DETERMINANTS OF OPIOID EFFECTS AND WITHDRAWAL AMONG METHADONE MAINTENANCE PATIENTS

by

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DECLARATION

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ABSTRACT

Methadone maintenance is the primary effective therapy for opioid dependence. The rationale for methadone programs is to stabilise the pharmacological condition of illicit opioid users, thereby providing an opportunity to normalise health and social functioning. The extent to which this is effective for any given individual will be governed by the degree to which methadone prevents opioid withdrawal symptoms in the absence of significant direct opioid adverse effects. However, not all patients respond to methadone in the same manner, and many complain of withdrawal symptoms during the 24-hour inter-dosing interval. The persistence of these complaints is a source of concern as they may signal unsanctioned drug use and poor treatment outcome. The principal aim of this thesis was to determine the factors associated with the occurrence of symptom complaints, particularly opioid withdrawal symptoms, among methadone patients.

The first study determined the frequency of symptom complaints and assessed possible patient and treatment characteristics associated with these complaints. A cross-sectional survey of 114 patients enrolled in the South Australian Public Methadone Maintenance Program was conducted, and comparisons were made with 55 age and gender matched non-opioid using controls. A checklist of 21 commonly reported symptom complaints associated with methadone maintenance treatment was administered. The methadone patients reported an average of 8 symptom complaints, with all patients reporting at least one symptom. The majority of symptoms measured were experienced by nearly one-third of the patients. The most frequently reported direct opioid effect symptoms were constipation and a dry mouth. Frequently reported opioid withdrawal symptoms were excessive sweating and muscle pain, while insomnia and reduced libido were also common. An assessment of the 7-day test re-test reliability among 38 randomly selected methadone patients indicated the consistency of these self-reports. Methadone patients also reported these symptoms to a far greater extent than non-opioid using controls. Approximately one-third of the patients reported that the methadone dose was consistently ineffective in preventing withdrawal symptoms for the

entire inter-dosing interval (i.e. the dose does 'not hold'). These patients could not be differentiated by demographic, health, other drug use or treatment characteristics.

In the second study the temporal pattern of methadone symptom complaints during the 24-hour inter-dosing interval was assessed among 51 methadone patients. The intensity of withdrawal symptoms and direct opioid effects were measured eight times over this period. Comparisons were made between patients who reported the oral dose not 'holding' and those who did not. Many of the symptom complaints were found to vary in intensity throughout the inter-dosing interval. Direct opioid effects were maximal approximately 2-3 hours after dosing and opioid withdrawal was maximal immediately prior to dosing. Despite receiving a higher oral methadone dose, patients reporting that their daily dose did not 'hold' experienced a smaller degree of opioid effect, and a greater intensity of opioid withdrawal, during the 24-hour period. These data demonstrated that there was a change in pharmacodynamic response over the 24-hour period for all methadone patients, but that the degree of change was greater in a sub-group of patients.

In the third study, conditioned responses to opioid-related stimuli were assessed among methadone patients, in order to demonstrate classical conditioning as another potential mechanism for producing opioid withdrawal. Fifteen stabilised methadone maintenance patients were exposed to drug-related stimuli and subjective and objective responses were recorded. It was found that the intensity of subjective opioid withdrawal reported by these patients increased after presentation of a drug-related stimulus. Approximately one-half of the patients exhibited an increase of 8.00 points or more on the 48-point subjective withdrawal scale. The increment in subjective withdrawal was negatively associated with the methadone dose level, such that patients prescribed higher methadone doses exhibited smaller increments in conditioned withdrawal severity.

The time course of direct opioid effects and opioid withdrawal symptoms reported in the second study suggested a relationship with changing plasma methadone concentration during

