, p = 0.34) detected in hair samples. The frequency of DAM or 6MAM detection did not differ significantly for methadone holders and non-holders during either methadone or SROM maintenance. It is notable, however, that heroin use for the non-holders was indicated more frequently than for the holders during methadone maintenance (4/7 vs. 2/8) but less frequently than for the holders during SROM maintenance (1/7 vs. 3/8). Only 1 non-holder returned a hair sample positive for heroin use during SROM maintenance, compared to 4 during methadone maintenance.

Table 7-1. Frequency of diacetylmorphine and 6-mono-acetylmorphine detection in hair samples for methadone and SROM: comparison for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.

	Methadone			SROM		
	All	Holders	Nonholders	All	Holders	Nonholders
DAM	**2**	0	2	**2**	1	1
6MAM	**6**	2	4	**4**	3	1
DAM/6MAM[a]	**6**	2	4	**4**	3	1

[a] Presence of either diacetylmorphine (DAM) or 6-mono-acetylmorphine (6MAM). $p > 0.05$ for all differences (methadone vs. SROM, holders vs. non-holders).

Table 7-2 shows the proportion of subjects self-reporting the use of additional drugs in the previous month. There were no significant differences in the frequency of self-reported use for the drug classes specified in Table 7-2 according to either the maintenance drug or

subjects' methadone holding status. The most commonly used drugs overall were tobacco (93%), benzodiazepines (80%) heroin (73%), marijuana (53%) and alcohol (53%), each of which were used by more than 50% of subjects at some stage during either the methadone or SROM evaluation periods. Use of diverted methadone, other opiates, cocaine, hallucinogens, amphetamines, ecstasy, and inhalants were reported at very low levels. There were no differences between methadone and SROM in the number of days that heroin (6.0 ± 10.2 vs. 3.6 ± 5.2, $t(14) = 1.29$, $p = 0.22$) marijuana (11.9 ± 15.0 vs. 13.2 ± 14.7, $t(14) = -0.45$, $p = 0.66$), benzodiazepines (6.4 ± 10.1 vs. 6.2 ± 11.0, $t(14) = 0.17$, $p = 0.86$) or alcohol (3.7 ± 7.1 vs. 3.7 ± 6.9, $t(14) = 0.00$, $p = 1.00$) were used in the previous month or in the average number of cigarettes used each day (13.8 ± 7.5 vs. 15.2 ± 8.7, $t(14) = -1.45$, $p = 0.17$; all subjects reported daily tobacco use). All cases of heroin use involved the intravenous route, indicating continued injecting behaviour was common amongst the subjects. However, only 1 subject reported sharing a needle at any stage during the study. Amongst those subjects who indicated they had injected heroin, the median number of injections per day of heroin use was 1 for both methadone (range 1-4) and SROM (range 1-2). The total number of different drug classes for which use was self-reported did not differ for methadone compared to SROM for all subjects (3.5 ± 1.5 vs. 3.7 ± 1.7, $t(14) = 0.63$, $p = 0.51$) or within the methadone holder (3.5 ± 1.6 vs. 3.6 ± 1.5, $t(14) = 0.24$, $p = 0.82$) and non-holder (3.4 ± 1.6 vs. 3.7 ± 1.9, $t(14) = 1.00$, $p = 0.37$) groups.

Table 7-2. Proportion of subjects self-reporting use of additional drugs in the previous month for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.

	Methadone			SROM		
	All (n, %)	Holders (n, %)	Nonholders (n, %)	All (n, %)	Holders (n, %)	Nonholders (n, %)
Tobacco	**14 (93)**	8 (100)	6 (86)	**14 (93)**	8 (100)	6 (86)
Benzodiazepines	**10 (67)**	6 (75)	4 (57)	**9 (60)**	5 (63)	4 (57)
Alcohol	**8 (53)**	4 (50)	4 (57)	**7 (47)**	3 (38)	4 (57)
Heroin	**7 (47)**	4 (50)	3 (43)	**10 (67)**	5 (63)	5 (71)
Marijuana	**6 (40)**	3 (38)	3 (43)	**8 (53)**	5 (63)	3 (43)
Other opiates[a]	**3 (20)**	2 (25)	1 (14)	**2 (13)**	2 (25)	0 (0)
Amphetamines	**2 (13)**	1 (13)	1 (14)	**1 (7)**	0 (0)	1 (14)
Ecstasy	**1 (7)**	0 (0)	1 (14)	**1 (7)**	0 (0)	1 (14)
Methadone[b]	**1 (7)**	0 (0)	1 (14)	**1 (7)**	0 (0)	1 (14)
Inhalants	**0 (0)**	0 (0)	0 (0)	**0 (0)**	0 (0)	0 (0)
Hallucinogens	**0 (0)**	0 (0)	0 (0)	**0 (0)**	0 (0)	0 (0)
Cocaine	**0 (0)**	0 (0)	0 (0)	**0 (0)**	0 (0)	1 (14)

[a] Use of opiates other than heroin or maintenance drug. [b] Use of diverted methadone. $p > 0.05$ for all differences (methadone vs. SROM, holders vs. non-holders).

7.3.2. Health and social functioning

SF-36 Health Survey scores for methadone and SROM are shown in relation to normative data for the general South Australian population (South Australian Health Commission, 1995) and a sample of heroin users upon entry to methadone maintenance (Ryan & White, 1996) in Figure 7-1. The the health status of the sample was consistently lower than population norms but above norms for heroin users entering maintenance treatment for both methadone and SROM. Health scores for SROM were equivalent or superior to methadone for 7 of the 8 scales, although improvements in social functioning were the only such difference ($p = 0.01$) to reach statistical significance. Notably, significant improvements in social functioning were evident for the holders ($p = 0.05$) but not the non-holders ($p = 0.08$), although the latter group showed a trend towards improvement. Conversely, significant improvements in the Bodily Pain scale were evident for the non-holders ($p = 0.03$) but not the holders ($p = 0.41$).

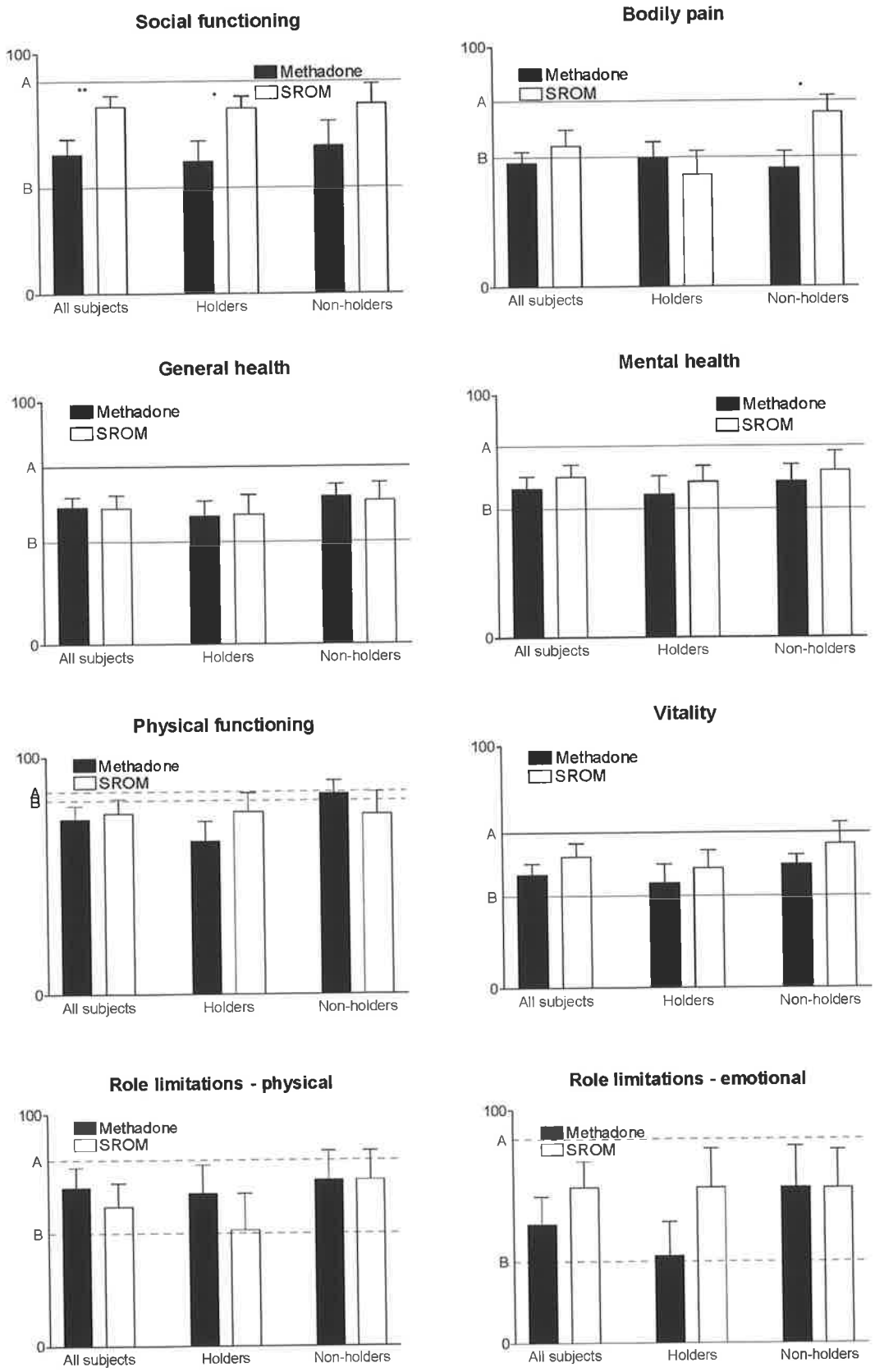

Figure 7-1. SF-36 Health Survey scores for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Dotted lines show normative means for (A) South Australia population norms and (B) a sample of heroin users upon entry to methadone maintenance. Data are presented as mean ± SE. $p < 0.05$, ** $p < 0.01$ (methadone vs. SROM).*

Response frequencies for OTI social functioning questions are contrasted for methadone and SROM in Table 7-3. There were no significant differences between methadone and SROM in the frequency with which subjects reported conflict with relatives, partners and friends, and contact with friends and heroin users. There were also no significant differences between holders and non-holders on these items. Frequent conflict ("often" or "very often") with friends, relatives and partners was relatively uncommon. Frequent conflict with partners was more common for SROM compared to methadone (5/8 vs. 2/10); however, this difference was not significant ($p = 0.08$). Fourteen of the 15 subjects reported having at least two good friends, two-thirds reported frequent contact with friends, and less than a fifth reported any level of dissatisfaction with the support they received from friends. Approximately one-third of the sample reported that more than a half or more of their friends were heroin users and a similar proportion of subjects reporting living with heroin users most or all of the time.

Table 7-3. Responses to social functioning items from the Opiate Treatment Index for methadone and SROM (n=15).

OTI Item		Response categories				
Conflict with relatives		Never	Rarely	Sometimes	Often	V. Often
	Meth	3	5	4	1	2
	SROM	4	5	3	0	3
Conflict with partner(s)		Never	Rarely	Sometimes	Often	V. Often
	Meth	2	6	0	1	1
	SROM	0	1	2	4	1
Conflict with friends		Never	Rarely	Sometimes	Often	V. Often
	Meth	6	6	3	0	0
	SROM	4	9	2	0	0
Number of close friends		≥ Four	Three	Two	One	None
	Meth	6	4	4	0	1
	SROM	9	2	3	1	0
Satisfaction with support		V. Satis	Satisfied	Reasonable	Not satisf	V. Unsat.
	Meth	4	2	6	2	1
	SROM	3	6	5	1	0
Contact with friends		V. Often	Often	Sometimes	Rarely	Never
	Meth	1	8	4	1	1
	SROM	2	6	5	2	0
Living with heroin users		None of the time	Some of the time	Half of the time	Most of the time	All of the time
	Meth	7	4	0	1	3
	SROM	8	3	0	1	3
Friends with users		None	< Half	About half	> Half	All
	Meth	5	5	2	3	0
	SROM	4	6	0	4	1

$p > 0.05$ for all differences (methadone vs. SROM).

Structured interviews indicated similar patient outcomes for methadone and SROM on health and social functioning indices relating to employment and social welfare, criminal behaviour

and legal problems, and the frequency of clinician contact, illnesses and medication usage. Only 1 patient for methadone and 3 patients for SROM reported paid employment in the month prior to assessment. All subjects received social welfare payments while receiving methadone and SROM, with a similar number stating the reason for support as unemployment (5 vs. 6), single-parent status (3 vs. 3), and disability (5 vs. 4) for each drug. Involvement in criminal behaviour was generally reported at low levels for both methadone and SROM and included isolated (n=1) incidences of shoplifting for both methadone and SROM and an injurious assault (n = 1) by one subject whilst maintained on SROM. By comparison, reports of drug dealing were more common for both methadone (n=4) and SROM (n=4), and included reports of heroin dealing (2 vs. 1) and dealing in other drugs (marijuana) (3 vs. 4) for both treatment phases. Reports of contact with law enforcement and judiciary bodies were also infrequent. During SROM maintenance, one subject reported receiving a police caution and another subject reported two court appearances related to an event pre-dating the study. Methadone and SROM showed similar results in terms of the frequency of contact with general practitioners (8vs. 8) and other specialist (2 vs. 3), and of illnesses (9 vs. 9) and use of additional medications (9 vs. 8). Notably, in comparison to methadone, SROM was associated with fewer appointments to see medical officers (8 vs. 3) and counsellors (8 vs. 1) at the methadone clinic in the month prior to assessment. Assessments of body weight indicated that body mass index showed a small percentage decline (1.2 ± 0.2%, $t(14) = 2.10$, $p = 0.05$) for SROM (23.1 ± 4.4) compared to methadone (23.4 ± 4.4).

7.3.3. Depression and self-esteem

BDI scores are contrasted for methadone and SROM in Figure 7-2. BDI scores were lower for SROM compared to methadone for the subjects as a whole and for both the methadone holder and non-holder subgroups, but these differences were not significant. There were also no significant differences between methadone and SROM in the proportion of subjects showing BDI scores within the normal (7 vs. 8), mild to moderate (3 vs. 4), and moderate to severe (5

vs. 3) ranges (p = 0.63). Mean BDI scores were within the mild to moderate range for both methadone and SROM. The test-retest (methadone-SROM) correlation for the BDI was significant (r = 0.67, p = 0.006). Analyses of individual BDI items indicated that, in comparison to methadone, SROM was associated with reductions in self-criticalness (p = 0.02), indecisiveness (p = 0.02) and appetite changes (p = 0.03).

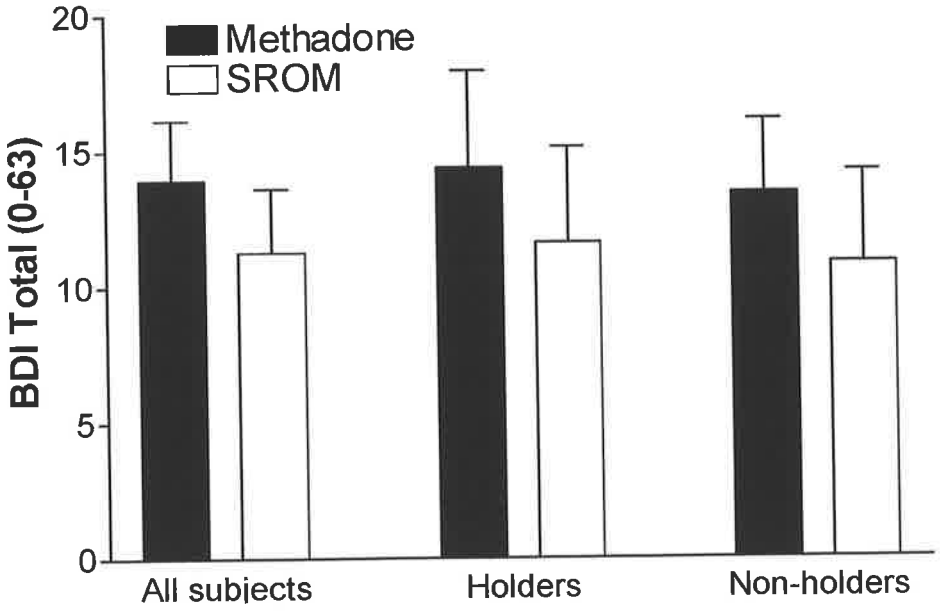

Figure 7-2. Beck Depression Inventory scores for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean ± SE. p > 0.05 for all differences (methadone vs. SROM).

Self-esteem scores for methadone and SROM are shown in relation to normative data provided by Bachman and O'Malley in Table 7-4. As there were no significant differences in mean self-esteem index scores for methadone holders and non-holders during either methadone (3.4 ± 0.7 vs. 3.4 ± 0.6, p = 0.82) or SROM (3.4 ± 0.7 vs. 3.3 ± 0.6, p = 0.86), data are presented for the subjects as a whole. The mean self-esteem index score for both methadone and SROM was 4.0 ± 0.6, which was similar to normative values (4.2 ± 0.5). Self-esteem scores showed a significant inverse correlation with BDI scores for both methadone (r = 0.66, p = 0.008) and SROM (r = 0.79, p < 0.001). The test-retest (methadone-SROM) correlation for self-esteem scores was also highly significant (r = 0.76, p = 0.001).

Table 7-4. Self-esteem responses for methadone and SROM (n=15).

	Methadone		SROM		Norms[c]	
Item	Mean	SD	Mean	SD	Mean	SD
I feel I am a person of worth, at least on an equal plane with others[a]	4.2	0.9	4.1	1.2	4.5	0.7
I feel I have a number of good qualities[a]	4.3	0.7	4.3	0.7	4.4	0.7
I am able to do things as well as most other people[a]	4.3	0.7	4.3	0.7	4.3	0.7
I feel I do not have much to be proud of[b]	3.4	1.1	3.6	1.1	4.0	1.0
I take a positive attitude towards myself[a]	3.6	0.8	3.5	1.3	4.1	0.9
I think I am no good at all[b]	4.2	0.8	4.3	1.0	4.1	0.9
I am a useful person to have around[a]	3.9	0.8	3.7	1.1	4.0	0.8
I feel I can't do anything right[b]	4.0	1.0	3.7	1.1	4.1	0.8
When I do a job, I do it well[a]	4.1	0.8	4.1	1.0	4.4	0.3
I feel my life is not very useful[b]	3.8	1.2	3.9	1.10	4.2	0.8
Self-esteem index	**4.0**	**0.6**	**4.0**	**0.6**	**4.2**	**0.5**

[a] Response of "almost always true" coded 5. [b] Response of "never true" coded 5. High scores indicated better self-esteem (max. = 5). [c] Data from Bachman and O'Malley based on 1608 males. $p > 0.05$ for all differences (methadone vs. SROM).

7.3.4. Sleep patterns

The time taken to get to sleep (sleep latency), total amount of sleep (sleep duration) and average number of nightly awakenings are contrasted for methadone and SROM in Table 7-5. These data indicate that the sleep duration was significantly less for SROM compared to methadone. This difference was common to both holders and non-holders, but only reached significance in the former group. The mean reduction in the total number of hours slept for SROM compared to methadone was approximately 1 hour. There were no significant differences between methadone and SROM in terms of sleep latency or the frequency of nightly awakenings.

Table 7-5. Sleep latency, duration and awakenings for methadone and SROM for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.

	Methadone			SROM		
Parameter	All	Holders	Nonholders	All	Holders	Nonholders
Latency (h)	1.0 ± .78	0.9 ± 0.7	1.2 ± 0.9	1.1 ± 1.1	0.8 ± 0.5	1.5 ± 1.6
Duration (h)	*7.3 ±1.6	*7.6 ± 1.7	6.9 ± 1.5	*6.2 ±1.6	*6.4 ± 1.6	5.9 ± 1.8
Awakenings	2.6 ± 1.4	2.1 ± 1.3	3.1 ± 1.1	2.9 ± 1.8	3.1 ± 2.4	1.1 ± 1.1

Values are mean ± SD. * $p < 0.01$ (methadone vs. SROM).

Comparisons of sleep satisfaction, waking behaviour and dreaming patterns for methadone and SROM are presented in Table 7-6. There were no differences on these parameters according to methadone holding status, except that non-holders reported less frequent sleep satisfaction than holders during methadone maintenance (2.4 ± 0.9 vs. 1.4 ± 0.5, $t(13) = 2.39$, $p = 0.03$). Data are thus presented for the subjects as a whole. The proportion of subjects reporting infrequent ("never" or "rarely") satisfaction with the amount of sleep they had each night was greater for methadone (12/15) compared to SROM (8/15), and exceeded 50% in both treatment phases. Difficulties getting up in the morning were similarly infrequent for methadone (10/15) and SROM (12/15). For both methadone and SROM, 60% subjects reported unpleasant dreams "sometimes", "often", or "very often". The majority (73%) of subjects reported "rarely" or "never" dreaming about things to do with drugs for both methadone and SROM, although it is notable that approximately three-quarters of subjects for each drug (80% and 73%, respectively) "rarely" or "never" remembered their dreams.

Table 7-6. Sleep satisfaction, waking behaviour and dreaming patterns for methadone and SROM (n=15).

Item		Response frequencies				
		Never	Rarely	Sometimes	Often	V. Often
Satisfied with amount of sleep	Meth	5	7	2	1	0
	SROM	1	7	3	3	0
		Never	Rarely	Sometimes	Often	V. Often
Difficulty getting up in the morning	Meth	1	9	3	2	0
	SROM	4	8	3	0	0
		Never	Rarely	Sometimes	Often	V. Often
Remembered dreams	Meth	6	6	2	1	0
	SROM	6	5	3	1	0
		Never	Rarely	Sometimes	Often	V. Often
Dreamt about things to do with drugs	Meth	3	8	3	1	0
	SROM	4	7	2	2	0
		Never	Rarely	Sometimes	Often	V. Often
Unpleasant dreams	Meth	2	4	6	1	2
	SROM	1	5	6	1	2

$p > 0.05$ for all differences (methadone vs. SROM).

Results for the LSEQ are presented in Table 7-7. Consistent with the results presented above, these data indicate no significant differences in terms of sleep latency, sleep quality or waking behaviour for methadone and SROM. However, SROM maintenance was associated with significantly less drowsiness whilst getting to sleep in comparison to methadone. Similarly, reductions in the time associated ($p = 0.06$) and clumsiness ($p = 0.07$) associated with awakening from sleep for SROM compared to methadone approached statistical significance. There were no significant differences between methadone holders and non-holders for any LSEQ item.

Table 7-7. Leeds Sleep Evaluation Questionnaire: assessments of sleep whilst maintained on SROM in comparison to sleep whilst maintained on methadone for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.

Visual Analogue Scale (0-100mm)	All subjects	Holders	Nonholders
Getting to sleep			
1. Difficulty	52 ± 28	43 ± 26	63 ± 26
2. Amount of time	48 ± 23	45 ± 24	52 ± 23
3. Drowsiness	**35 ±17	29 ± 14	41 ± 19
Sleep quality			
4. Restlessness	50 ± 29	43 ± 26	58 ± 22
5. Periods of wakefulness	52 ± 23	54 ± 22	51 ± 25
Awakening from sleep			
6. Difficulty	51 ± 23	47 ± 24	56 ± 21
7. Amount of time	59 ± 17	61 ± 12	57 ± 32
Behaviour following wakefulness			
8. Alertness upon awakening	52 ± 24	44 ± 21	61 ± 26
9. Alertness now	40 ± 26	40 ± 20	41 ± 33
10. Sense of balance upon awakening	56 ± 13	56 ± 14	56 ± 11

Values are mean ± SD. For each item (except item 9), subjects were asked to compare their sleep whilst maintained on SROM with their sleep whilst maintained on methadone on 10 VAS ratings, anchored 0-100 mm as follows: (1) Harder than usual – easier than usual; (2) slower than usual – quicker than usual; (3) felt less drowsy than usual – felt more drowsy than usual; (4) more restless than usual – less drowsy than usual; (5) more periods of wakefulness – fewer periods of wakefulness; (6) more difficult than usual – easier than usual; (7) took longer than usual- took shorter than usual; (8) tired – alert; (9) tired – alert; (10) more clumsy than usual – less clumsy than usual. * $p < 01$ (significantly different from 50 mm 'no-change' scale midpoint).

7.3.5. Treatment satisfaction and preference

VAS ratings of treatment satisfaction are contrasted for methadone and SROM in Figure 7-3. Compared to methadone, SROM was associated with significant reductions in the number and severity of side effects and the extent of heroin craving, and significant increases in the extent to which subjects liked and felt more normal on the drug. This pattern of findings was more clearly evident for the non-holders than the holders, but was common to both groups. Notably, reductions in the number of side effects for SROM compared to methadone reached significance for the holders but not the non-holders. Conversely, significant improvement in

withdrawal suppression for SROM compared to methadone was evident for the non-holders but not the holders. Ratings of the extent to which subjects reported getting a "buzz" from their maintenance drug were low for both methadone and SROM, suggesting neither drug produced strong positive opioid effects.

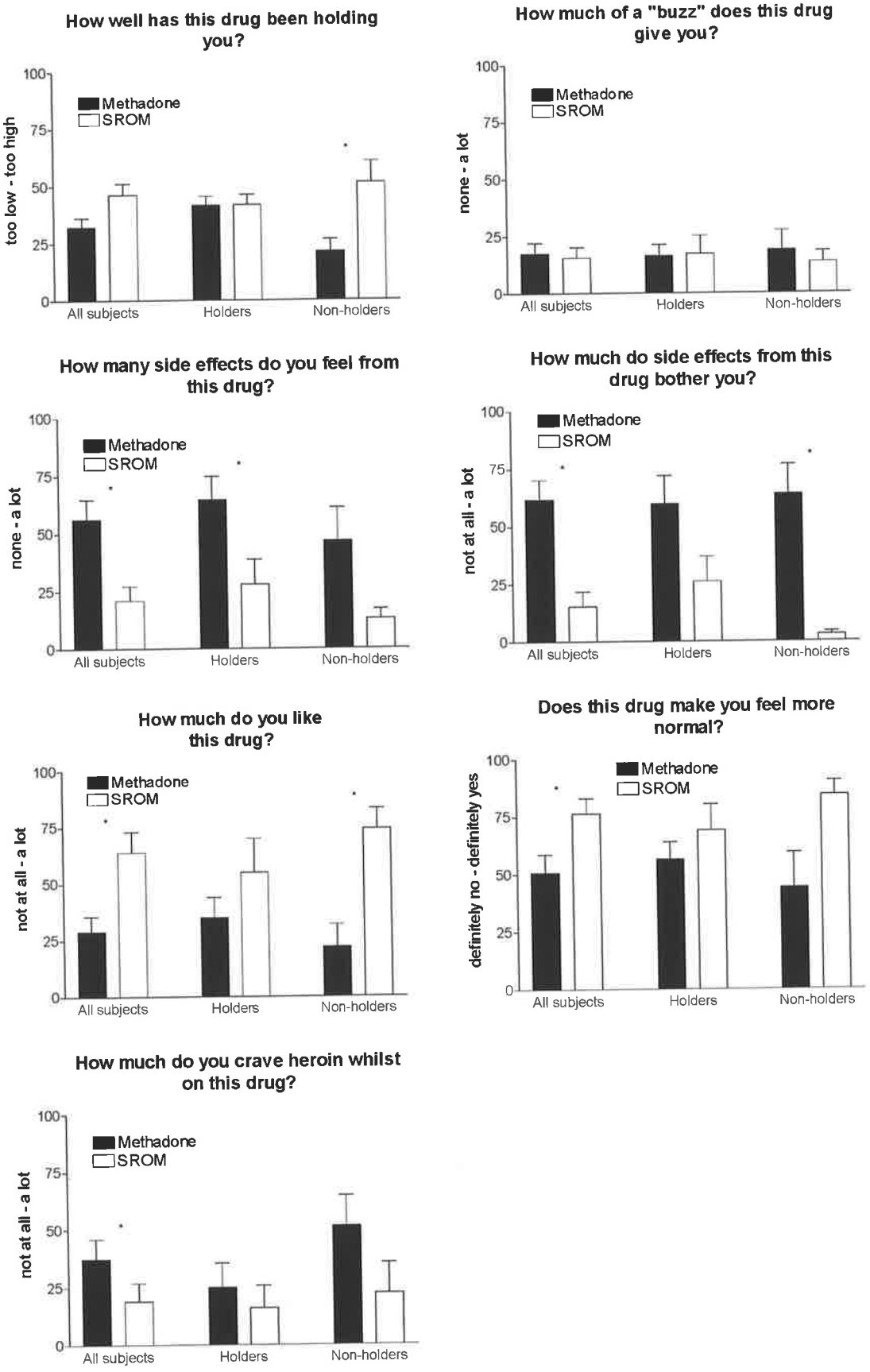

*Figure 7-3. VAS (0-100mm) ratings of treatment satisfaction for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean ± SE. $p < 0.05$ methadone vs. SROM. * $p < 0.05$ (methadone vs. SROM).*

A significantly greater proportion of subjects preferred SROM to methadone (13/15 vs. 2/15, $\chi(1)^2 = 8.07$, $p = 0.005$), even when subjects who dropped-out of the study were included in the comparison (14/18 vs. 4/18, $\chi(1)^2 = 5.56$, $p = 0.02$). A preference for SROM over methadone was stated by 8 of the 9 methadone non-holders and 6 of the 9 methadone holders. VAS ratings of the strength of preference for methadone or SROM are presented in Figure 7-4 for the 15 subjects who completed the study. The strength of preference for SROM over methadone was statistically significant for the subjects as a whole and for the non-holder group, and approached significance in the holder group ($p = 0.12$).

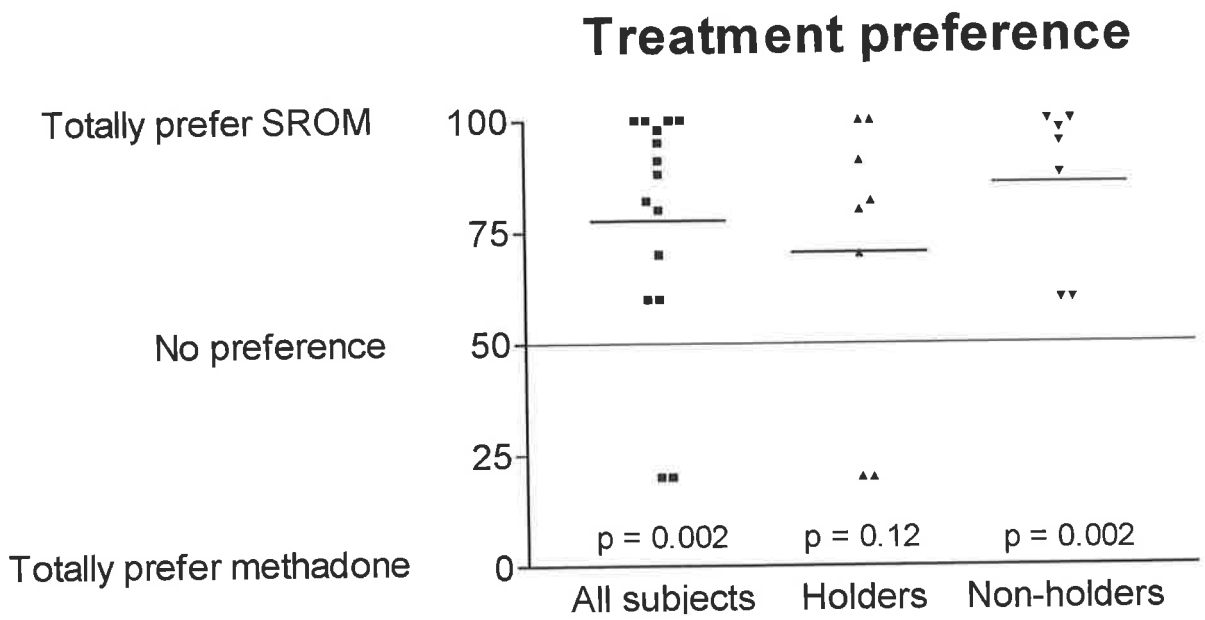

Figure 7-4. VAS (0-100mm) preference for methadone or SROM for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean ± SE. P values denote significance of difference between the mean for each group and the 50mm 'no preference' scale midpoint.

The relationship between VAS preference scores and outcomes for the SF-36 and VAS ratings of treatment satisfaction are presented in Table 7-8. These results indicate that preference for SROM was associated with a greater degree of improvement for SROM compared to methadone on measures of health and treatment satisfaction, with significant correlations found for the SF-36 health scales, Social Functioning and Role Limitations (Physical), and VAS ratings of the number and severity of side effects, drug liking, and the

extent to which subjects felt more normal. Notably, improvements in VAS-rated withdrawal suppression for SROM compared to methadone were not significantly associated with a stronger preference for SROM. VAS preference for SROM was also significantly associated with a reduction in body mass index ($r = 0.63$, $p = 0.01$) and improved sleep satisfaction ($r = 0.70$, $p = 0.004$) for SROM compared to methadone.

Table 7-8. Relationship between VAS-rated preference for methadone or SROM and outcomes for the SF-36 Health Survey and VAS-rated treatment satisfaction (n=15).

SF-36 Health Survey		VAS Treatment Satisfaction	
Scale	r	Scale	r
Role limitations – physical	**0.65	Number of side effects	**-0.75
Social functioning	*0.54	Drug liking	**0.73
General health	0.48	Severity of side effects	**-0.68
Bodily pain	0.47	Feel more normal	**0.65
Vitality	0.46	Heroin cravings	-0.47
Role limitations – emotional	0.45	Withdrawal suppression	0.34
Mental health	0.42	Positive opioid effects ("buzz")	0.33
Physical functioning	0.03		

Correlations are between VAS preference ratings (0 mm = methadone to 100 mm = SROM) and difference in outcomes (methadone scores subtracted from SROM scores) for methadone and SROM. * $p < 0.05$, ** $p < 0.01$.

Reasons for subjects preferring methadone or SROM are presented for the 15 subjects who completed the study in Table 7-9. Multiple response analysis identified 21 different responses from subjects when asked to list all the reasons for their treatment preference. For the subjects as a whole, the most frequently cited reasons for preferring SROM were fewer side effects (54%), improved withdrawal suppression (46%), improved sleep (46%), feeling more normal (38%), improved health (38%), and improved energy (31%). Reasons for preferring SROM differed according to methadone holding status. The methadone holders cited fewer side effects (50%) and improved energy (38%) most frequently; the non-holders cited better withdrawal suppression (86%), improved sleep (50%), fewer side effects (43%), feeling more normal (43%), improved health (43%) and reduced cravings (43%) most frequently. The two

subjects stating a preference for methadone both cited improved withdrawal suppression as the main reason for their choice.

Of the three subjects who dropped out of the study, two preferred methadone and one preferred SROM. Case notes for one subject (id. no. 4: male, holder), who dropped-out after approximately 3 weeks on SROM, indicated that he felt his daily SROM dose was inadequate to cover withdrawal. It is noteworthy that this subject was commenced on the lowest initial SROM:methadone dose ratio (2.94:1) of all the subjects and reported considerable withdrawal upon initiation of SROM maintenance. His final SROM dose was 4.12 times his methadone dose, which was below the mean ratio for all subjects (4.6:1). During informal discussions, this subject also lamented the fact that SROM did not make him feel "stoned" the way methadone did, even expressing envy at the fact that his brother (maintained on methadone) seemed to get a stronger opioid effect than he did from his daily maintenance dose. A second subject (id. no. 12: male, non-holder) dropped-out of the study in order to begin detoxification from methadone for reasons relating to employment. Prior to dropping out, this subject expressed a strong preference for SROM over methadone, citing improved withdrawal suppression and 'feeling more normal' as the main reason for this preference. The third subject (id. no. 18: male, non-holder) reported adverse effects including dizziness and tingling in the hands whilst maintained on SROM and elected to resume methadone maintenance as a consequence of these effects.

Table 7-9. Reasons for preferring methadone or SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.

	All subjects (n=15)		Holders (n=8)		Nonholders (n=7)	
Reasons for preference	All	Main	All	Main	All	Main
Prefer SROM	n = 13		n = 6		n = 7	
Fewer side effects	7	2	4	2	3	0
Better withdrawal suppression	6	4	0	0	6	4
Improved sleep	6	0	2	0	4	0
Feel more normal	5	3	2	1	3	2
Improved health	5	2	2	1	3	1
More energy	4	0	3	0	1	0
Increased alertness	3	1	2	1	1	0
Smoother profile of effects	3	1	0	1	2	0
Reduced cravings	3	0	0	0	3	0
Reduced depression and irritability	3	0	1	0	2	0
Effects more "natural" than methadone	3	0	2	0	1	0
Improved libido	2	0	1	0	1	0
Reduced opioid dependence	2	0	1	0	1	0
Stronger effects from heroin when used	2	0	1	0	1	0
Improved social functioning	2	0	1	0	1	0
More euphoric effects	1	0	1	0	0	0
Less muscle aches	1	0	1	0	0	0
Reduced sweating	1	0	1	0	0	0
Less constipation	1	0	1	0	0	0
More salivation	1	0	1	0	0	0
Weaker effects from heroin when used	1	0	0	0	1	0
Weight loss	1	0	0	0	1	0
Prefer methadone	n = 2		n = 2		n = 0	
Fewer side effects	1	0	1	0	0	0
Better withdrawal suppression	2	2	2	2	0	0
Improved sleep	0	0	0	0	0	0
Feel more normal	1	0	1	0	0	0
More euphoric effects	1	0	1	0	0	0

Subjects were asked to specify all the reasons, and the main reason, for their preference.

Responses to qualitative questionnaire items investigating subjects' perceptions of the best and worst things about methadone and SROM and inviting additional comments and feedback about their experiences during the study were consistent with their specified reasons for preferring either drug. For methadone, subjects cited its capacity to suppress heroin withdrawal, provide stability, reduce crime and the likelihood of jail as among the best aspects of the drug; factors cited as the worst aspects of the drug included numerous side effects (e.g., constipation, sweating, rotting teeth, depression, lethargy), the dose not-holding, the addictiveness of methadone, and disliking the subjective effects of the drug. For SROM, the best aspects of the drug included feeling more normal, energetic, and clear-headed, and improvements in withdrawal suppression, health, and libido relative to methadone; the worst aspects included perceptions that the drug took too long to act and did not hold for long enough, and the occurrence of side effects (e.g., constipation, sleep loss, appetite suppression).