the 24-hour inter-dosing interval. The fourth study was designed to determine plasma racemic methadone concentration-effect relationships for subjective and objective responses and whether pharmacokinetic and/or pharmacodynamic factors influenced withdrawal severity. Eighteen methadone patients, nine of whom experienced significant withdrawal (designated the non-holders), met the inclusion criteria of a minimum of six months enrolment and a constant methadone dose once daily for at least two months. During a single 24-hour inter-dosing interval, 13 blood samples were collected to measure plasma racemic methadone concentration; subjective (withdrawal severity, direct opioid effects, mood state and pain threshold) and objective (blood pressure, heart rate, respiration rate, saliva production, skin temperature, sweating and pupil size) responses were quantified on 11 occasions. The inclusion of 10 non-opioid using controls, and the absence of significant changes in subjective and objective responses among these participants, suggested that the changes recorded among the methadone patients could be reasonably interpreted as resulting from methadone ingestion. There was an inverse relationship between plasma methadone concentrations and withdrawal severity, heart rate and respiration rate, as well as a direct relationship with subjective opioid effect, pain threshold and pupil diameter. In comparison with controls, methadone patients exhibited increased anger, depression, tension, confusion and fatigue, and decreased vigour. The mood states of methadone patients were most similar to, but not equivalent with, non-opioid using controls only at peak plasma methadone concentrations. Analyses of plasma methadone concentration-effect relationships, conducted with the sigmoid E_{max} model, indicated that for the subjective responses, notably withdrawal severity and mood disturbance, small changes in plasma methadone concentrations translated into relatively large changes in effect. Withdrawal severity and mood disturbance were significantly associated with the rate of plasma decrease in the period from peak plasma concentrations to trough.

When compared with methadone patients who did not report significant subjective opioid withdrawal, the non-holders exhibited a significantly shorter period of direct opioid effect and more pronounced time-dependent changes in the subjective and physiological response

to methadone. Differences between these groups of patients were not related to oral methadone dose, other drug use, trough plasma methadone concentrations or the mean area under the plasma concentration versus time curve, but rather to the significantly more rapid hourly rate of decline in the period from the peak plasma concentration until the next dose.

Finally, a single-case study of a patient who exhibited significant opioid withdrawal despite a large trough plasma methadone concentration was conducted. Data were collected from the patient, using the same measures and procedures described above, during a once-daily dosage regimen and again during a divided dosage regimen. The reduction and division of the patient's daily methadone dose reduced the plasma methadone concentration-time profile and thereby reduced opioid withdrawal severity and mood disturbance.

It was concluded that clinically important opioid withdrawal among methadone maintenance patients was a consequence of a more rapid rate of decline in plasma methadone concentration. The standard once-daily dosage regimen may not be suitable for a significant proportion of methadone patients. An appropriate clinical response for these patients is to shorten the inter-dosing interval. The collection of serial plasma methadone concentrations as a technique for the diagnosis and management of methadone patients who respond poorly to methadone is justified.

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CHAPTER ONE

INTRODUCTION

1.1 General Introduction

Since its development during the 1960s, and introduction to Australia in 1970, methadone maintenance has become the primary form of therapy for opioid dependence. To be effective methadone programs must attract and then retain patients in treatment. A principle factor associated with patient retention and outcome is the setting of a methadone dose level that alleviates the discomfort of opioid withdrawal without producing significant direct opioid effects. However, not all methadone patients respond to methadone in the same manner, and many will complain of symptoms that they attribute to methadone. The persistence of these symptom complaints is a source of concern as they may signal unsanctioned drug use and poor treatment outcome. Hence, any studies that provide insight into the occurrence of symptom complaints will have direct clinical relevance.

The primary aim of this thesis was to determine the factors that may be associated with these symptom complaints among methadone patients. The present chapter will provide a general description of methadone maintenance, the factors associated with treatment effectiveness, and a discussion of the pertinent pharmacokinetic and pharmacodynamic characteristics of methadone. These general considerations will serve as a background for the studies, and associated literature reviews, presented in subsequent chapters.

1.2 The rationale for methadone maintenance

It is estimated that between 1 and 2% of the Australian population will use heroin in any one year, with 0.2% to 0.7% of the Australian adult population becoming dependent upon the drug (Hall, 1995; Hall et al., 1999). The regular use of heroin is associated with significant adverse health and social problems for the individual and the wider community. In Australia, the economic costs associated with harmful drug use amount to over Aus$18 billion each year (Collins & Lapsley, 1996). During 1992, the cost of lost productivity, drug treatment and law enforcement associated with illicit drug use was estimated to be over Aus$1 billion (Collins and Lapsley, 1996). Similarly high economic costs have been reported in other countries. For instance, the financial costs to the individual and society associated with opioid dependence in the United States has been estimated at approximately US$20 billion per year (NIH, 1997).