Of particular interest is the observation that 6 subjects (id. numbers: 2, 3, 6, 7, 9, and 14) made reference to SROM not-holding either regularly or occasionally. Of these subjects, which included 4 methadone holders and 2 methadone non-holders, only 1 (id. no. 6: female, methadone holder) preferred methadone to SROM. This means that 3 subjects (id. numbers: 3, 7 and 9) preferred SROM to methadone, despite being methadone holders but likely SROM non-holders. Subject 7 cited as the best thing about SROM its "very smooth and consistent" effects, and whilst commenting that it "sometimes doesn't last the distance", the subject also cited "withdrawals" as the worst thing about methadone. This suggests that some degree of non-holding was experienced by the subject for both medications. However, for subjects 3 and 9, characteristics of methadone and SROM other than their efficacy in suppressing withdrawal appear to have been more important determinants of treatment preference in these subjects, as shown by the following comments:

"I hate methadone and only use it because I can't afford heroin and it stops me withdrawing – I dislike the constipation, the stomach pains, the "greyness" associated with its daily use, the lethargy it causes and the depression that often results. I found that Kapanol was much better except that it didn't hold me quite long enough, but that would have been solved by dosing twice daily instead of just once – apart from that it had none of the side effects of methadone!". (Subject 3)

"Kapanol is very good and holds me for 22 hours. I also feel I have more energy than on methadone, so I am more active as a result....Methadone tends to make you less motivated and socially non-acceptable." (Subject 9)

7.4.Discussion

The purpose of the present study was to compare the clinical efficacy and patient acceptability of methadone and SROM as maintenance pharmacotherapies for opioid dependence. Using a crossover design, indices of treatment outcome (e.g., drug use, health, social functioning, depression, self-esteem, sleep behaviour) and acceptability (e.g., VAS ratings of treatment satisfaction and preference) were assessed after at least 4 weeks on stable dose for each medication. Of 18 subjects recruited to participate and transferred to SROM, 15 (83%) completed the study. Compared to methadone, SROM was associated with improved social functioning, fewer and less severe side effects, greater drug liking, reduced heroin cravings, an enhanced sense of feeling 'normal' and similar outcomes for measures of unsanctioned drug use, depression and health. Subjects showed a preference for SROM (78%) over methadone (22%) that was correlated with the degree of improvement in outcomes. Consistent with hypotheses 1 and 2, improvements on these measures of treatment efficacy and acceptability for SROM compared to methadone were most clearly evident for the methadone non-holders but also applied to the non-holders. None of the measures considered in this study showed superiority for methadone over SROM.

A primary objective of maintenance programs is to facilitate abstinence from heroin and other illicit drugs. Results of the present investigation indicate that the frequency with which either heroin (diacetylmorphine- DAM) or its specific metabolite 6-mono-acteylmorphine were detected in hair samples was similar for methadone (40%) and SROM (27%). This result is particularly notable, as no previous evaluations of SROM maintenance have utilised objective and specific biological markers for illicit heroin use. There were also no differences in the frequencies of self-reported use for heroin, which was indicated by 73% of subjects at some stage during the study, or other drug classes including tobacco (93%), benzodiazepines (80%), marijuana (53%), and alcohol (53%), for which use was indicated by at least 50% of the sample. In spite of these high frequencies, the mean number of days on which use of heroin and other drug classes were used was considerably lower than pre-treatment levels

estimated during the screening interview for the study (e.g., for heroin: 6 days for methadone vs. 30 days pre-treatment; see Chapter 2). Overall, these results indicate SROM was at least as effective as methadone in facilitating abstinence from drug use. Notably, two patients (id. numbers: 2 and 11) admitted to having tried heroin whilst maintained on SROM out of curiosity as to whether the strength of opioid effect would differ in comparison to methadone.

Previous studies indicate that problems relating to health and social functioning, rather than heavy drug use per se, are often the principal reason why illicit opioid users enter and remain in maintenance treatment (Rounsaville & Kleber, 1985). Results for the SF-36 Health Survey indicate that the health status of subjects in the present study was generally below that of the general population in South Australia (South Australian Health Commission, 1995), but above that previously demonstrated for a large sample of heroin users upon entry to methadone maintenance (Ryan & White, 1996). This finding supports the benefits associated with retention in maintenance treatment. Results further indicated that in comparison to methadone, SROM was associated with superior Social Functioning and equivalent outcomes on all other SF-36 health scales. Notably, improvements in Social Functioning were significant for methadone holders but not non-holders, highlighting the fact that even patients responding well to methadone maintenance experienced positive outcomes whilst maintained on SROM. Conversely, improvements in Bodily Pain were significant for the methadone non-holders but not the holders. This difference may be related to the greater improvement in withdrawal suppression evident for the non-holders compared to the holders for SROM compared to methadone (see Chapter 4).

In addition to the SF-36, other instruments including the OTI social functioning scale and structured interviews similarly suggested equivalent outcomes for methadone and SROM in terms of health and social functioning. Overall, responses to OTI items suggested that the majority of subjects were functioning adequately in their personal relationships and avoiding

frequent contact with other heroin users. However, structured interviews highlighted a number of areas in which optimal functioning was yet to be achieved. Only 20% of the subjects undertook paid employment during the study and 100% reported receiving social welfare payments of some form. Nevertheless, a reliance on social welfare for finance is preferable to criminal behaviour, which interviews suggested was a rare occurrence during both the methadone and SROM assessment period. The exception to this pattern was that 26% of subjects reported dealing drugs of any kind (marijuana and heroin), of whom 13% reported dealing heroin.

Depression is commonly associated with opioid dependence and sometimes cited as a side effect of methadone amongst patients undergoing methadone maintenance treatment (Fischer et al., 1996; Sherman, 1996). Results of the present study indicated a decline in mean BDI scores for SROM compared to methadone (11 vs. 14). Although this overall difference was not significant, examination of individual BDI items indicated significant differences in favour of SROM for ratings of self-criticalness, indecisiveness, and the degree of appetite change. Approximately half of the sample showed BDI scores within the normal range (0-9), with the remainder showing mild to moderate (10-19) and moderate to severe (20-29) levels of depression. The finding that mean BDI scores were within the mildly depressed range is consistent with former studies conducted in heroin users seeking methadone maintenance treatment (Steer et al., 1980). BDI scores were inversely related to self-esteem index scores, which were only slightly below self-esteem scores previously reported for a large normative male sample (Bachman & O'Malley, 1977).

Previous investigators have reported reductions in sleep disturbances and body weight following transfer of maintenance patients from methadone to SROM (Fischer et al., 1996; Schneider, 1995), but have not provided quantitative data to support this conclusion. In the present study, assessments of sleep showed that in comparison to methadone SROM was

associated with significant reductions in both sleep duration and drowsiness whilst getting to sleep. However, there were no significant differences between methadone and SROM in terms of sleep satisfaction or the number of nightly awakenings. Overall, results indicated that deficiencies in the perceived duration, quality and satisfaction with sleep were evident for both drugs. A high proportion of subjects reported being rarely or never satisfied with the amount of nightly sleep for both methadone (80%) and SROM (53%), whilst approximately two-thirds of subjects reporting unpleasant dreams as occurring either sometimes, often or very often for both drugs. The finding that methadone holders reported a significantly greater frequency of sleep satisfaction compared to non-holders during methadone maintenance highlights another important consequence of inadequate withdrawal suppression. Given the well-documented relationship between sleep deficiencies and negative mood states (Ford & Cooper-Patrick, 2001), it is possible that sleep disturbance may contribute to the elevated and inconsistent patterns of mood states shown by subjects in Chapter 5. In regard to body weight, the finding that body mass index scores were significantly reduced for SROM compared to methadone is consistent with earlier reports documenting weight loss upon transfer from methadone to SROM (Fischer et al., 1996; Schneider, 1995; Steer et al., 1980), although notably the degree of weight loss observed was small (mean difference 1.2%). Weight loss was cited by one subject as a reason for preferring SROM to methadone.

Differences in VAS ratings of treatment satisfaction for methadone and SROM emerge as one of the most important findings of the present study. Ratings of the number and severity of side effects and the extent to which subjects liked, felt more normal, and craved heroin whilst maintained on each drug significantly favoured SROM over methadone. This pattern of results was most clearly evident for the methadone non-holders, who also showed significant improvement for SROM on ratings of withdrawal suppression, but also applied to the holders. The fact that both methadone holders and non-holders showed significant reductions in the severity of side effects for SROM compared to methadone indicates that transfer from

methadone to SROM may also improve outcomes amongst methadone maintenance patients who report adequate withdrawal suppression but nonetheless experience significant adverse effects. There were no significant differences between methadone and SROM in ratings of the extent to which subjects experienced a "buzz" from their maintenance drug, which was low in both cases. This suggests that higher overall levels of treatment satisfaction evident for SROM in comparison to methadone were not readily attributable to differences in the degree of subjective opioid effects associated with either drug.

The open-label study design needs to be taken into account when interpreting these findings. It is possible that factors such as patient expectations regarding SROM and their attitudes towards methadone may have influenced results for certain measures. This may be particularly true for VAS measures of treatment preference and acceptability. Subjects may have been biased towards a novel medication relative to an existing one, for example.

Consistent with the observed differences in VAS ratings of treatment satisfaction, a significantly greater proportion of subjects preferred SROM to methadone (86% vs. 14%). Preference for SROM over methadone remained highly significant when study drop-outs were included in the comparison (78% vs. 22%), such that 6 of the 9 methadone holders and 8 of the 9 non-holders indicated a preference for SROM. The strength of VAS preference for SROM over methadone correlated significantly with the degree of improvement observed for treatment outcome indices including: SF-36 scales for Social Functioning and Role Limitations (due to physical problems); VAS ratings of the number and severity of side effects, drug liking and the extent to which subjects felt more normal; weight loss; and sleep satisfaction. These findings suggest that the provision of SROM as an alternative choice to methadone in maintenance programs is likely facilitate improvements in treatment retention and outcomes for some patients.

The reasons cited by subjects in the present study for preferring either methadone or SROM provide further evidence of the association between treatment preference and outcomes. Among those preferring SROM, the most commonly cited reasons were fewer side effects (54%), better withdrawal suppression (46%), improved sleep (46%), feeling more normal (38%), improved health (38%), and improved energy (38%). Reasons for preferring SROM differed for methadone holders and non-holders. Improvements in withdrawal suppression and reductions in cravings were cited by 86% and 43% of the non-holders, respectively, but none of the holders. Nevertheless, it is notable that reductions in side effects and improved energy were cited by 50% and 38% of the holders who preferred SROM, respectively, indicating that even patients reporting adequate withdrawal suppression on methadone may benefit from transfer to SROM. All four subjects who preferred methadone to SROM cited superior withdrawal suppression as the reason for this choice. Notably, two of these subjects (id. numbers: 4 and 6) commented during the study that their families considered them to be functioning more effectively on SROM, despite their own preference for methadone. It was similarly noteworthy that of 6 subjects who reported the occurrence of non-holding whilst maintained on SROM, including 4 who did not experience the same problem whilst maintained on methadone, only 1 preferred methadone to SROM. Comments made by these and other subjects suggested that their subjective well-being and the occurrence of side effects were at least as important as withdrawal suppression in determining treatment satisfaction.

Qualitative comments provided by subjects regarding their perceptions of the best and worst things about methadone and SROM were highly consistent with their stated reasons for preferring either drug. In addition, these comments help to identify patient outcomes for which differences may exist between each medication and hence for which inclusion in future investigations may be advisable. In this respect, anecdotal comments made by subjects during the study are also relevant. One of the most striking features of SROM in this regard was the frequency with which subjects expressed the belief that morphine would be easier to

withdraw from than methadone (i.e., physical dependence on opioids is less severe for SROM than methadone). Although few subjects made explicit mention of this in their written comments, several did refer to the "addictiveness" of methadone as one of its worst features, which is consistent with attitudes expressed towards methadone by subjects prior to commencing the study (described in Chapter 2). In addition to expressing the opinion that withdrawal would be easier for SROM than for methadone, many subjects asked whether it would be possible to use SROM as a "stepping stone" to buprenorphine, believing that a direct transition from methadone to buprenorphine would elicit severe withdrawal, and two of the subjects who dropped-out of the study did so for this reason. Given evidence that morphine exhibits reduced *in vitro* intrinsic efficacy compared to methadone (Adams et al., 1990), and that less intrinsically efficacious opioids are generally associated with less severe opioid dependence (Quinn et al., 1997), subjects' perceptions of SROM as being less dependence-inducing than methadone may have a pharmacological basis and thus deserves research attention.

Another frequently cited difference between methadone and SROM was subjects' perception of feeling more clear-headed and awake whilst maintained on SROM in comparison to methadone. This opinion is reflected to some extent in the qualitative responses of some subjects, but anecdotally was one of the most frequently mentioned differences between each drug during informal conversations with the researcher and clinic staff. Although this "clear-headedness" was considered by most patients to be a major advantage associated with SROM, in that it made them feel "more normal", at least one subject (id. no. 4) indicated that he missed the more intense opioid effect he perceived whilst maintained on methadone. These reports are consistent with a preliminary study that indicated improvements in "concentration abilities" for patients following transfer from methadone to SROM (Fischer et al., 1996; Schneider, 1995). On the basis of this apparent difference between methadone and SROM, the

inclusion of cognitive functioning assessments in future comparisons of each treatment may prove an interesting avenue of investigation.

In conclusion, results of the present study suggest that SROM is an efficacious and acceptable alternative once-daily agonist option to methadone for maintenance treatment of opioid dependence. For the range of outcome measures considered in the present study, none showed clear superiority for methadone over SROM. To the contrary, superiority for SROM over methadone was clearly evident for measures of treatment satisfaction and preference. Whilst outcomes including drug use, health and depression showed similar outcomes for both medications, it is possible that differences for these variables may also emerge over longer evaluation period than that used in the present study, particularly if larger subject numbers were used. The finding that treatment preference was strongly related to improvements in treatment outcome indicates that the provision of SROM as an alternative to methadone is likely to facilitate better treatment retentions and outcomes during maintenance treatment. Advantages for SROM over methadone in terms of treatment satisfaction and preference were most obvious for patients reporting inadequate withdrawal suppression on methadone, but were also evident for those responding well to methadone. This suggests that in addition to most immediate clinical application as an alternative option for patients responding poorly to methadone, SROM may also be worth investigating in the future as a first-choice treatment option. A more immediate research priority, however, concerns the need to conduct further large-scale, longer-duration comparisons of methadone and SROM using double-blind, randomised research designs, since the findings of the present study are subject to potential biases associated with open-label designs. The results of this investigation provide an ethical and scientific basis upon which these future studies can further advance the knowledge base regarding the utility of SROM in maintenance programs for opioid dependence.

8. OPIOID WITHDRAWAL AND DOSING SCHEDULES DURING THE TRANSFER BETWEEN METHADONE AND SROM

8.1.Introduction

Despite evidence that SROM is an effective alternative maintenance medication for opioid dependence patients who respond poorly to methadone (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), its use in such patients is presently impeded by the paucity of information currently available regarding the most appropriate means of transferring patients from methadone to SROM maintenance. This information is also necessary to evaluate a potential advantage of SROM over buprenorphine, which is currently the only long-acting oral medication other than methadone recommended for maintenance treatment in most countries. Specifically, since morphine shows significantly greater intrinsic efficacy than buprenorphine at the mu opioid receptor (Yu et al., 1997), it is less likely to result in the precipitation of opioid withdrawal upon transfer from methadone. For buprenorphine, withdrawal precipitation upon transfer from methadone is sometimes prohibitive, particularly in patients whose daily methadone doses exceeds 40 mg (Bouchez et al., 1998; Ling et al., 1994). In the present study, maintenance patients were switched from methadone to SROM and, upon completion of the study requirement, vice versa. To facilitate the development of dosing guidelines for future use of SROM in maintenance programs, the present study assessed patient outcomes (e.g., severity of opioid withdrawal, time to achieve a stable dose) in relation to the dosing regimen used during the transitions between these two medications. As the most likely initial use of SROM will involve its implementation in patients responding poorly to methadone, an emphasis will be placed on the transition from methadone to SROM.

8.1.1. Optimising patient outcomes during the transfer between methadone and SROM

Although patient outcomes during the transfer from methadone to SROM have not been previously investigated in the context of maintenance treatment for opioid dependence, a number of recent studies have investigated the transfer between these medications in patients

receiving opioids for the relief of chronic pain (Gagnon & Bruera, 1999; Mercadante et al., 2001; Ripamonti et al., 1998a; Ripamonti et al., 1998b). In contrast to maintenance programs, the treatment of chronic pain is not normally restricted by the requirements of supervised patient dosing and hence both short- (e.g., morphine, hydromorphone) and long- (e.g., methadone) acting opioids can be used alternatively with greater ease. The strategy of transferring patients from one opioid to another for the purposes of eliminating idiosyncratic and unmanageable adverse effects associated with the initial drug, termed 'opioid rotation', is often effective (Levy, 1996). Morphine and methadone are frequently used in this rotative and interchangeable manner.

The extent to which clinical experience with rotations between methadone and morphine during pain management can inform similar scenarios during maintenance treatment for opioid dependence is limited by certain factors. Firstly, in pain management, methadone is predominantly used as an alternative to morphine, rather than vice versa, as is the most likely scenario in maintenance programs. Second, the pharmacokinetics of methadone and morphine may differ for pain patients and methadone maintenance patients as a consequence of differences between these two patient groups on variables such as age, renal and hepatic function (Andersen et al., 2003). Despite these limitations, many of the pharmacological factors that need to be considered in order to ensure that treatment efficacy and safety are maintained during conversions between methadone and morphine apply to both of the above clinical settings, irrespective of the order in which each drug is used. In the absence of published information regarding transfers between methadone and morphine as maintenance treatments, the evidence-base for such rotations during pain management is thus highly informative to the present discussion.

One of the primary objectives during transfer from methadone to SROM maintenance should be to select a SROM dose that is likely to maintain treatment efficacy (e.g., suppress opioid

withdrawal) without causing unmanageable adverse effects (Levy, 1996). This involves achieving an appropriate balance between the risks associated with both inadequate and excessive dosing. Whereas excessive dosing of long-acting opioid agonists is associated with the risks of opioid toxicity (e.g., sedation, respiratory depression), inadequate dosing in maintenance patients may predispose the patient to similar risks by increasing the likelihood of compensatory drug use (e.g., sedatives such as heroin, alcohol and benzodiazepines) and reducing the likelihood of treatment retention (Bell & Zador, 2000; Caplehorn & Drummer, 2002a; Drummer et al., 1992; Zador & Sunjic, 2000; Zador & Sunjic, 2002). In addition to ensuring that treatment efficacy and safety are maintained during the transfer between methadone and SROM, it is preferable that the frequency and complexity of the dosing regimen is minimised (Levy, 1996). These characteristics are associated with improved patient compliance and lower treatment delivery costs (Sbarbaro, 1985).

Based on the above considerations, the selection of an appropriate dosing protocol for transfer from methadone to SROM maintenance involves three main considerations. The first two of these, highlighted by Ripamonti et al. (1998a), relate to the selection of an appropriate (1) switching modality (i.e., the dosing schedule used to transfer patients between opioids) and (2) dose conversion ratio (i.e., for determining the initial SROM dose as a function of the methadone dose). A third consideration is (3) the rate at which SROM doses should be increased, if necessary, following initiation of treatment in order to achieve an appropriate balance between withdrawal suppression and possible adverse effects. Each of these factors will now be considered.

In transferring pain patients from morphine to methadone, two main types of switching modality have been used. The first strategy involves immediate replacement of morphine with methadone at the end of the final morphine inter-dosing interval (e.g., Morley and Makin, 1997). The second strategy involves gradually replacing morphine with methadone over a

period of several days (Ripamonti et al., 1998). The latter method has been advocated as a means of allowing for individualised patient monitoring and dose titration in order to avoid delayed opioid toxicity associated with the accumulation of methadone upon commencement of treatment (Bruera & Fainsinger, 1997). Disadvantages of this approach include the increased costs and inconvenience associated with individualised patient monitoring and dosing. In the present study, the need for a gradual and individualised approach to methadone dosing following the transfer from methadone to SROM (at the end of the SROM maintenance phase) is largely offset by knowledge of the methadone dose prescribed to patients prior to transferring to SROM. Conversely, for the transition from methadone to SROM, the need for gradual increased in dosage to avoid toxicity is also partially offset by the shorter-half life of SROM, which entails a reduced risk of delayed toxicity than applies to methadone (Levy, 1996; Savarese et al., 1986). To this extent, an immediate switching modality (i.e., involving a change of medication at the end of the 24-hour inter-dosing interval) is likely to be adequate in maintaining treatment efficacy and safety during the transfer of maintenance patients between methadone and SROM, providing that an appropriate initial starting dose is selected.