By the time most heroin users seek treatment they display significant tolerance to the positive effects of the drug (e.g. euphoria), and much of their use of heroin is to avoid uncomfortable withdrawal symptoms (e.g. O'Brien et al., 1986). Racemic methadone was first shown to alleviate the effects of heroin withdrawal in 1948 (Isbell et al., 1948). It was introduced as an opioid replacement therapy for illicit opioid dependence in the United States in 1965 (Dole & Nyswander, 1965) and Australia in 1970 (Dalton et al., 1976).

Methadone maintenance aids the rehabilitation of opioid users in variety of ways. Firstly, the pharmacological properties of methadone make it an ideal drug for an opioid replacement pharmacotherapy. Methadone has a relatively high oral bioavailability (>90%) and relatively long elimination half-life (mean 35 hours with substantial inter-patient variability) (Meresaar et al., 1981). As such, a single oral dose will generally take effect

gradually and then wear-off slowly, producing a reasonably stable physiological state across the 24 hour interdosing interval for many patients (Gerstein, 1992; O'Brien, 1993). Due to the principles of cross-tolerance, the reward produced by the injection of heroin will be diminished (O'Brien, 1993). Secondly, by reducing the necessity to alleviate opioid withdrawal, patients on methadone maintenance are amenable to many forms of psychotherapy (O'Brien, 1993; Woody et al., 1983). The policies and procedures of many programs, such as strict hours of opening, codes of behaviour, urinalyses and so forth, may also assist in the reduction of drug seeking behaviour (Gerstein, 1992).

1.3 Evidence for the effectiveness of methadone maintenance

The main aims of methadone maintenance programs are to reduce illicit drug consumption, reduce (and hopefully eliminate) concomitant criminal behaviour, reduce the very large mortality associated with injecting opioid use, reduce the spread of potentially lethal infectious diseases such as HIV, and hepatitis, and to improve the individuals' medical, psychological and social function (Dobinson & Ward, 1987; Gerstein & Harwood, 1990; Senay & Uchtenhagen, 1990). By achieving these aims there are economic and social benefits for the wider community.

Methadone maintenance has been shown to be effective in realising these aims (e.g. Dole et al., 1969; McLellan et al., 1992; Newman and Whitehill, 1979; Gunne and Grondbladh, 1981). The present section will provide a brief review of randomised controlled and observational studies of effectiveness (for a comprehensive review see Ward et al., 1998).

There have been six randomised controlled trials of methadone maintenance (Vanichseni et al., 1991; Yancovitz et al., 1991; Dole et al., 1969; Newman & Whitehill, 1979; Strain et al.,

1993; Gunne & Gronbladh, 1981). In general, these studies have reported significant reductions in heroin use &/or crime as a result of entry to methadone maintenance.

The first randomised controlled trial of methadone maintenance was conducted in New York (Dole et al., 1969). Thirty-two male ex-prisoners with at least a four-year history of heroin use were randomly assigned to either methadone maintenance or a no-treatment waiting list, and follow-up data were collected for 12 months. Despite a small sample, methadone maintenance was associated with a significantly reduced risk of returning to daily heroin use and re-incarceration.

In a trial conducted in Hong Kong (Newman and Whitehill, 1979), 100 male heroin users, who had at least one prior treatment episode, were randomly assigned to methadone or placebo maintenance. Both groups were offered extensive counseling and support. There were significant differences between the groups in retention rates, with 76% of methadone patients retained in treatment at 32 weeks compared with 10% of the control group. At the end of the three-year follow-up, 56% of the methadone patients remained in treatment compared with 2% of the control patients.

Gunne and Gronbladh (1981) conducted a trial in Sweden where patients were assigned to either a six-month residential methadone program including intensive vocational counseling, or were given a referral to a drug-free treatment. A sequential design was used, with a significant difference between the groups occurring when 17 methadone patients and 19 control patients were included in the study. After two years, 71% of the methadone patients had ceased the use of heroin and other drugs, and were either employed or undertaking further education. This compared with the generally poor results of the control group, where only 6% had ceased drug use, 12% had died and 12% were incarcerated.