The selection of an appropriate starting dose when initiating SROM maintenance in methadone maintenance patients depends largely on the oral equivalence (i.e., dose conversion ratio) of these drugs. Traditional equi-analgesic tables used to calculate equivalent oral doses of morphine and methadone in the treatment of pain suggest SROM:methadone dose conversion ratios of between 1:1 and 4:1 (Ripamonti et al., 1998b). Since these ratios are based upon single-dose studies using opioid-naïve volunteers, it has been argued that they may be grossly inaccurate in the context of chronic dosing in pain patients (Ripamonti et al., 1998b). Recent studies in pain patients have reported a wide variation in morphine:methadone oral dose ratios (e.g., 1:1 – 20:1) (Berland, 2000; Bruera & Fainsinger, 1997; Gagnon & Bruera, 1999; Mercadante, Casuccio, & Calderone, 1999; Mercadante et al., 2001; Ripamonti

et al., 1998a; Ripamonti et al., 1998b), such that methadone is often found to be much more potent relative to morphine than previously thought. The dose conversion ratio of morphine:methadone may also be dependent on the degree of opioid tolerance. Studies indicate that the ratio of morphine:methadone is higher in patients previously maintained on high doses of morphine, but may not differ markedly from ratios prescribed in traditional equi-analgesic tables for patients on low morphine doses and opioid naïve individuals (Mercadante et al., 1999; Ripamonti et al., 1998a). Unfortunately, SROM:methadone dose ratios have not been specified in previous investigations in which methadone maintenance patients were switched to SROM maintenance, with the exception of Sherman's (1996) single-case study (4:1). Nevertheless, the ratio of mean doses for morphine:methadone reported in some studies suggests that SROM:methadone dose ratios may approximate 5:1 to 6:1 (Fischer et al., 1999b; Fischer et al., 1996) at steady-state for maintenance treatment of opioid dependence.

To account for the possibility of incomplete cross-tolerance, it has been suggested that chronic pain patients transferring from morphine to methadone should be commenced on a methadone dose that is somewhat less than the estimated dose requirement (Levy, 1996). Although others have described this method as a "rather vague indication and only partially applicable" (Ripamonti et al., 1998b), certain additional factors need to be taken into account when transferring methadone maintenance patients onto SROM maintenance. This includes the possibility that the long half-life of methadone may entail continued opioid action following cessation of methadone dosing in some patients. Individuals are also likely to show variable morphine disposition and different degrees of cross-tolerance. To minimise the likelihood that individual variability in response to methadone or morphine may precipitate adverse effects (e.g., opioid toxicity), it may be better to use an initial SROM dose somewhat below that expected at steady-state. Previous studies indicate a SROM:methadone dose ratio between 4:1 and 6:1 for maintenance treatment of opioid dependence (Fischer et al., 1999b;

Fischer et al., 1996; Sherman, 1996) and an initial ratio of 3:1 has been suggested as an appropriate starting point for the first dose (Fischer et al., 1996).

Another important consideration during transfers between methadone and SROM maintenance is the rate at which doses should be increased following commencement of treatment with either drug. Upon commencement of methadone dosing, standard practice guidelines in South Australia indicate daily increases of 5 to 10 mg should be used where necessary to achieve optimal balance between therapeutic and adverse effects. There are currently no specific guidelines regarding the most appropriate rate of increase in dose following the initial transfer from methadone to SROM. In the absence of such information, a suitable strategy would involve daily increments in SROM doses approximately equivalent to those commonly used for methadone maintenance. Based on indications that the initial SROM:methadone dose ratio should approximate 3:1, and the limited capsules strengths of Kapanol™ (doses limited to 10 mg increments), initial daily increases in SROM doses of 10 to 30 mg would thus appear appropriate.

Ethical considerations must also apply when determining an appropriate strategy for transferring patients from methadone to SROM. Based on the literature reviewed above, it is apparent that clinical experience in this area is extremely limited in the context of maintenance treatment. Even in the context of pain management, for which transfers between methadone and SROM are routinely employed, clear consensus regarding the transfer process has yet to emerge. Noting inconsistencies in the research literature, Ripamonti et al (1998b) concluded that: "from all the different published indications regarding the modalities of the switch and the dose ratios to be used for the achievement of equi-analgesia, it is obvious that there is no standardisation in this practice". Taking these uncertainties into account, an ethical approach to transferring patients from methadone to SROM must allow for clinician flexibility and the capacity to individualise dosing regimens, so as not to jeopardise the well-

being of research participants. In the present study, this means allowing for the possibility that the initial dose ratio may vary between subjects during the course of the research, if deemed inadequate or excessive relative to initial expectations.

Since use of SROM for treatment of opioid dependence is currently approved for clinical trials only in Australia, participants in the present study were required to transfer back to methadone at the conclusion of the study protocol. Patient outcomes during the resumption of methadone maintenance are of lesser clinical significance, since the predominant use of SROM is likely to involve its implementation as an alternative to methadone and not vice versa. Nonetheless, as morphine and methadone exhibit different profiles of interactions with numerous neurotransmitter systems, including those mediated by mu opioid and NMDA receptors (Codd et al., 1995), it is possible that some alterations in the degree of tolerance could occur during the period of SROM maintenance. The assessment of patient outcomes upon transfer from SROM to methadone is therefore of interest. It is anticipated that patients could return to their original methadone dose upon completion of the SROM maintenance phases without experiencing marked changes in treatment efficacy or safety.

8.1.2. The present study

To facilitate further evaluation and clinical implementation of SROM maintenance, the present study investigated the severity of opioid withdrawal associated with transfer from methadone to SROM and vice versa. Based upon consideration of the clinical pharmacology of methadone and morphine, and relevant experience in the domain of pain management, it was established that an appropriate dosing protocol for transferring patients from methadone to SROM would have the following features. Firstly, the switching modality would involve initiating SROM maintenance 24 hours following the final methadone dose. Second, based upon an expected SROM:methadone equivalence of between 4:1 and 6:1 (Fischer et al., 1996; Sherman, 1996), and the need to account for possible delayed methadone action and variability in morphine response and metabolism, the appropriate initial SROM:methadone

dose ratio would approximate 3:1-4:1. Third, the rate at which daily SROM doses should be increased should resemble equivalent rates applicable for the adjustment of methadone doses during maintenance treatment (e.g., daily increase: 5-10 mg methadone; 10-30 mg SROM). Finally, given the limited evidence base in this area, allowance for flexibility and individualisation in dosing during the course of the study was recommended in order to maintain the ethical integrity of the study and the well-being of those who voluntarily participated.

8.1.2.1. Aims

The aims of the present study were:

- To characterise the degree of opioid withdrawal associated with transfer from methadone to SROM and vice versa.
- To characterise the relationship between SROM:methadone dose ratio and the degree of opioid withdrawal during these transition periods.

8.1.2.2. Hypotheses

1. The severity of opioid withdrawal during the transfer from methadone to SROM will be inversely related to the initial SROM:methadone dose ratio.

8.2.Methods

8.2.1. Subjects, procedures, and measures

Subjects and methods for transferring subjects from methadone to SROM and vice versa were described in Chapter 2. Subjects completed the Methadone Symptoms Checklist prior to dosing at 3, 6 and 12 hours following dosing for the first five days following a change of maintenance medication. This yielded measures of the total number (maximum 16) and intensity (maximum 64) of withdrawal symptoms. Additionally, records were kept of the daily maintenance dose for the first ten days following changes of the maintenance medication, the number of days taken until a stable dose had been achieved (i.e., no further changes required), and the total number of dose changes required to achieve a stable dose.

8.2.2. Statistical analyses

Repeated-measures ANOVA was used to examine the effects of the day of treatment, time since dosing, and methadone holding status on withdrawal responses during the transfer between methadone and SROM and vice versa. Additional comparisons of mean withdrawal responses according to the day of treatment and time since dosing were conducted using paired t-tests; comparisons according to methadone holding status were conducted using independent t-tests. Pearson correlation coefficients and scatter plots were used to examine linear associations between paired variables. Analyses were conducted using SPSS™ for Windows (SPSS Inc, Chicago, Illinois, USA). An alpha level of 0.05 was used for all analyses. Data are presented as mean ± SD (range) unless otherwise indicated.

8.3.Results

8.3.1. Transfer from methadone to SROM

8.3.1.1. Comparisons for all subjects

Upon transfer from methadone maintenance, the mean initial SROM dose (268 ± 112 mg, 90-420 mg) was 3.46 ± 0.22 (2.94-3.78) times greater than the original methadone dose. Upon achievement of a stable SROM dose, the mean SROM:methadone dose ratio was 4.60 ± 0.93 (3.82 – 8.00). The final SROM:methadone dose ratio was equal to or less than 5:1 for all subjects except one, a male non-holder who required a SROM dose 8 times his original methadone dose. Medical officers attributed this high ratio to regular use of heroin by the subject on top of his daily methadone dose during methadone maintenance (45 mg). In spite of this outlier, there was a strong linear relationship between methadone and SROM doses ($r = 0.93$, $p < 0.0001$; Figure 8-1). There was no relationship between the initial and final SROM:methadone dose ratio ($r = 0.13$, $p = 0.57$).

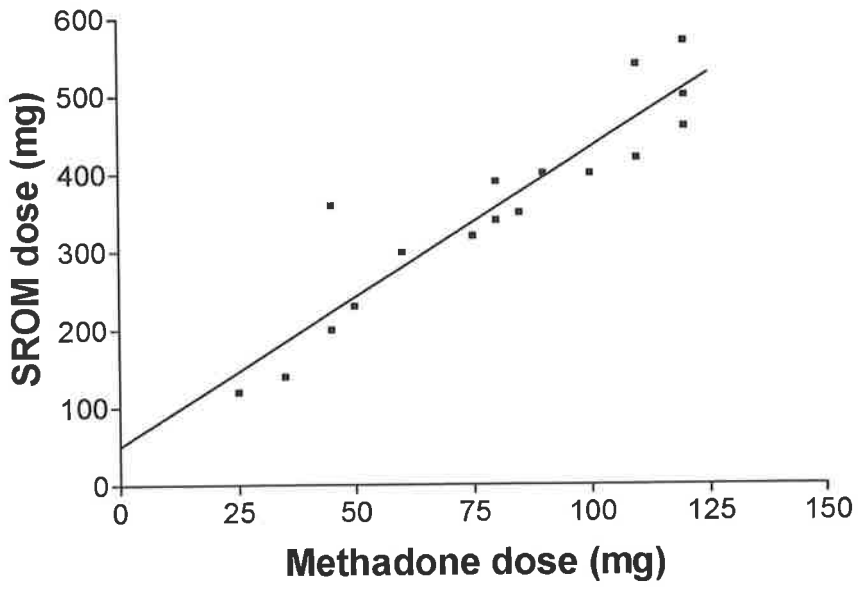

Figure 8-1. Relationship between original methadone doses and SROM doses at the end of the SROM stabilisation period (n=18).

Following commencement of SROM maintenance, all subjects required increases in the daily SROM dose. The mean number of dose increases and total percentage increase in dose

(relative to day 1) in the first 10 days of SROM maintenance were 3.9 ± 1.8 (1-7) and 20 ± 8% (5-39%), respectively. The maximum increase in the daily SROM dose during the first 10 days, expressed as a percentage of the previous day's dose, showed a mean value of 9.7 ± 4.2% (5-20%). The time taken for a stable SROM dose to be achieved (i.e., no further dose increases required) showed a median value of 6 (2-25) days. Figure 8-2 shows changes in the daily maintenance dose for the first 10 days of SROM maintenance.

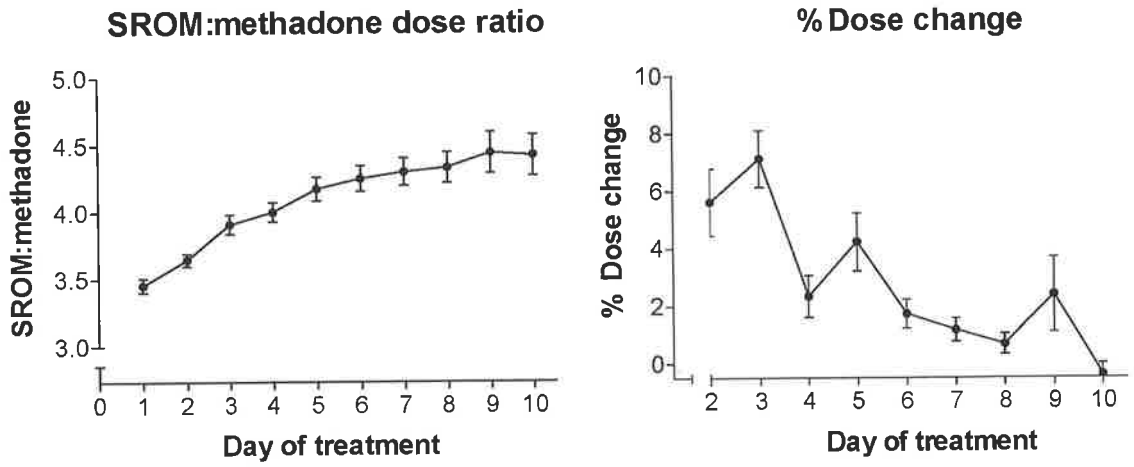

Figure 8-2. Changes in SROM dose as a function of the original methadone dose and the previous day's dose for the first 10 days of SROM maintenance (n=18). Data are presented as mean ± SE.

Patterns of opioid withdrawal during the first 5 days of SROM maintenance are shown in Figure 8-3. These data indicate that the degree of withdrawal suppression associated with administration of the maintenance dose differed during the first 5 days of treatment. On day 1, in particular, it is evident that the number and intensity of opioid withdrawal symptoms showed no decline following dosing. By comparison, significant suppression of opioid withdrawal following dosing was evident to some extent on day 2 and to a greater extent on days 3 to 5. The pattern of opioid withdrawal shown on days 3 to 5, whereby withdrawal was minimal later in the dosing interval (i.e., at 6 h and 12 h), is consistent with the plasma morphine concentration-time profile shown for SROM in Chapter 3. The number and

intensity of opioid withdrawal symptoms prior to dosing were slightly higher for days 2-5 compared to day 1, but these differences were not significant ($p > 0.10$).

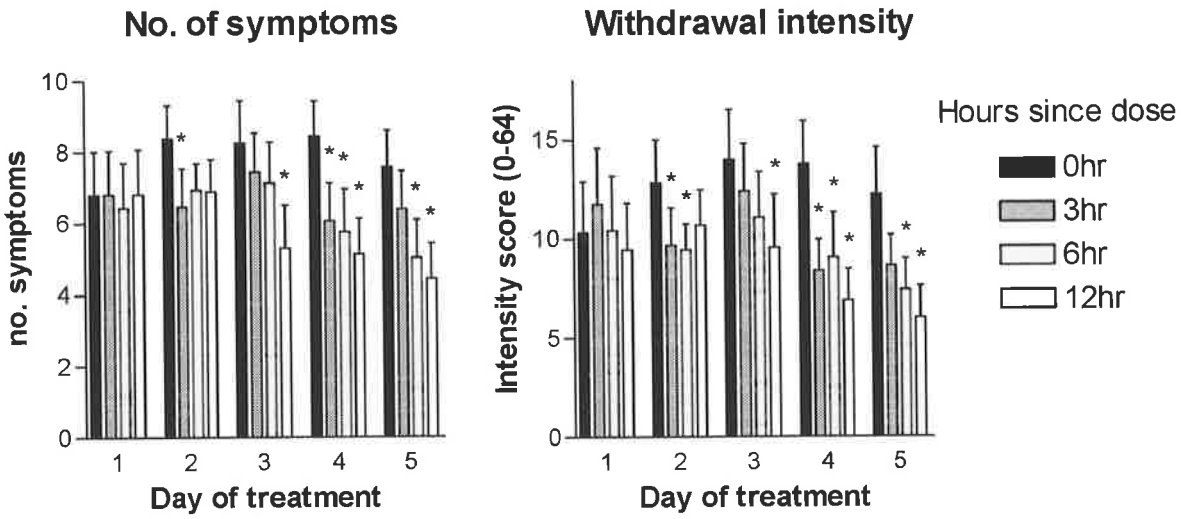

Figure 8-3. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from methadone to SROM (n=16). Data are presented as mean ± SE. * p < 0.05 (3, 6 and 12 h compared to 0 h each day).

Repeated-measures ANOVA used to investigate changes in withdrawal following commencement of SROM maintenance as a function of the time since dosing and the day of treatment are summarised in Table 8-1. The main effect for time since dosing was not statistically significant for the first two days of SROM maintenance, but was significant for days 3 to 5. Differences in the pattern of opioid withdrawal following dosing were further evidenced by a significant day of treatment × time since dosing interaction. Additional analyses showed that these withdrawal patterns were mediated by the initial SROM:methadone dose ratio, as evidenced by a significant day of treatment × time since dosing × dose ratio interaction ($F(12, 168) = 2.62$, $p = 0.003$). The SROM:methadone dose ratio showed a consistent inverse relationship with withdrawal scores, but this effect only reached statistical significance on day 2 ($F(1, 14) = 5.01$, $p = 0.04$). Although the temporal pattern of withdrawal following dosing differed significantly according to the day of treatment, the main effect for day of treatment was not statistically significant.

Table 8-1. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance (n=16).

ANOVA effect[a]	Df	Withdrawal symptoms	Withdrawal intensity
		Within-day analyses	
Time			
Day 1	3, 45	0.07	0.49
Day 2	3, 45	2.42	2.15
Day 3	3, 45	**4.51	2.64
Day 4	3, 45	**5.02	**6.00
Day 5	3, 45	*3.95	**4.88
		Between-day analyses	
Day	4, 60	1.60	1.41
Time	3, 45	*1.84	1.60
Time x Day	12, 180	**4.55	**5.86

Values are F ratios. * $p < 0.05$, ** $p < 0.01$ [a] ANOVA effects were time since dosing (Time), and day of treatment (Day).

To further determine the clinical importance of the initial SROM:methadone dose ratio in explaining patient outcomes upon transfer from methadone to SROM, the relationships between the initial SROM:methadone dose ratio and both the time taken to achieve a stable SROM dose and the average pre-dose withdrawal severity on days 2-5 of SROM maintenance were explored. Scatter plots of these relationships are shown in Figure 8-4. Significant relationships between the initial SROM:methadone dose ratio and both the time to stabilisation (r^2= 0.23, p = 0.04) and mean pre-dose withdrawal severity for days 2-5 (r^2= 0.27, p = 0.04) were observed, such that higher ratios were associated with more rapid stabilisation and less severe withdrawal.