In a trial conducted in Bangkok (Vanichseni et al., 1991) 240 male heroin users who had at least six prior detoxification episodes, were randomly assigned to either a 45-day methadone detoxification regime or 45 days of methadone maintenance. At the end of the study period 66% of the detoxification group had dropped out of treatment compared with 24% of the maintenance group, while 53% of the detoxification group had positive urinalyses for morphine compared with 28% of the maintenance patients.

Yancovitz and colleagues (1991) assessed the utility of an interim methadone clinic that involved the provision of limited services to heroin users waiting entry into a comprehensive methadone maintenance program. A sample of 301 volunteers, recruited from the waiting list of a New York methadone program, was randomly assigned to either the interim clinic or a waiting list control group. It was found that participation in the interim clinic was associated with a substantial decline in illicit opioid use (as measured by urinalyses) while increasing the percentage eventually entering the comprehensive program.

Strain and colleagues (1993b, 1993c) conducted a randomised, double blind, placebo-controlled study involving 247 opioid-dependent patients. The patients were initially treated with methadone for a minimum of 5 weeks and then received 15 weeks of 50, 20, or 0 mg of methadone per day. Individual counselling and group therapy were included for all patients. At the end of the study period, 52% of the 50-mg group and 42% of the 20-mg had remained in treatment compared with only 21% of the placebo group. Furthermore, a dose-response relationship was found, with patients receiving 50 mg of methadone having significantly fewer opioid positive urinalyses (36% compared with 73%), and self-reporting fewer days of heroin use (3 days versus 12 days per month) than patients maintained on 20mg/day. These results illustrate the dose-related efficacy of methadone in decreasing illicit opioid use

and improving drug-related behaviour (this will be discussed in more detail in Section 1.4.5).

Numerous comparative and observational studies have also indicated that methadone maintenance can be more effective than other forms of opioid treatment (such as short-term detoxification or no treatment) in reducing illicit heroin use or criminal behaviour (e.g. Anglin et al., 1984; Ball & Ross, 1991; Bale et al., 1980; Glanz et al., 1997; Judson et al., 1980; Hubbard et al., 1989; McLellan et al., 1992; Simpson and Sells, 1982; Winburn et al., 1974). Methadone can also be more cost-effective than residential and other forms of treatment (Bale et al., 1980; Gerstein, 1992; Hubbard et al., 1989; Ling et al., 1994).

Participation in methadone maintenance has been associated with significant improvements to the health and social functioning of patients (e.g. Novick et al., 1993; Newman, 1991; Ryan & White, 1996; Weinstein et al., 1993). Concomitant criminal behaviour (e.g. Marsch, 1998; Torrens et al., 1997), risk of infection with diseases such as HIV (e.g. Caplehorn et al., 1996; Dyer et al., 1992; Nemoto, 1992; Nolimal & Crowley, 1989; Torrens et al., 1997) and mortality rates (e.g. Caplehorn et al., 1994; Grondbladh et al., 1990; Hall et al., 1998; Zador et al., 1996; Zanis & Woody, 1998) have all been reliably demonstrated to decrease with participation in a methadone program. These observational and controlled trials have been conducted in different political and cultural settings (e.g. Hong Kong, Sweden, Thailand and the USA) and with different program policies and procedures. Despite these differences, methadone maintenance has consistently been evaluated as an effective treatment of opioid dependence and related harms.

1.4. Patient and program factors associated with the effectiveness of methadone maintenance

To be effective, methadone maintenance programs need to be able to attract and then retain patients, often indefinitely. However, there are a variety of patient characteristics and program practices that influence the degree to which heroin users are attracted to methadone and retained in treatment for a sufficient length of time. This section will review these factors.