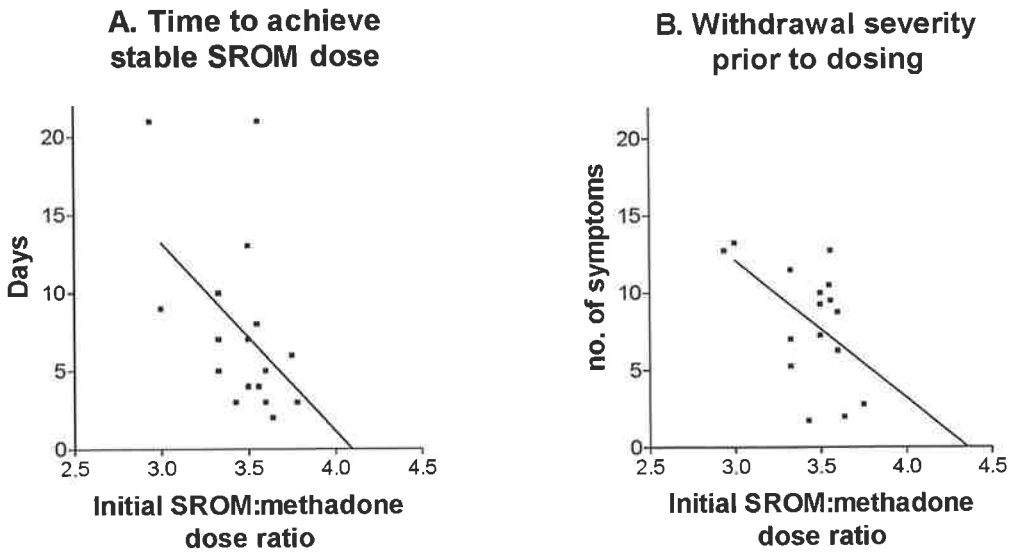

Figure 8-4. Relationship between initial SROM:methadone dose ratio and the (A) time to achieve a stable SROM dose (n=18) and (B) average withdrawal prior to dosing for days 2-5 of SROM maintenance (n=16).

8.3.1.2. Comparisons for methadone holders and non-holders

Figure 8-5 shows changes in the daily SROM dose (as a function of the original methadone dose and the previous day's dose) for the first ten days of SROM maintenance in methadone holders and non-holders. The magnitude and rate of increase in SROM doses during the stabilisation period was similar for holders and non-holders. There were also no differences between holders and non-holders in terms of the time taken to achieve a stable SROM dose (7.2 ± 5.4 days vs. 8.1 ± 6.1 days, $t(16) = 0.33$, $p = 0.75$) or the final SROM:methadone dose ratio (4.5 ± 0.4 vs. 4.7 ± 1.3, $t(16) = 0.57$, $p = 0.58$).

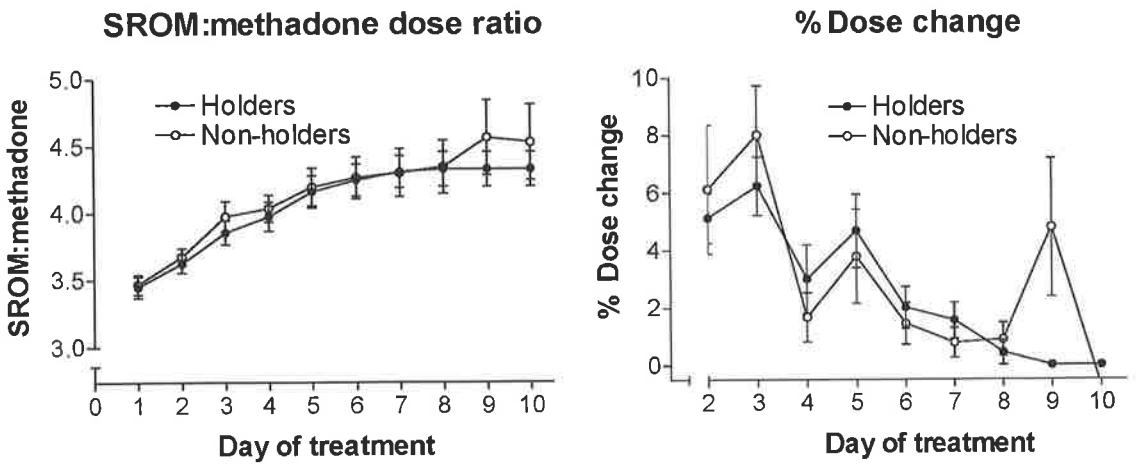

Figure 8-5. Changes in SROM dose as a function of the original methadone dose and the previous day's dose for the first 10 days of SROM maintenance: comparisons for the methadone holder (n=9) and non-holder (n=9) subgroups. Data are presented as mean ± SE. $p > 0.05$ for all differences (holders vs. non-holders).

Figure 8-6 shows patterns of opioid withdrawal during the first 5 days of SROM maintenance for methadone holders and non-holders. As similar patterns were observed for both the number and intensity of opioid withdrawal symptoms, only results for the former measure are shown. Different patterns of withdrawal were evident for each group. For the holders, withdrawal severity prior to dosing was greater compared to baseline on days 2 to 5, although the differences were only statistically significant on days 2 ($p= 0.03$) and 4 ($p = 0.05$). By comparison, pre-dose withdrawal for the non-holders showed very little change relative to baseline during the first 5 days of SROM maintenance ($p > 0.61$). There were also differences between these two groups in the way withdrawal changed following administration of the daily maintenance dose during the first 5 days of SROM maintenance. The holders experienced no significant reduction in withdrawal following dosing until day 3 and actually showed small increases following dosing on day 1. By comparison, the non-holders showed reductions in withdrawal following dosing throughout the first 5 days, although these changes were only significant on day 2.

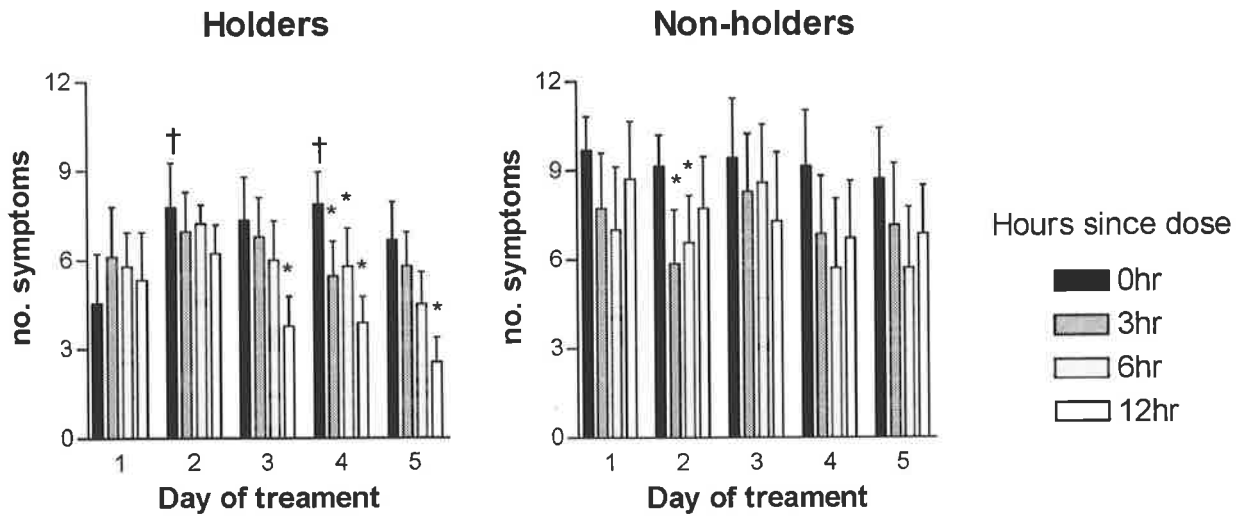

Figure 8-6. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from methadone to SROM: comparisons for the methadone holder (n=9) and non-holder (n=7) subgroups. Data are presented as mean ± SE. †p < 0.05 (0 h days 2-5 compared to 0 h day 1), * p < 0.05 (3, 6 and 12 h compared to 0 h each day).

Repeated-measures ANOVA used to investigate differences in withdrawal patterns during the first 5 days of SROM maintenance for methadone holders and non-holders are summarised in Table 8-2. In spite of the differences in temporal withdrawal patterns for these groups shown in Figure 8-6, ANOVA indicated that the effects of day of treatment, time since dosing, and the day of treatment × time since dosing interaction were not significantly mediated by methadone holding status.

Table 8-2. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance according to methadone holding status (n=16).

ANOVA effect[a]	Df	Withdrawal symptoms	Withdrawal intensity
Hold	1,14	1.09	1.87
Hold × Day	4, 56	1.49	0.95
Hold × Time	3, 42	1.70	1.19
Hold × Time x Day	12, 168	0.70	0.26

Values are F ratios. * $p < 0.05$, ** $p < 0.01$ [a] ANOVA effects were time since dosing (Time), day of treatment (Day), and methadone holding status (Hold). $p > 0.05$ for all effects.

8.3.1.3. Comparisons of withdrawal during stabilisation and at steady-state

To further characterise patient outcomes during the transition from methadone to SROM maintenance, withdrawal severity prior to dosing during the SROM stabilisation period (averaged for days 2-5) was compared to pre-dose withdrawal scores obtained for methadone and SROM at steady-state, after at least 4 weeks on a stable dose of each drug. These analyses were performed for the 14 subjects included in the 24-hour inter-dosing study (Chapters 3 to 6) and are summarised in Figure 8-7. For both methadone holders and non-holders, the intensity of pre-dose opioid withdrawal during the first 5 days of SROM maintenance was significantly greater than steady-state levels for SROM but not for methadone. A similar pattern was evident for the number of withdrawal symptoms. Thus, the severity of opioid withdrawal upon initiation of SROM maintenance, whilst greater than observed after 4 weeks on a stable SROM dose, was not significantly worse than the withdrawal levels shown by subjects on a stable methadone dose.

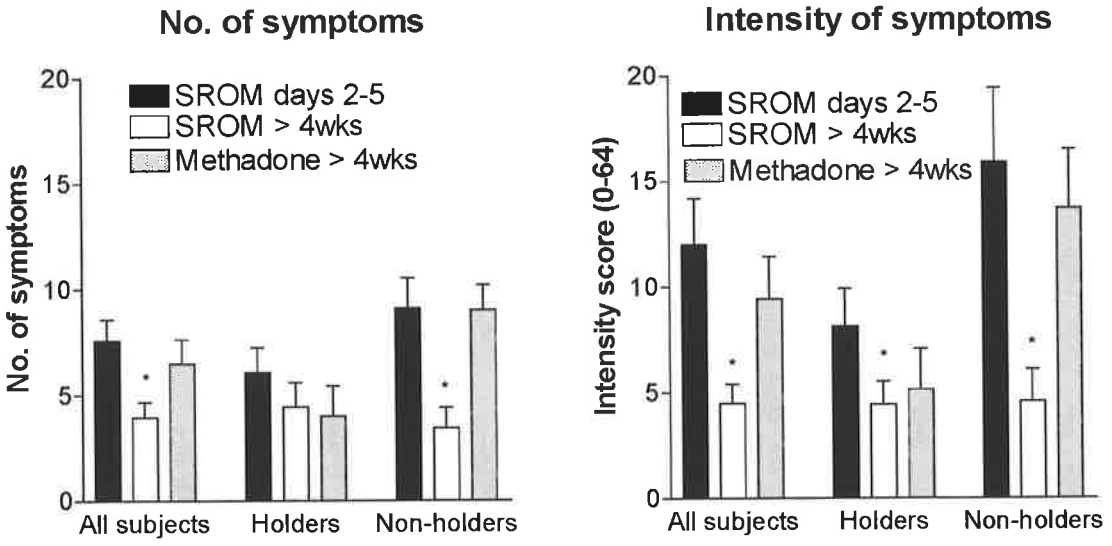

Figure 8-7. Pre-dose opioid withdrawal during stabilisation (averaged days 2 to 5) on SROM and at steady-state after at least 4 weeks on a stable dose of methadone and SROM: comparisons for all subjects (n=14) and the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean ± SE. * $p < 0.05$ (steady-state vs. stabilisation).

8.3.2. Transfer from SROM back to methadone

8.3.2.1. Comparisons for all subjects

Upon completion or termination of the SROM maintenance phase, fifteen subjects resumed methadone maintenance at their prior dosage levels. Two subjects required small adjustments, involving a single 5 mg increase (id. no. 14: from 45 mg to 50 mg) on day 5 in the first case and two consecutive increases of 5 mg (id. no. 13: from 120 mg to 130 mg) on days 2 and 3 in the second case. The first of these subjects (i.d. no. 14) had been maintained on a relatively high SROM:methadone dose ratio of 8:1 and found his original methadone dose to be slightly inadequate upon resumption of methadone maintenance. Case notes for the other subject (i.d. no. 13) similarly indicated reports of feelings slightly uncomfortable upon return to methadone. However, during informal discussions, this subject reported a stronger opioid effect than normal upon returning to methadone. During the course of the study, this subject had expressed curiosity regarding the likelihood that transfer from methadone back to SROM may entail a stronger opioid effect from methadone, an effect this subject considered positive. None of the other 13 subjects who resumed methadone maintenance required a change of dose from their previous level.

Of the three subjects who did not resume methadone maintenance, two elected to discontinue the study (having completed 24-hour assessments for both methadone and SROM; id. numbers: 1 and 16) and transfer immediately to buprenorphine. A third subject (id. no. 11), who was a methadone non-holder, was given special permission from local health authorities to continue SROM maintenance after this course of treatment was advocated by a medical officer in view of particularly improved outcomes whilst maintained on SROM. In addition to these three subjects, withdrawal data for a further 4 subjects were not obtained. This included the three subjects (id. numbers: 4, 12, and 18) who dropped out of the study without completing 24-hour assessments for either methadone or SROM, and a fourth subject (id. no. 10) who did not comply with the requirement to fill in withdrawal questionnaires during this

period. Thus, withdrawal data for the resumption of methadone maintenance were available for 11 of the original 18 subjects.

Patterns of opioid withdrawal during the first 5 days following transfer from SROM back to methadone are shown in Figure 8-8. The number and intensity of withdrawal symptoms prior to dosing increased slightly on days 2 to 5 in comparison to day 1, although this difference only reached significance on day 2. Withdrawal severity appeared consistently lower post-dose (3, 6 and 12hr) in comparison to pre-dose levels throughout the methadone re-stabilisation period, with significant declines evident for days 1, 3 and 4 for the number of withdrawal symptoms and on day 3 for the intensity of withdrawal symptoms.

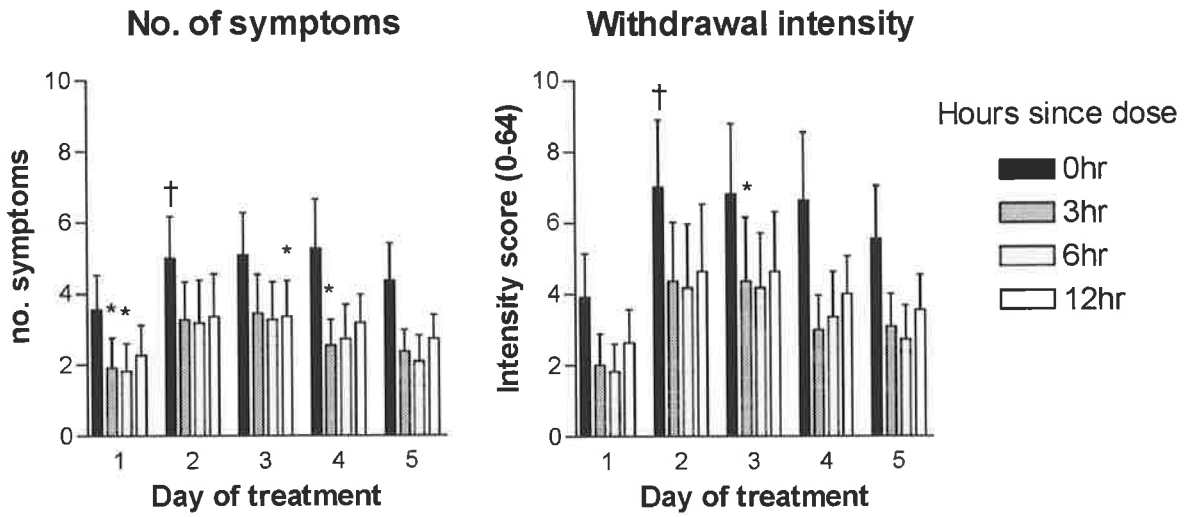

Figure 8-8. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from SROM back to methadone (n=11). Data are presented as mean ± SE. †p < 0.05 (0 h days 2-5 compared to 0 h day 1,)* p < 0.05 (3, 6 and 12 h compared to 0 h each day).

Repeated-measures ANOVA of withdrawal scores for the first five days following transfer from SROM back to methadone are shown in Table 8-3. The main effect for time since dosing was significant for the number of withdrawal symptoms, reflecting the consistently lower levels of withdrawal seen post-dose compared to pre-dose upon resumption of methadone maintenance. The main effect for time since dosing reached significance on days

1, 4 and 5 and not days 2 and 3, but the day of treatment × time since dosing interaction was not statistically significant. There were no main effects for day of treatment, indicating no significant change in the overall levels of withdrawal shown for the first 5 days during the methadone re-stabilisation period.

Table 8-3. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days following transfer from SROM back to methadone (n=11)

ANOVA effect[a]	Df	Withdrawal symptoms	Withdrawal intensity
		Within-day analyses	
Time			
Day 1	3, 45	**4.48	*3.32
Day 2	3, 45	1.98	2.04
Day 3	3, 45	2.37	2.47
Day 4	3, 45	*4.00	*3.74
Day 5	3, 45	*3.53	*3.05
		Between-day analyses	
Day	4, 60	2.53	3.54
Time	3, 45	*4.43	3.85
Time x Day	12, 180	0.39	0.40

Values are F ratios. * $p < 0.05$, ** $p < 0.01$ [a] ANOVA effects were time since dosing (Time) and day of treatment (Day).

8.3.2.2. Comparisons for methadone holders and non-holders

The 11 subjects for whom withdrawal data are available for the methadone re-stabilisation period included 7 holders and 4 non-holders. Patterns of withdrawal for these two groups for the first 5 days following transfer from SROM back to methadone are shown in Figure 8-9. Different patterns of withdrawal for each group were evident during this period. Whereas the holders showed low and stable withdrawal scores each day, the non-holder group showed increasing pre-dose withdrawal scores on days 2 to 5 in comparison to baseline levels associated with SROM maintenance. This increase in pre-dose withdrawal reached significance on day 4, despite the low numbers of non-holders available for this analysis. These patterns of withdrawal suggest that following approximately 6 weeks on SROM

maintenance, during which both groups showed withdrawal scores consistent with adequate 'holding', the holders remained holders and the non-holders returned to being non-holders upon resumption of methadone maintenance.

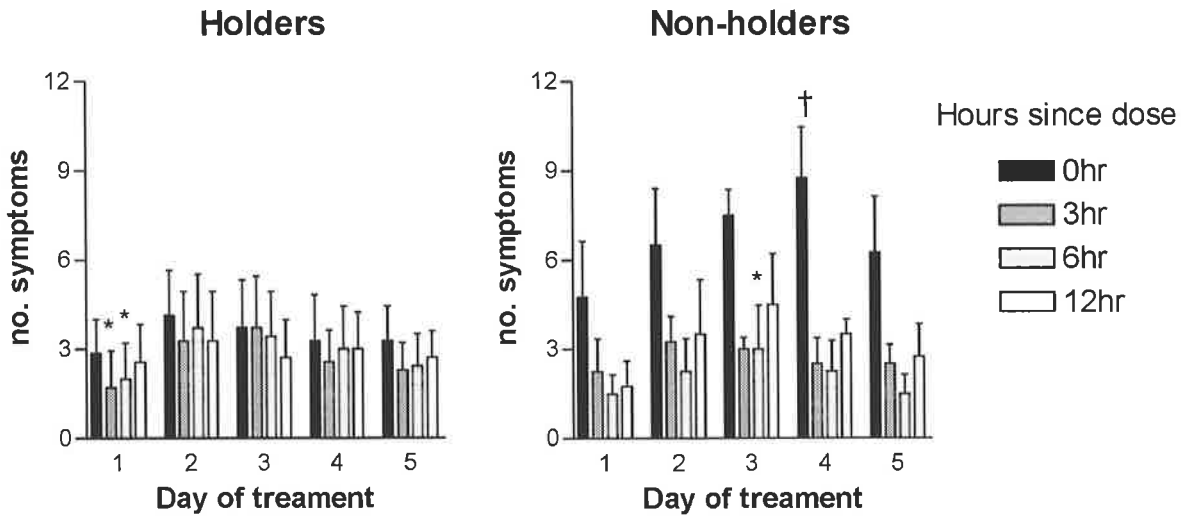

Figure 8-9. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from SROM back to methadone: comparisons for the methadone holder (n=7) and non-holder (n=4) subgroups. Data are presented as mean ± SE. $^{\dagger}p < 0.05$ (0 h days 2-5 compared to 0 h day 1), $*p < 0.05$ (3, 6 and 12 h compared to 0 h each day).

Repeated-measures ANOVA of the number and intensity of withdrawal symptoms for methadone holders and non-holders for the first five days following transfer from SROM back to methadone are summarised in Table 8-4. Consistent with patterns shown at steady-state whilst maintained on methadone, significant holding status × time since dosing interactions were observed for the number and intensity of withdrawal symptoms, reflecting the more pronounced changes in withdrawal severity seen for the non-holders compared to the holders. The effects for holding status, holding status × day of treatment, and holding status × time since dosing × day of treatment were not significant.

Table 8-4. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance according to methadone holding status (n=16).

ANOVA effect[a]	Df	Withdrawal symptoms	Withdrawal intensity
Hold	1, 9	0.16	0.11
Hold × Day	4, 36	0.31	0.15
Hold × Time	3, 27	**5.10	**5.27
Hold × Time x Day	12, 108	1.55	1.40

Values are F ratios. * $p < 0.05$, ** $p < 0.01$ [a] ANOVA effects were time since dosing (Time), day of treatment (Day), and methadone holding status (Hold). $p > 0.05$ for all effects.

8.3.2.3. Comparisons of withdrawal during stabilisation and at steady-state

To further characterise patient outcomes during the transition from SROM back to methadone maintenance, withdrawal severity prior to dosing during the methadone re-stabilisation period (averaged days 2 to 5) was compared to pre-dose withdrawal scores obtained for methadone and SROM at steady-state, after at least 4 weeks on a stable dose of each drug (Figure 8-10). These analyses were permitted for 10 subjects who completed the 24-hour assessments for methadone and SROM and for whom withdrawal data during the methadone re-stabilisation period were available. For the holders, there were no significant differences in the number or intensity of opioid withdrawal symptoms prior to dosing during the methadone re-stabilisation period compared to steady-state levels for methadone and SROM. For the non-holders, the number of pre-dose withdrawal symptoms was significantly less during methadone re-stabilisation compared to steady-state levels for methadone. A similar trend was evident for the intensity of withdrawal symptoms. Though limited to a sample of 4 non-holders, this analysis suggests that upon transferring from SROM back to methadone the non-holder group did not immediately experience the same deficiency in withdrawal suppression associated with steady-state levels.

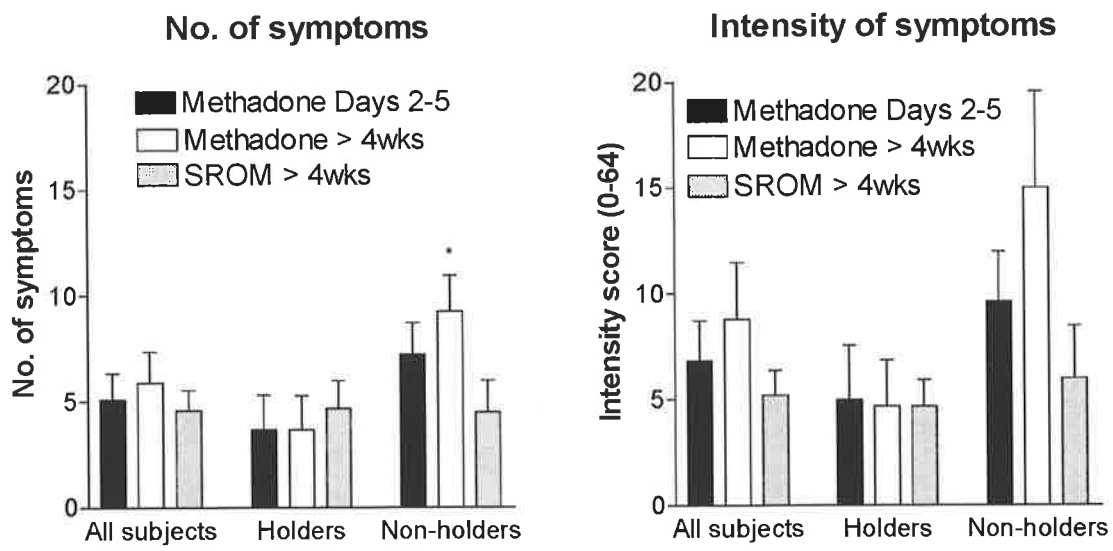

Figure 8-10. Pre-dose opioid withdrawal during re-stabilisation (averaged days 2 to 5) on methadone and at steady-state after at least 4 weeks on a stable dose of methadone and SROM: comparisons for all subjects (n=10) and the methadone holder (n=6) and non-holder (n=4) subgroups. Data are presented as mean ± SE. * $p < 0.05$ (steady-state vs. stabilisation).

8.3.3. Comparisons of transfer from methadone to SROM and vice versa

To further characterise patient outcomes during the transfer from methadone to SROM and vice versa, withdrawal data during these two transition periods were directly compared in the 11 subjects for whom such an analysis was possible. Repeated-measures ANOVA of the number and intensity of withdrawal symptoms for the first five days following transfer from methadone to SROM and from SROM back to methadone are summarised in Table 8-5. A significant main effect for drug was found, reflecting a greater overall degree of withdrawal for stabilisation on SROM compared to stabilisation on methadone. The effects for drug × day of treatment, drug × time since dosing, and drug × time since dosing × day of treatment were not significant. None of these effects were significantly mediated by methadone holding status for either the number ($p > 0.22$) or intensity ($p > 0.43$) of withdrawal symptoms, when holding status was included in these ANOVA models.

Table 8-5. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days following transfer from methadone to SROM and vice versa (n=11).

ANOVA effect[a]	Df	Withdrawal symptoms	Withdrawal intensity
Drug	1, 10	*7.75	*6.31
Drug × Day	4, 40	0.38	2.61
Drug × Time	3, 30	1.58	0.99
Drug × Time × Day	12, 120	0.93	0.41

Values are F ratios. * $p < 0.05$, ** $p < 0.01$ [a] ANOVA effects were time since dosing (Time), day of treatment (Day), and methadone holding status (Hold).

Pre-dose withdrawal scores (averaged over days 2-5) during transfer from SROM to methadone (SROM stabilisation) and vice versa (methadone re-stabilisation) are shown in Figure 8-11. The number and intensity of withdrawal symptoms prior to dosing was greater for SROM stabilisation than for methadone re-stabilisation. Although these differences were not statistically significant for either methadone holders or non-holders when each group was considered separately, they approached significance for the subjects as a whole ($p < 0.07$).

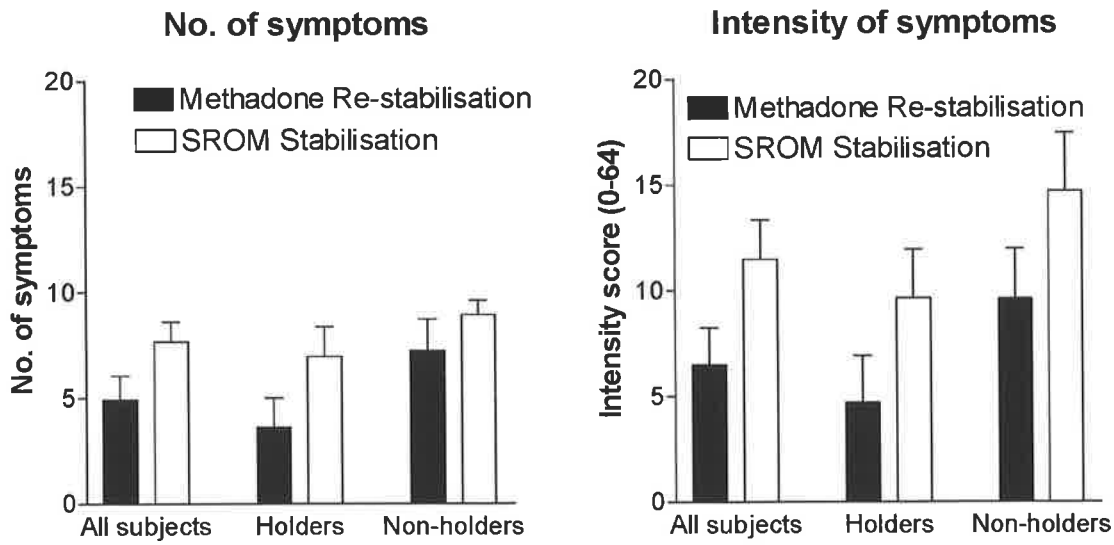

Figure 8-11. Withdrawal prior to dosing (averaged days 2 to 5) for the first 5 days following transfer from methadone to SROM (SROM stabilisation) and vice versa (methadone re-stabilisation): comparisons for all subjects (n=11) and the methadone holder (n=7) and non-holder (n=4) subgroups. Data are presented as mean ± SE. $p > 0.05$ for all differences (methadone re-stabilisation vs. SROM stabilisation).

8.4.Discussion

The present study investigated patterns of opioid withdrawal during the 24-hour inter-dosing interval for the first 5 days following the transfer of opioid dependent maintenance patients from methadone to SROM and vice versa. The protocol for switching patients from methadone to SROM involved administering the first SROM dose 24-hours following the last methadone dose. Results indicated that transfer from methadone to SROM was associated with significant changes in temporal patterns of withdrawal, such that administration of the daily SROM dose did not produce significant overall reductions in pre-dose withdrawal levels until day 3 of treatment. Withdrawal severity prior to dosing during the first 5 days of treatment was also greater than observed after at least 4 weeks on a stable dose. The time taken for a stable SROM dose to be achieved (median 6 days) and the average number of pre-dose withdrawal symptoms during the first 5 days of treatment were both inversely related to the initial SROM:methadone dose ratio. Doses increased for all subjects by an average of 20% following the initiation of treatment until a stable SROM dose was achieved, at a mean SROM:methadone dose ratio of 4.6:1. By comparison, transfer from SROM back to methadone was achieved without dose adjustment or significant changes in opioid withdrawal relative to original levels (i.e., prior to the SROM maintenance phase) in the majority of subjects. These findings have important ramifications regarding the clinical utility of SROM maintenance and the most appropriate means of transferring patients from methadone to SROM.

SROM has yielded promising outcomes in previous evaluations of its safety and efficacy as a maintenance pharmacotherapy for opioid dependence (Eder et al., 2002; Fischer et al., 1999b; Kraigher et al., 2002). Consistent with these findings, results presented in previous chapters of this thesis also suggest that SROM (administered once-daily as Kapanol™) is suitable for use in maintenance programs, particularly for patients who report inadequate suppression of withdrawal between doses whilst maintained on methadone. Although the clinical utility of SROM maintenance is therefore partly dependent on the ease with which it can be initiated in

patients already maintained on methadone, quantitative analyses of patient outcomes and dosing schedules during this transition phase have not been previously reported. The present study found that transfer from methadone to SROM was associated with changes in the temporal pattern of opioid withdrawal following dosing. However, there were no clinically or statistically significant increases in overall withdrawal severity. This finding is important because transfer from methadone to buprenorphine, which is presently the major long-acting oral alternative to methadone, is sometimes associated with significant withdrawal precipitation, most notably in patients whose daily methadone dose exceeds 40 mg (Bouchez et al., 1998; Ling et al., 1994). Transfer to SROM may thus be a particularly advantageous option for patients who require a change of maintenance medication from methadone but for whom transfer to buprenorphine is not feasible.

The findings of the present study are also likely to facilitate further evaluation and clinical implementation of SROM maintenance by helping to identify the most safe and effective means by which transfers from methadone to SROM can be achieved. The switching modality (i.e., immediate or gradual), dose conversion ratio, and rate of dosage increase are all important considerations in this regard (Ripamonti et al., 1998b). However, controlled evaluations of these factors in relation to patient outcomes have not been previously undertaken in maintenance patients and have also failed to deliver consensus or standardised practices in the related area of pain management (Ripamonti et al., 1998b). To the extent that immediate switching, whereby SROM maintenance was initiated 24-hours following the last methadone dose, did not precipitate a prohibitive degree of withdrawal, this approach is likely to be advantageous in minimising demands on treatment providers and inconvenience to patients. Nevertheless, it is possible that the outcomes achieved using this method may be improved by giving consideration to the most appropriate SROM:methadone conversion ratio and the rate at which SROM doses should be increased.

In the present study, the initial SROM:methadone dose was 3.5:1 on average and ranged from 2.94 to 3.78. This variation in part reflects the limited capsule strengths in which Kapanol™ is available, which preclude a precise and standardised conversion ratio. Variability in the initial SROM:methadone dose ratio also reflects the discretion of clinicians who, in recognising the limited existing evidence base in this area, applied an individualised and flexible approach to dosing in order to maintain the ethical integrity of the study and the well-being of patients. Analyses confirmed an inverse relationship between the initial SROM:methadone dose ratio and both withdrawal severity during the first 5 days of treatment and the time it took to achieve a stable dose. Notably, initial and final SROM:methadone dose ratios showed no relationship, indicating that variance in starting doses did not influence stabilised doses.

Following commencement of SROM maintenance, all subjects required dose increases. The average number of dose increases and total percentage increase in SROM dose during the first 10 days were 4 (range 1-7) and 20% (range 5-39%), with the average maximum increase on any one occasion being 10% (range 5-20%). Final stabilised SROM doses were closely correlated with methadone doses ($r = 0.93$) and approximately 4.6 times greater (range 3.8 – 8.0). This is within the range of SROM:methadone dose ratios evident in previous studies of opioid dependent maintenance patients (4:1-6:1) (Fischer et al., 1996; Sherman, 1996) and slightly lower than most recent estimates for the management of pain (e.g., 5:1 - 14:1) (Bruera & Fainsinger, 1997; Mercadante et al., 1999; Ripamonti et al., 1998b). The wide variation in morphine:methadone dose ratios observed in pain patients highlights the need for an individualised approach to dosing in maintenance patients, as it possible that further evaluations using greater subject numbers may reveal similar variability in SROM dose requirements for maintenance patients.

The appropriateness of the dosing protocol for converting patients from methadone to SROM in the present study depends largely on the extent to which withdrawal was adequately

suppressed in the absence of significant adverse effects during the transition period. Results indicated that transfer from methadone to SROM was associated with significant changes in the temporal pattern of opioid withdrawal during the inter-dosing interval for the first 5 days of treatment. Although pre-dose withdrawal showed only small and non-significant differences on average (e.g., 6 vs. 8 symptoms), significant overall reductions in withdrawal severity relative to pre-dose levels following administration of the SROM dose were not found until day 3 of treatment. Moreover, average pre-dose withdrawal during the first 5 days of SROM maintenance was greater than observed at steady-state, after at least 4 weeks on a stable dose, providing further evidence of an inadequacy in opioid effect during the early stages of treatment. Pre-dose withdrawal severity was also related to the initial SROM:methadone dose ratio, such that some patients starting on lower SROM:methadone dose ratios (e.g., 3:1) did experience pronounced increases in withdrawal severity during the first 5 days.

The use of higher initial SROM:methadone dose ratios is one strategy that may have facilitated superior withdrawal suppression immediately following transfer from methadone to SROM, particularly since the initial ratio in the present study (mean 3.5:1) was considerably lower than that observed at steady-state (mean 4.6:1). The use of somewhat lower than expected initial dose ratios is necessary in order to allow for individual variability in the pharmacokinetics of methadone and morphine, including the possibility of continued methadone action due to its long half-life. However, the observed relationship between withdrawal responses and initial doses, and the fact that all patients showed a final SROM:methadone dose ratio of at least 3.8:1, suggest that the minimum initial SROM:methadone dose ratio may be conservatively estimated at 3.5:1. Given recent evidence that methadone maintenance patients are extremely tolerant to the effects of morphine (Doverty et al., 2001a), even when administered at high concentrations in addition to the

normal methadone dose (Athanasos et al., 2002), it also seems unlikely that higher SROM:methadone dose ratios approximating 3.75:1 to 4:1 would jeopardise patient safety.

A second strategy that may facilitate improved withdrawal suppression during transfer from methadone to SROM involves increasing the daily SROM dose more rapidly. In the present study, the average dose increase of 20% relative to initial doses took place over a median of 6 days, indicating only a modest overall daily rate of increase in SROM dosage. For immediate release morphine, it has been suggested that daily doses can be increased at a rate of 25% to 50% daily in patients with moderate unrelieved pain and by 50% to 100% daily in patients with severe, unrelieved pain (Levy, 1996). By comparison, the extended half-life of SROM requires a more conservative approach to dosing in order to avoid accumulation and also to allow for the possibility of prolonged methadone action following the cessation of methadone dosing. Nevertheless, the magnitude of this discrepancy suggests that, in addition to using higher initial SROM:methadone dose ratios, it may be possible to use higher rates of increase in SROM doses without compromising patient safety; a perception that was prevalent amongst the subjects in this study.

In addition to increasing the magnitude of initial doses or the daily rate at which doses are increased, there are a number of other strategies that may facilitate better patient outcomes during the transfer from methadone to SROM. Since SROM has a slower onset of action in comparison to methadone (Chapter 4), any deficiency in opioid effect during the transition from methadone to SROM is likely to be particularly marked in the first few hours following the first SROM dose. This is highly consistent with the pattern of opioid withdrawal seen on day 1 of SROM maintenance in the present study, which showed no evidence of decline following administration of the maintenance dose. For this reason, it may be beneficial to use a loading dose consisting of either immediate-release morphine or a shorter-acting SROM

formulation in order to facilitate a more rapid increase in plasma morphine concentrations and hence more immediate suppression of opioid withdrawal.

In a study by Hoskin et al. (1989), 19 patients with advanced cancer pain were switched from immediate-release oral morphine (IMOR) to SROM (MS Contin™) and were randomised to receive either placebo or a final dose of IMOR in conjunction with the first SROM dose. Results indicated that this 'loading dose' strategy was effective in achieving a shorter Tmax for plasma morphine concentrations. The groups were not differentiated by patient or clinician ratings of pain intensity, leading the authors to conclude that there is no need for a loading dose in the situation considered in their study. Nevertheless, the need for a loading dose is likely to be greater when transferring patients to a once-daily SROM formulation such as Kapanol™, which shows a longer Tmax than MS Contin™ (Gourlay et al., 1997). Hoskin et al.'s study demonstrates that a combination of SROM and a shorter-acting morphine formulation may be effective in producing a more rapid onset of withdrawal suppression (i.e., more rapid Tmax) following transfer from methadone. Alternatively, it should be noted that other once-daily formulations presently unavailable in Australia (e.g., Reliadol™) have been shown to have pharmacokinetic profiles similar to Kapanol™ except for a shorter Tmax (Bochner et al., 1999). Use of such formulations, where available, may similarly provide a more rapid onset of effect and thus facilitate more immediate withdrawal suppression upon transfer to SROM.