Previous research has demonstrated that the rate of decline in drug use and associated criminal behaviours is most dramatic during the first month or two of methadone treatment (Cacciola et al., 1998; Strain et al., 1993c). This rate of improvement then plateaus, with many patients continuing to have considerable drug use and health problems during the initial phase of treatment (Ball & Ross, 1991; Best et al., 1997; Howard et al., 1995). In general, the length of time spent in treatment is associated with a decline in the frequency of drug use (e.g. Abdul-Quader et al., 1987; Ball et al., 1988; Maddux & Desmond, 1992b; Maddux et al., 1991; Simpson & Sells, 1982; White et al., 1994) and better post-treatment functioning (for a comprehensive review see Ward et al., 1998). A minimum of three to six months of methadone treatment is usually required before there is evidence of long-term change (e.g. DeLeon & Schwartz, 1984; NIH, 1997; Simpson, 1981). However, after leaving a methadone maintenance program, many patients will relapse to illicit opioid use even if social and health improvements have been achieved (e.g. Anglin et al., 1989; Ball & Ross, 1991; Condelli & Dunteman, 1993; Cooper et al., 1983; Hargreaves, 1983). Nevertheless, there is evidence that patients who detoxify with staff approval tend to have better post-treatment outcome than those who are expelled, imprisoned or leave against staff advice (e.g. Ward et al., 1994). It has been concluded by some that maintenance spanning

fifteen years or more may be required for many patients (Novick et al., 1993; Weinstein et al., 1993).

Although methadone maintenance is able to retain patients in treatment more effectively than residential or drug free outpatient modalities (Gerstein and Harwood, 1990; Hubbard et al., 1989, 1995), the retention rates of many methadone programs remain less than optimal. A study of six methadone programs in the United States found that the one-year attrition rate for new admissions to methadone was approximately 60% (Ball & Ross, 1991). This finding was consistent with the earlier National Treatment Outcome Prospective Study (TOPS) which reported that 66% of patients were discharged before completing one year of methadone treatment (Hubbard et al., 1989).

1.4.1 Individual characteristics associated with methadone treatment entry and retention

In general, the decision by many heroin users to enter treatment is made in the context of significant social, legal, medical and psychological problems that have developed as a consequence of illicit drug use. For example, heroin users who enrol in methadone maintenance tend to have used the drug for a substantial period of time (e.g. McLellan et al., 1992; Facy et al., 1991), have tried other forms of treatment (e.g. Facy et al., 1991), and have a high degree of personal concern about their drug use and associated problems (e.g. financial, medical, psychological and legal) (e.g. Grenyer et al., 1992; McLellan et al., 1992; Power et al., 1992; Rounsaville & Kleber, 1985).

Weatherburn & Lind, (1997) conducted a 2-year study where the price and purity of street-level heroin were regularly monitored in Sydney, Australia. It was found that police seizures

of heroin had no effect on the price, purity or perceived availability of heroin at street level. It was also found that admissions to methadone programs were not affected by the price or perceived availability of heroin, or by the frequency of local arrests for heroin use or possession. Nevertheless, two-thirds of those who did enter methadone programs indicated the price of heroin as a reason for wanting to stop heroin use. Other reasons cited by people seeking admission to a methadone program included being tired of the lifestyle (97%), family support (41%), trouble with police (30%) and inability to obtain heroin (1%). These results suggest that law enforcement activity and street level price of heroin may be less important than personal factors in the decision to seek treatment.

Schultz and colleagues (1994) collected data prospectively from 1039 active opioid users. Six months after being first interviewed, 144 of these users entered a detoxification program and 64 entered methadone maintenance. Using multiple logistic regression, it was found that a recent opioid overdose, higher frequency of injecting drugs and a history of prior arrest or treatment were independent predictors of entry into detoxification, while being married or living with a partner, being female, a lengthy duration of drug use (> 10 years) (but not age) and a history of prior treatment were independent predictors of entry into methadone. Knowledge of HIV status did not predict entry into either treatment. The authors hypothesised that those variables characterising treatment continuation and positive treatment outcome are the same characteristics that predict treatment entry.