Another focus of the present study was the transition period from SROM back to methadone. To the extent that SROM may primarily be used as an alternative for patients responding poorly to methadone, this scenario may represent a rarity in clinical practice. Nevertheless, in the instances where SROM may be found to be ineffective or unacceptable to the patient, it is important to understand the most appropriate means of achieving this medication change. The present study shows that resumption of methadone maintenance at original levels is likely to

be the most straightforward and acceptable strategy. Of 15 patients who were transferred from SROM back to methadone, only 2 required small dose increases. One subject had been maintained on a uniquely high SROM:methadone dose ratio of 8:1, which was attributed to his regular supplementary use of heroin whilst on methadone, and found his original methadone dose slightly inadequate upon re-stabilisation. Case notes for the other subject similarly indicated complaints of mild withdrawal, which seemed in contradiction with comments made by the subject during informal discussions in which he indicated a stronger than normal opioid effect from his maintenance dose upon returning from methadone. Resumption of methadone maintenance was not associated with clinically significant changes in opioid withdrawal. In the 11 subjects for whom the comparison was possible, withdrawal upon transfer from SROM back to methadone was significantly less than observed during the reverse transfer.

To the extent that transfer from methadone to SROM can be achieved without major complications, clinical utilisation of this option is most likely to occur in patients responding poorly to methadone. This includes the significant proportion of patients who report inadequate withdrawal suppression, or the failure of their dose to 'hold', between doses. In Chapter 4, it was shown that methadone non-holders exhibited greater withdrawal than holders whilst maintained on methadone, but a similar and satisfactory level of withdrawal suppression whilst maintained on SROM. The present study shows that these changes in withdrawal responses had not yet appeared in the first 5 days of SROM maintenance. However, there were differences in withdrawal patterns for each group during the SROM induction phase. The holders showed significant increases in pre-dose withdrawal scores on days 2 and 4 relative to day 1 and also showed very little evidence of declines in withdrawal severity following dosing on days 1 and 2. In fact, mean withdrawal severity actually increased following dosing on the first day of SROM maintenance. In comparison to the holders, the non-holders showed somewhat higher levels of withdrawal prior to dosing, but a

more consistent pattern of decline following dosing during the first 5 days of SROM maintenance. There were no differences between the groups in initial or final SROM:methadone dose ratios or the time taken to achieve a stable SROM dose. For the 7 holders and 4 non-holders in whom the analysis was possible, withdrawal patterns following transfer from SROM back to methadone were consistent with their original holding status classification on methadone. Specifically, whereas the holders showed low and stable withdrawal following resumption of methadone maintenance, the non-holders showed steady increases in pre-dose withdrawal for the first few days of treatment.

In conclusion, the present study has shown that transfer from methadone to SROM using an immediate switching modality was associated with significant changes in withdrawal patterns during the first 5 days of treatment. Although the SROM dose failed to produce significant overall declines in withdrawal severity for the first two days of treatment, subsequent analyses showed that this pattern only applied to subjects reporting adequate suppression of withdrawal whilst maintained on methadone. These patients are less likely to require transfer to SROM than those reporting inadequate withdrawal suppression on methadone, for whom no significant changes in withdrawal patterns were evident across the first 5 days of SROM maintenance. Moreover, it is likely that higher initial SROM:methadone dose ratios and rates of increase in the daily SROM dose would facilitate better withdrawal suppression without compromising patient safety. To this extent, transfer to SROM is unlikely to be associated with the prohibitive degree of withdrawal and safety concerns that are likely to apply when switching most methadone maintenance patients to buprenorphine and LAAM, respectively. In instances where SROM is found to be ineffective or unacceptable to the patient, transfer back to methadone at original dosage levels can be achieved without complication. These findings underscore the potentially valuable role that SROM may have in maintenance programs for opioid dependence and are likely to facilitate further evaluation and clinical implementation of SROM maintenance where deemed appropriate. The potential for shorter-

and longer-acting morphine formulations to be used in combination to achieve greater control over plasma morphine concentrations and more effective maintenance of treatment efficacy and safety during the transition period from methadone to SROM is one area worthy of further investigation.

9. GENERAL SUMMARY AND DISCUSSION

9.1. Introduction

The primary objective of this thesis was to examine the clinical utility of slow-release oral morphine (SROM) as an alternative to methadone for maintenance treatment of opioid dependence. To achieve this objective, eighteen methadone maintenance patients reporting adequate (holders) or inadequate (non-holders) withdrawal suppression between doses were recruited to participate in an open-label, randomly-ordered, crossover clinical trial of methadone and SROM. The study was designed to assess each drug with respect to their comparative pharmacokinetics and pharmacodynamics, clinical efficacy and acceptability, and the level of withdrawal associated with transfers between each medication. The following discussion will begin by summarising the major findings and clinical implications of this research, before identifying and prioritising future research directions regarding the use of SROM in maintenance programs for opioid dependence.

9.2. Summary of major findings

9.2.1. Pharmacokinetics and pharmacodynamics

The clinical utility of SROM for once-daily dosing in maintenance programs depends largely on its efficacy in providing sustained withdrawal suppression between doses in the absence of significant adverse effects. This in turn depends on the achievement of a prolonged and relatively stable profile of plasma morphine concentrations during the inter-dosing interval. Although preliminary reports indicate that SROM is a safe and efficacious alternative maintenance option to methadone (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), studies of morphine disposition and effects following once-daily SROM dosing have not been previously undertaken in an opioid dependent or methadone maintained population. A primary focus of the present thesis was a comparison of the steady-state pharmacokinetics and pharmacodynamics of methadone and SROM. This involved the concurrent measurement of plasma (R)- and (S)-methadone and morphine concentrations and both subjective and physiological indices of opioid effects throughout a 24-hour inter-dosing interval on one occasion for methadone and SROM, after at least 4 weeks on a stable dose.

The pharmacokinetics of methadone and SROM were compared in Chapter 3. Results indicated relatively stable and prolonged plasma concentration-time profiles for both (R)-methadone and morphine. Although peak to trough variation was slightly higher for morphine compared to (R)-methadone, these fluctuations occurred more gradually, as evidenced by a significantly longer time associated with peak concentrations following dosing (6.5 h vs. 2.5 h). A significant and similar degree of individual variability was observed for most pharmacokinetic parameters for both methadone and SROM. However, the relationship between dose and plasma concentrations (area under the curve) was markedly stronger for morphine (r^2 = 0.86) compared to (R)-methadone (r^2= 0.40). To the extent that plasma morphine and methadone concentrations exhibit equivalent predictive value regarding treatment response, the latter characteristic may entail a stronger dose-response relationship

for SROM compared to methadone. Larger scale studies are needed to assess this possibility. Collectively, these findings suggest that with an individualised approach to dosing, the dispositional characteristics of SROM are appropriate for once-daily dosing in maintenance programs.

To the extent that SROM is suitable for use in maintenance programs, this option may be particularly advantageous for methadone maintenance patients reporting the failure of their dose to 'hold' despite apparently adequate methadone doses and plasma concentrations (Dyer et al., 1999; Dyer & White, 1997). In the present study, the non-holders showed higher mean methadone doses and plasma concentrations throughout the inter-dosing interval in comparison to holders, suggesting that differences in withdrawal complaints between the groups were not readily attributable to inadequate methadone dosing. Compared to the holders, the non-holders were differentiated by a more rapid time associated with peak plasma (R)-methadone concentrations following dosing (3.4 h vs. 1.7 h). This finding is partly consistent with previous suggestions that cases of non-holding may be related to more rapid changes in plasma methadone concentrations between doses (Dyer et al., 1999; Nilsson et al., 1983). There were no significant differences in the pharmacokinetics of SROM for the methadone holders and non-holders.

The magnitude and duration of opioid effects during the inter-dosing interval and the overall frequency of symptom complaints was compared for methadone and SROM in Chapter 4. Consistent with previous studies (Dyer et al., 1999; Dyer & White, 1997; McCaul et al., 1982), self-reported withdrawal severity and physiological indices of opioid effect such as pupil diameter and respiratory rate showed temporal patterns of change consistent with plasma concentration-time profiles for both methadone and SROM. Accordingly, SROM differed from methadone by showing a delayed onset of action following dosing. In addition to highlighting differences in the temporal profile of effects for each drug, these measures

indicated that the magnitude and duration of opioid effects was at least as strong overall for SROM as for methadone. These findings suggest that SROM is sufficiently long-acting to permit once-daily dosing in maintenance programs.

The suitability of SROM for once-daily dosing in maintenance patients was most clearly evident in comparisons of withdrawal responses and other symptom complaints for the methadone holders and non-holders. The holders showed equivalent and satisfactory withdrawal suppression and a similar overall frequency of symptom complaints for methadone and SROM. By comparison, the non-holders showed significant reductions for SROM compared to methadone in both withdrawal at the end of the inter-dosing interval and the overall frequency of symptom complaints. Whilst the non-holders showed greater withdrawal, craving and side effects than the holders during methadone maintenance, these groups were not readily distinguished on pharmacodynamic measures during SROM maintenance. The high overall prevalence of symptom complaints in both groups during methadone maintenance highlights the fact that a balance between withdrawal suppression and adverse effects is sometimes difficult to achieve using methadone. Notably, although 5 subjects classified themselves as non-holders for SROM, only 2 were also non-holders on methadone. This means that if both medications were available, instead of just methadone, the proportion of these subjects that would be classified as non-holders would decrease from 50% to 14%. The finding that methadone non-holders were significantly more likely than holders to report cravings for opioids on at least one occasion during the methadone inter-dosing interval (86% vs. 14%) highlights the threat posed by inadequate withdrawal suppression to treatment outcomes and the potential advantages that offering both methadone and SROM may have in this regard.

The intensity, temporal patterns and determinants of mood responses during the inter-dosing interval were compared for methadone and SROM in Chapter 5. Consistent with previous

studies (Dyer et al., 2001; Hiltunen et al., 1999), mood responses for methadone and SROM showed significant changes during the inter-dosing interval in response to fluctuating plasma (R)-methadone and morphine concentrations. The amplitude of these mood changes was proportional to the severity of withdrawal. Whereas holders showed a relatively stable profile of mood disturbance for both drugs, non-holders showed significant improvements in mood stability for SROM compared to methadone. Notably, overall levels of mood disturbance did not differ for holders and non-holders, and were greater than levels previously reported for healthy controls using the same experimental paradigm. This is consistent with evidence that chronic opioid exposure may be associated with a shift towards negative mood states and highlights the need to consider affective states in addition to withdrawal and other symptom complaints when monitoring patient outcomes.

Another major finding of the present study was the detection of a relationship between the intensity of negative mood states and the ratio of (S)- to (R)-methadone in plasma (AUC). Consistent with previous studies in healthy volunteers (Fraser & Isbell, 1962; Olsen et al., 1977; Scott et al., 1948), this result suggests the possibility of a different profile of mood effects for each enantiomer. Differences in the mood effects of (R)- and (S)-methadone may arise from known differences in the pharmacological actions of each drug. In particular, whereas the opioid properties of racemic methadone are almost entirely attributable to (R)-methadone, both (R)- and (S)-methadone display significant NMDA antagonist characteristics. Since NMDA antagonists have been frequently associated with significant adverse mood responses (Abi-Saab et al., 1998; Adler et al., 1999; Curran & Monaghan, 2001; Curran & Morgan, 2000; Krystal et al., 1994; Malhotra et al., 1996), NMDA antagonism may contribute to an adverse profile of mood effects for (S)-compared to (R)-methadone (Fraser & Isbell, 1962; Olsen et al., 1977; Scott et al., 1948). Further studies are needed to examine the casual factors that may explain a relationship between enantiomeric

ratio and mood responses in methadone maintenance patients and the potential clinical applications that such a relationship may have.

Sensitivity to pain induced by electrical stimulation of the earlobe and the cold pressor test were compared for methadone and SROM in Chapter 6. To the best of my knowledge, this is the first study to have assessed pain responses amongst opioid dependent patients whilst maintained on two different opioids. Responses to both of these stimuli were highly stable between assessments for methadone and SROM and showed no significant differences between each drug. The consistency of pain responses for methadone and SROM was notable given the subjective nature of pain measurement, the time interval (approximately 6-weeks) separating each assessment, and the differential interaction of methadone and morphine with neurotransmitter systems involved in the perception of pain (e.g., opioid, NMDA, serotonin, noradrenaline). Although both measures yielded consistent results, responses to each procedure were unrelated. This highlights the need to use multiple methods of pain induction and suggests that one or both of these measures may lack external validity. In this regard, it is notable that electrical stimulation responses were not sensitive to large changes in plasma (R)-methadone and morphine concentrations, suggesting this stimulus may produce a sensation distinct from that associated with clinically-encountered pain conditions.

In comparison to the electrical stimulation procedure, the cold pressor method is likely to provide a more authentic simulation of pain encountered in clinical settings (Le Bars et al., 2001). Results of the present study were highly consistent with previous research in suggesting an abnormally low pain tolerance amongst opioid dependent maintenance patients relative to levels previously reported for normal populations (Doverty et al., 2001a; Doverty et al., 2001b). The consistency of pain responses despite a change to a maintenance medication suggests that hyperalgesia may be an enduring consequence of chronic exposure to all opioids. This scenario is of concern given the likelihood that hyperalgesia may facilitate

continued opioid seeking behaviour (e.g., to relieve pain and associated negative mood states) (Unnithan et al., 1992) and complicate pain management in methadone maintenance patients (Compton & McCaffery, 2001; Doverty et al., 2001b). The results of this study suggest that these problems are also likely to apply when the maintenance medication is changed from methadone to morphine. An understanding of the mechanisms responsible for this hyperalgesia and the means through which these problems can be overcome remains a research priority.

9.2.2. Clinical efficacy and acceptability

The second major emphasis of the present thesis involved assessing the clinical efficacy and acceptability of once-daily SROM as an alternative to methadone for maintenance treatment of opioid dependence. Despite preliminary evidence that SROM is both a safe and efficacious alternative to methadone (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), quantitative comparisons of these two treatments regarding clinical outcomes (e.g., drug use, health) and treatment preference are presently lacking. A review of the literature revealed a number of factors that limit the applicability and validity of findings presented in previous reports in regard to the objectives of the present research. In particular, although initial use of SROM in Australia is most likely to involve its use as an alternative for patients responding poorly to methadone, there had also been no controlled evaluations of once-daily SROM in methadone maintenance patients. To address these limitations in the existing evidence base for SROM maintenance, the present study compared methadone and SROM with respect to subjective and objective indices of illicit drug use, health, social functioning, depression, self-esteem, sleep patterns, and the relationship between treatment outcomes and treatment preference. Results for this component of the study were presented in Chapter 7.

Assessments of clinical efficacy indicated that overall outcomes were at least as good for SROM as for methadone. Compared to methadone, SROM was associated with improved social functioning, weight loss, fewer and less severe side effects, greater drug liking, reduced

heroin cravings, an enhanced sense of feeling 'normal' and similar overall outcomes for drug use, depression and health. Moreover, subjects showed a preference for SROM (78%) over methadone (22%), the strength of which was correlated with the degree of improvement in outcomes. This pattern of findings applied to both methadone holders and non-holders, but was most clearly evident in the latter group. The most frequently cited reasons for preferring SROM included fewer side effects (54%), better withdrawal suppression (46%), improved sleep (46%), feeling more normal (38%), improved health (38%), and improved energy (38%). For methadone holders that preferred SROM, fewer side effects (50%) and improved energy (38%) were the most frequently cited reasons; for the non-holders, improved withdrawal suppression (86%) was the most commonly cited reason. The four subjects who preferred methadone cited superior withdrawal suppression as the factor determining their choice. Notably, of 4 methadone holders whose responses to qualitative questionnaire items indicated regular or occasional non-holding on SROM, only 1 preferred methadone to SROM. For these subjects, improvements in subjective well-being and reductions in side effects apparently outweighed any perceived inadequacy in the duration of withdrawal suppression associated with SROM. Other comments made by subjects indicated a frequent belief that SROM was less dependence-inducing than methadone and would thus entail a less severe withdrawal phase. Subjects also frequently expressed a perception of SROM being associated with enhanced cognitive abilities (e.g., improved concentration, clear-headedness). Limitations of the present study, including potential biases associated with open-label and variable-dose designs, necessitate a degree of caution in interpreting these findings. In assessing whether methadone and SROM doses were equivalent, and the possibility that dose relativity may have affected the outcomes observed, it should be noted that the resumption of methadone maintenance at the end of the SROM maintenance phase was not associated with significant changes in methadone dose (compared to dose prior to the SROM phase) or opioid withdrawal. This result suggests doses for the two treatments were approximately equivalent.

Further large-scale evaluations using a double-blind approach represent an important next step in the evaluation of SROM maintenance.

9.2.3. Transfer between medications

The third major emphasis of the present thesis involved assessing the level of opioid withdrawal associated with transfer from methadone to SROM and vice versa. Transfer from methadone to another maintenance medication may occur in a variety of clinical scenarios. This includes cases where inadequate withdrawal suppression and other symptom complaints cannot be ameliorated by adjustments of the methadone dose or dosing interval (Dyer et al., 1999; Dyer & White, 1997; Nilsson et al., 1983). Unfortunately, transfer from methadone to the partial agonist buprenorphine can result in significant precipitated withdrawal, particularly in patients maintained on methadone doses of 40 mg per day or more (Bouchez et al., 1998; Ling et al., 1994), whereas transfer to LAAM is considered advisable only in exceptional cases due to safety fears relating to cardiac abnormalities (Schwetz, 2001). SROM is an opioid agonist and thus unlikely to precipitate the same degree of withdrawal as buprenorphine and, unlike LAAM, is not associated with potentially serious cardiac abnormalities. These factors indicate that in certain cases transfer to SROM may be advantageous over existing treatment options with respect to treatment efficacy, safety and acceptability. However, no previous studies have examined patient outcomes during the transfer from methadone to SROM. To address these shortcomings in the existing evidence base for SROM maintenance, the present study investigated patterns of opioid withdrawal during the 24-hour inter-dosing interval for the first 5 days following the transfer from methadone to SROM and vice versa using an immediate switching modality.

Results indicated that transfer from methadone to SROM was not associated with a prohibitive degree of opioid withdrawal. Although significant reductions in withdrawal severity following administration of the maintenance dose were not observed until day 3 of treatment, there were no significant increases in overall withdrawal severity. Moreover,

deficiencies in withdrawal suppression in the first few days of SROM maintenance were related to the initial SROM:methadone dose conversion ratio (which ranged from 2.94:1 to 3.78:1) and were most clearly evident amongst the methadone holders, who by definition are less likely to require transfer to another maintenance medication. Strategies that may facilitate a more acceptable transition between methadone and SROM include using a higher initial SROM:methadone dose conversion ratio, more rapidly increasing SROM doses, and possibly administering a shorter-acting morphine formulation in conjunction with the first SROM dose to produce a 'loading dose' effect on plasma morphine concentrations. Transfer from SROM back to methadone was achieved without dose adjustment or significant changes in opioid withdrawal relative to original (pre-SROM) levels in the majority of subjects, indicating that resumption of methadone maintenance is likely to be straightforward in instances where transfer to SROM fails to yield the desired outcomes.

The mean SROM:methadone dose ratio (4.6:1) at steady-state was within the range evident in previous evaluations of SROM maintenance (e.g., 4:1-6:1) (Fischer et al., 1996; Sherman, 1996), but somewhat lower than recent mean estimates of the oral equivalence of methadone and morphine for management of cancer related pain (e.g., morphine:methadone dose ratios up to 20:1) (Bruera & Fainsinger, 1997; Mercadante et al., 1999; Ripamonti et al., 1998b). Assessments of morphine to methadone equivalence in the field of pain management suggest that, in addition to showing considerable variation between individuals, the SROM:methadone dose ratio may be dependent on the degree of prior opioid exposure. Specifically, in patients transferring from morphine to methadone, the relative potency of methadone compared to morphine has been shown to be proportional to the original morphine dose (Mercadante et al., 1999; Ripamonti et al., 1998b). It is possible that further studies of SROM maintenance using large sample sizes may reveal similar variation between individuals in SROM dose requirements and a relationship between the SROM:methadone dose ratio and the original methadone dose.

9.3.Clinical implications of research findings

The results of this thesis support the clinical utility of SROM as maintenance pharmacotherapy for opioid dependence. In light of the preponderance of evidence supporting methadone as the first-choice option for maintenance treatment (Eap et al., 2002; Strain & Stitzer, 1999; Ward et al., 1994), it is probable that the immediate clinical utility of SROM will involve its use as an alternative for patients who respond poorly to methadone maintenance. In instances where alterations in the methadone dosing regimen (e.g., increased dose, shortened dosing interval) are ineffective, unsafe or unacceptable to the patients as a means of ameliorating withdrawal, transfer to another maintenance medication may be considered. As highlighted earlier, transfer to existing alternatives such as buprenorphine and LAAM is not always feasible. In the present study, methadone non-holders showed a significantly reduced and satisfactory level of opioid withdrawal at the end of the inter-dosing interval when assessed on SROM compared to methadone. Moreover, nearly all of the methadone non-holders (8 of 9) preferred SROM to methadone. These findings identify methadone non-holders as a patient group in which transfer to SROM may be particularly advantageous. SROM was also associated with similar outcomes to methadone on self-report and objective measures of heroin use. This is important because a major objective of maintenance pharmacotherapies, in addition to suppressing opioid withdrawal, is to block the effects of illicit opioids.

Even when once-daily oral methadone is effective in suppressing opioid withdrawal for the duration of the inter-dosing interval, a significant proportion of patients report adverse effects attributable to methadone (Dyer & White, 1997). In the present study, more than 70% of the subjects classifying themselves as methadone holders reported symptom complaints including the dose not-holding, runny nose, sweating, hot flushes, yawning, constipation and decreased appetite on at least one occasion during the methadone inter-dosing interval. Although the

holders showed a similar overall level of withdrawal for both methadone and SROM, VAS ratings indicated significantly fewer side effects for the latter drug. Indeed, 6 of the 9 methadone holders stated a preference for SROM over methadone. This included 3 of 4 subjects who classified themselves as non-holders for SROM but not methadone. These results suggest that the clinical utility of SROM in methadone maintenance programs should not be restricted to non-holders but should also include patients experiencing adverse effects or dissatisfaction with methadone despite adequate withdrawal suppression. Pending confirmation of these findings in larger studies, the high degree of patient acceptability associated with SROM in the present study suggests it could also eventually be considered as an alternative first-choice option to methadone in maintenance programs. Given the ambivalent attitudes shown by many opioid users both in and out of treatment towards methadone (Bell et al., 1995; Rounsaville & Kleber, 1985; Stancliff et al., 2002), the capacity of an alternative such as SROM to facilitate improved treatment entry and retention should not be ignored. Earlier studies indicate SROM is efficacious and well-accepted by heroin users entering treatment (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002).

Clinical implementation of SROM maintenance is likely to be complicated by a number of issues, including several potential threats to patient compliance. Firstly, since the oral bioavailability of morphine is approximately 30% (Westerling, Persson, & Hoglund, 1995), intravenously injected doses could deliver several times the oral dose equivalent. Decisions regarding the availability of SROM maintenance, and in particular the provision of "take-away" doses, will therefore require prudent clinical judgement, given the potential for morphine to be extracted from SROM formulations for inappropriate use. Nevertheless, it should be noted that the granulated capsule formulation of Kapanol™ is probably less readily injectable than methadone syrup. Moreover, intravenous morphine use is sometimes associated with histamine reactions that may act to further limit its abuse liability in comparison to methadone (Derks, 1990a, 1990b).

Second, although Kapanol™ is not readily injectable, some means of preventing chewing of the granulated Kapanol™ formulation needs to be employed, as this leads to compromised slow-release characteristics. To limit this possibility in the present study, Kapanol™ capsules were emptied into a liquid which subjects were required to consume through a drinking straw. The time required for pharmacists to dispense and supervise dosing of SROM may therefore be longer than for methadone, but is unlikely to be significantly longer than for buprenorphine, for which sublingual dosing requires patients to demonstrate that tablets have completely dissolved. This issue should be considered further in view of the likelihood that initial use of SROM is unlikely to occur on a widespread basis and that chewing of doses is likely to result in withdrawal towards the end of the inter-dosing interval and is thus not in the interests of the patient.

Third, traditional urinary screening to detect morphine as an index of illicit heroin use cannot be used in patients maintained on SROM and alternatives will need to be sought. There are several alternative biological markers that may enable this problem to be overcome. These include assaying biological specimens for heroin (diacetylmorphine), the specific heroin metabolite 6-mono-acetylmorphine, and impurities in illicit heroin (e.g., opium alkaloids) that are not common to pharmaceutical grade diacetylmorphine or morphine (McLachlan-Troup, Taylor, & Trathen, 2001). As some of these compounds have short urinary detection times (Reiter et al., 2001), it may be necessary to supplement urinalyses with cumulative indices of illicit drug use including analyses of hair samples and sweat patches (Kintz et al., 1998; Taylor et al., 1998).

In addition to these threats to patient compliance, another possible impediment to the use of SROM in maintenance programs is its increased cost relative to methadone. At the time of writing, commercial prices for methadone syrup indicated a cost (all costs expressed in

AUD$) of $0.006/mg ($6 per 200mL at 5 mg/mL). The cost of Kapanol™, which is dependent on the capsule strengths required (e.g., per capsule: 100 mg = $2.42; 50 mg = $1.33; 20 mg = $0.66; 10 mg = $0.52), is comparatively higher. Based on the doses of subjects in the present study, these prices equate to a mean cost per dose of $0.47 (range $0.15 to $0.72) for methadone and $8.60 (range $3.08 to $14.08) for Kapanol™, such that the annual medication costs would be approximately $3,000 greater for SROM compared to methadone. The extent to which this price difference prohibits implementation of SROM is likely to be partly dependent on the frequency with which SROM is prescribed and the degree to which the cost of treatment is subsidised by government. It should also be considered that, for patients who respond poorly to methadone but well to SROM, the increased costs associated with the latter may be less than those associated with failure to retain the patient in treatment (e.g., crime, lost productivity, social welfare).

In spite of these obstacles, methadone and SROM maintenance share several important characteristics that should facilitate clinical implementation of the latter where deemed appropriate. In the present study, both were characterised by once-daily dosing regimens, similar inter-individual variability with respect to dose and relevant pharmacokinetic parameters, and a close concordance between time-dependent changes in plasma drug concentrations and indices of opioid effects. In addition, utilisation of SROM is likely to be further facilitated by both the widespread availability and clinical experience associated with SROM due to its frequent use in the management of pain. Moreover, the present study indicates that the relationship between plasma drug concentrations (area under the curve) and weight-adjusted dose was stronger for SROM compared to methadone. To the extent that plasma methadone and morphine concentrations predict therapeutic response, this may entail a stronger dose-response relationship for SROM; however, larger-studies are needed to confirm this possibility.

9.4.Directions for further research

The potential advantages and disadvantages of using SROM in maintenance programs described above are ultimately questions for future studies to address. In demonstrating the efficacy of SROM in suppressing opioid withdrawal without adverse effects, and showing comparable clinical outcomes to methadone, the present study provides ethical justification for such studies to be conducted. The following areas constitute research priorities in this regard.

Firstly, the most appropriate next stage in the evaluation of SROM maintenance would involve a large-scale assessment of its clinical efficacy using a randomised, double-blind approach and standard treatment outcomes indicators. For ethical and practical reasons outlined in Chapter 2, the present study opted for a statistically powerful crossover study using an open-label design. Whilst results suggest similar overall efficacy for SROM compared to methadone, and enhanced efficacy for methadone non-holders, these findings need to be confirmed in studies using larger sample sizes, longer evaluation periods (e.g., 6 months), and in which subjects are blinded to their maintenance drug. Notably, evidence of significant subjective differences between methadone and SROM in the present study (e.g., SROM associated with slower onset of effects, improvements in energy and concentration) suggests that effective blinding may be difficult in patients accustomed to methadone. At this stage, evaluations of SROM should continue to address its utility as a supplementary option for patients who first respond poorly to methadone. Pending further evidence of SROM's long-term clinical efficacy, larger clinical trials in heroin users entering treatment should be considered given the possibility that high patient acceptance of SROM (as observed in this study) may facilitate recruitment of new individuals into treatment who are disinterested in methadone.

Second, to enhance the validity of future evaluations of SROM maintenance, attention should also be devoted to developing effective means of monitoring heroin use and patient

compliance for morphine maintained subjects. As mentioned earlier, candidate biological compounds including diacetylmorphine, 6-mon-acetylmorphine, and various opium alkaloids are likely to provide alternative means of indexing heroin use in such patients (McLachlan-Troup et al., 2001). Nevertheless, the short urinary detection windows for some of these compounds (e.g., diacetylmorphine, 6-mon-acetylmorphine) may necessitate a new style of compliance monitoring characterised by multiple assessment techniques. Cumulative measures of drug use obtained by periodic analysis of hair or sweat patches, in conjunction with urinalyses, are worthy of investigation in this regard (Kintz et al., 1998; Taylor et al., 1998).

Third, further evaluations of SROM maintenance in patients reporting dissatisfaction with methadone maintenance should also incorporate a continued emphasis on determining the most effective means of transferring patients between each medication. Results of the present study suggest that an immediate switching modality is likely to be an effective and simple means of transferring patients from methadone to SROM, providing that an appropriate SROM:methadone dose conversion ratio is applied and that SROM doses are increased with appropriate rapidity. The goal of these efforts should be to establish a standardised transfer protocol that can be applied universally in instances where transfer from SROM to methadone is required. To the extent that dosing guidelines and the oral equivalence of methadone and morphine may differ for opioid dependent and pain patients, the development of dosing guidelines may be particularly important for clinicians accustomed to prescribing SROM to the latter patient group.

Fourth, future comparisons of methadone and SROM should also investigate possible differences in cognitive performance for each drug. In the present study, subjects commonly indicated perceptions of feeling more alert, clear-headed and normal in comparison to how they ordinarily felt on methadone. This is consistent with earlier reports in which transfer

from methadone to SROM was reported to have produced improvements in concentration abilities (Fischer et al., 1996; Schneider, 1995). Quantification of these types of cognitive and neuropsychological outcomes in future studies will help to ascertain the clinical significance and pharmacological basis of any such effects. As detailed throughout this thesis, methadone differs from morphine by showing greater in vitro intrinsic efficacy (Adams et al., 1990) and selectivity for the mu opioid receptor (Codd et al., 1995), NMDA antagonist characteristics (Gorman et al., 1997), and the capacity to inhibit the re-uptake of noradrenaline and serotonin (Codd et al., 1995). It is possible that these pharmacological differences may result in different patterns of cognitive performance. Since NMDA antagonists have been associated with impairments in learning and cognitive functioning (Rammsayer, 2001), this difference may be particularly relevant to the possibility of different cognitive and mood effects for methadone and morphine.

Fifth, the potential role of morphine's metabolites, M6G and M3G, in mediating the therapeutic effects of the parent drug needs to be determined. *In vitro* and *in vivo* animal studies indicate that both M6G and M3G are pharmacologically active. As M6G binds with high affinity to mu opioid receptors and shows significant analgesic efficacy, it may contribute significantly to withdrawal suppression during SROM maintenance (Frances et al., 1992; Paul et al., 1989). By comparison, M3G shows only weak affinity for mu opioid receptors, but may nonetheless be important in mediating opioid effects including hyperalgesia and tolerance (Andersen et al., 2003). The clinical significance of M6G and M3G in mediating the pharmacological effects of morphine is yet to be fully elucidated (Andersen et al., 2003).

Sixth, in addition to its potential during the maintenance phase of treatment, SROM may have clinical utility during both the induction and detoxification phases of treatment. SROM is associated with a shorter-half life in comparison to methadone (Broomhead et al., 1997b;

Broomhead et al., 1997c; Gourlay et al., 1986; Maccarone et al., 1994), which may entail a reduced risk of delayed opioid toxicity associated with drug accumulation following treatment induction. Due to its lower intrinsic efficacy at the mu opioid receptor, morphine administered as SROM may also entail a less severe withdrawal phase than methadone (Adams et al., 1990), a belief frequently expressed by subjects in the present study. Given the occurrences of numerous fatalities following commencement of methadone maintenance (Caplehorn & Drummer, 1999, 2002a; Drummer et al., 1992; Zador & Sunjic, 2000; Zador et al., 1996; Zador & Sunjic, 2002), and the regularity with which patients express an interest in detoxifying from treatment (Caplehorn & Drummer, 1999, 2002a; Drummer et al., 1992; Lenne et al., 2001; Zador & Sunjic, 2000; Zador et al., 1996; Zador & Sunjic, 2002), these possibilities are worth investigating. A particularly interesting question is whether SROM may have clinical utility as a means of facilitating transitions between high-dose methadone and buprenorphine maintenance.

Seventh, in exploring potential additional uses for SROM in maintenance programs, it is possible that the multiplicity of different morphine formulations now available may yield specific benefits in comparison to methadone. Variation in the pharmacokinetic profiles of different SROM formulations may allow for greater individualisation of treatment. Comments of subjects in the present study indicate that whereas some subjects liked the delayed and stable onset of action associated with SROM, others preferred the more rapid onset of opioid effects associated with methadone. Once-daily SROM formulations such as Reliadol™ and Kapanol™ differ mainly in terms of the time associated with maximum plasma morphine concentrations, which occur earlier for the former option (Bochner et al., 1999), and may thus enable greater clinician and patient flexibility in finding the most acceptable medication if offered as alternatives. As explained in Chapter 8, it is likely that the use of immediate release morphine or shorter-acting SROM formulations, possibly in combination with a once-daily formulation such as Kapanol™, may also facilitate more rapid and effective withdrawal

suppression immediately following initiation of SROM maintenance. Beyond the use of morphine, it should be considered that once-daily slow-release formulations for other short-acting opioids such as hydromorphone are currently being evaluated for use in pain management and may potentially have clinical utility in maintenance programs (Angst et al., 2001; Drover et al., 2002; Palangio et al., 2002).

Finally, recently developed medications comprising a combination of morphine and the NMDA antagonist dextromethorphan in slow-release formulations (Caruso, 2000) may also be worthy of consideration for their potential utility in maintenance programs for opioid dependence. Animal studies suggest that co-administration of NMDA antagonists with opioid agonists attenuates and even reverses the development of opioid tolerance and dependence (Bisaga & Popik, 2000). There is also clinical evidence indicating that dextromethorphan may potentiate morphine analgesia, and thus reduce morphine dose requirements, in pain patients (Caruso, 2000). To this extent, it may be worth investigating whether opioid-mediated suppression of opioid withdrawal in maintenance patients is also potentiated by co-administration of dextromethorphan.

9.5. Summary

Opioid dependence is a complex condition that requires a diversity of therapeutic approaches in order to adequately satisfy the needs of all patients. Since first being introduced nearly four decades ago, methadone maintenance has expanded to become the most commonly utilised pharmacological intervention for opioid dependence worldwide (Weddington, 1994). Although the proliferation of methadone maintenance programs has conferred significant benefit to both treatment recipients and the wider community, once-daily oral methadone dosing is not a panacea for opioid problems (Johns, 1994). A significant number of methadone maintenance patients report sub-optimal outcomes including inadequate suppression of opioid withdrawal and the occurrence of adverse effects during the inter-dosing interval (Dyer & White, 1997). The shortcomings of methadone are further illustrated by the frequency with which the target population and providers of methadone maintenance express ambivalence towards treatment (Bell et al., 1995; Rounsaville & Kleber, 1985; Stancliff et al., 2002), and the number of patients who attempt to leave treatment prematurely (Lenne et al., 2001), despite recognition of the beneficial effects it has on their lives and the high probability of relapse during detoxification (Magura & Rosenblum, 2001). These factors underscore the need for alternative treatment options that retain methadone's most desirable characteristics (e.g., infrequent oral dosing), yet provide greater flexibility and choice for patients and clinicians.

Morphine is effective in suppressing opioid withdrawal but has a short duration of action that has traditionally limited its value as an alternative opioid agonist option to methadone in maintenance programs (Derks, 1990a, 1990b). In principle, the advent of once-daily SROM formulations should enable this impediment to morphine's use in maintenance programs to be overcome. Preliminary reports indicate that SROM is efficacious and well accepted by opioid dependent patients (Eder et al., 2002; Fischer et al., 1996; Kraigher et al., 2002), but have failed to address a number of important issues. There have been three previous evaluations of once-daily SROM maintenance, each of which sampled heroin users entering treatment and

showed certain methodological shortcomings (Eder et al., 2002; Giacomuzzi et al., 2001; Kraigher et al., 2002). Therefore, although initial use of SROM is likely to involve its use as an alternative for patients responding poorly to methadone, quantitative comparisons of methadone and once-daily SROM have not been previously conducted in a methadone maintenance population.

The present thesis involved a crossover clinical trial of methadone and SROM in which quantitative comparisons were made with respect to disposition and effects during the inter-dosing interval, clinical outcomes in the month prior to assessments, and the level of withdrawal associated with transfers between each medication. Outcomes for SROM were at least as good as those for methadone on measures of withdrawal severity, mood states, and adverse effects during the inter-dosing interval and indices of treatment efficacy including drug use, health, social functioning, and depression. A significant proportion of subjects showed a preference for SROM over methadone (78% vs. 22%) and cited improvements in withdrawal suppression, health, adverse effects, and the extent to which they felt 'more normal' as reasons for their choice. Transfer from methadone to SROM was not associated with a prohibitive degree of opioid withdrawal and is unlikely to entail significant perturbations of treatment efficacy and safety providing that an appropriate dose conversion ratio is applied. These findings support the clinical utility of SROM as an alternative to methadone and significantly advance the existing evidence base for SROM maintenance in this regard.

A major focus of the present study was a comparison of outcomes for methadone and SROM in patients reporting either adequate (holders) or inadequate (non-holders) withdrawal suppression between doses whilst maintained on methadone. Results showed that the methadone non-holders experienced significantly greater withdrawal, less stable mood, and a greater overall prevalence of symptom complaints than holders whilst maintained on

methadone. Both groups showed similar patterns of withdrawal, mood and symptom complaints whilst maintained on SROM, which were similar to those shown by the holders whilst maintained on methadone. The potential advantages of SROM were thus most clearly evident for the non-holders, of whom 89% preferred SROM to methadone. Nevertheless, it is notable that the holders rated side effects as significantly less severe for SROM compared to methadone. Moreover, 6 of 9 holders, including 3 who reported non-holding for SROM but not methadone, stated a preference for SROM over methadone. These findings suggest that SROM is likely to have specific clinical utility as an alternative treatment option for patients who respond poorly to methadone. This includes those reporting the problem of non-holding and those who report satisfactory withdrawal suppression but nonetheless experience significant adverse effects whilst maintained on methadone.

The experimental approach used in the present study featured the use of a randomly-ordered crossover design. This strategy was ethically advantageous in maximising statistical power, but nevertheless made it difficult to conduct the study under double-blind conditions due to the likelihood that subjects would experience withdrawal and other subjective effects upon transfer from methadone to SROM. The next stage in the evaluation of SROM maintenance should consist of a large-scale clinical trial featuring a parallel-group, double-blind research design and a longer duration of evaluation (e.g., 6 months). Proposed foci for these future studies include the development of objective markers for illicit heroin use in SROM-maintained patients, the standardisation of dosing guidelines for initiating SROM maintenance, assessments of cognitive and neuropsychological outcomes, determination of the therapeutic importance of M6G and M3G, exploration of other possible clinical utilities of SROM in maintenance programs (e.g., during the induction and detoxification phases of treatment), and consideration of the ways in which the multiplicity of available morphine formulations may be used for clinical advantage. The results of this thesis warrant further evaluation of SROM for use in maintenance programs for opioid dependence.

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