Several studies have examined predictors of treatment retention focussing on the admission and demographic characteristics of patients. (A summary of these papers is provided in Appendix 1). Although complex, in general one may develop a profile of methadone patients who are likely to be successful in terms of a variety of outcome measures. These patients tend to be Caucasian (e.g. Kosten et al., 1989; Joe et al., 1991; Simpson et al.,

1995), older (e.g. Condelli, 1993; McLellan, 1993; Nwakeze et al., 1997), employed (e.g. Szapacoznik & Ladner, 1977), and well educated (e.g. Joe et al., 1991; Zanis et al., 1994). They report stable personal relationships (e.g. Costantini et al., 1992; Hubbard et al., 1989; Rosenberg et al., 1972), relationships outside the drug sub-subculture (e.g. Caplehorn et al., 1993; Judson & Goldstein, 1982; Spunt, 1993), and have few current legal problems (e.g. McGlothin & Anglin, 1981; Simpson et al., 1995). They have used drugs for longer periods before treatment (e.g. Ball & Ross, 1991; Kosten et al., 1992; Rosenberg et al., 1972), have less poly-drug use (Hubbard et al., 1989; Joe et al., 1991; NIH, 1997) and do not use unsanctioned drugs while in treatment (e.g. Kosten et al., 1989; Perkins & Bloch, 1971). They include those who respond well to the pharmacological properties of methadone in terms of adequate plasma methadone concentrations (e.g. Tennant, 1987) and experience few aversive physical consequences (e.g. Iguchi et al., 1988; Reynolds & Magro, 1975). Further, patients who are highly motivated for treatment and compliant with program policies (e.g. Gerstein, 1992; Gerstein & Harwood, 1990; p147; Saunders et al., 1995), have previous treatment episodes (e.g. Dolan et al., 1986; Joe & Simpson, 1975; Rawson & Ling, 1991), and are more committed to change (e.g. Belding et al., 1995) will tend to be more successful.

These findings are of little clinical utility however, as patients with this profile may be successful in many forms of medical/psychological intervention. It is also possible that these patients will be more acceptable and non-threatening to program staff, be expected to perform well, and perhaps be treated in a manner more conducive for change. Furthermore, previous research has yielded results suggesting that admission and demographic variables explain only a small amount of the variance in treatment retention and other outcomes (Stark, 1992; Simpson & Sells, 1982; Ball & Ross, 1991, Condelli, 1993). Analysis of the literature also indicates that there are many covariates to the relationship between patient

characteristics and treatment retention or a positive treatment outcome. For instance, patient characteristics at treatment entry may influence the content of treatment offered (dose, counselling etc). These treatment factors may be in themselves predictive of outcome. Drug use while in treatment, unemployment and psychological difficulties are potential reasons for discharge in some methadone programs. As such, any correlation between patient characteristics and treatment retention is likely to be confounded by methadone program policies and procedures.

1.4.2 Methadone program policies and procedures associated with treatment entry and retention

The effectiveness of methadone programs should also be evaluated by the extent to which program policies and procedures attract patients into treatment. While it has been concluded that methadone itself can serve as a means of attracting opioid dependent persons into treatment (e.g. Arif et al., 1990; Yancovitz et al., 1991), other factors may also affect recruitment.

A published review of the various treatment entry criteria that have been in place at different times and in different countries, indicates that the implementation of more restrictive criteria (e.g. Canada's 1971 Narcotic Control Act) can lead to a considerable decline in the total number of patients attracted to treatment (Uchtenhagen, 1990). It is also apparent that many opioid users will avoid entering abstinence-oriented programs and either seek out programs that do not set rigid goals and rules or remain outside the treatment domain (e.g. Fisher & Anglin, 1987; Glanz & Schneider, 1990; Reynolds & Magro, 1975).

In Australia, methadone maintenance was formally endorsed as a primary strategy in the management of opioid dependence at the inception of the National Campaign Against Drug Abuse (now the National Drug Strategy) in 1985 (National Drug Strategy, 1997). The policy framework for methadone maintenance in Australia is one of harm minimisation (National Drug Strategy, 1997). Within this approach, the primary aim of treatment is to reduce the harm associated with illicit drug use, with progression toward a drug-free lifestyle being a desirable rather than a necessary aim (e.g. Brown et al., 1991; Kelsall et al., 1992; Newman, 1991). A harm minimisation approach to methadone also aims to meet the public health objective of limiting the spread of blood-borne viruses (e.g. HIV and Hepatitis) among injecting drug users, and from injecting drug users to the wider community.

Since 1985 the number of people enrolled on methadone maintenance programs in Australia has increased from 2000 to around 13000 in 1993 (di Pramo, 1992; Ward, et al., 1994). This represents an increase of approximately 15% per annum, and this rate of growth continues (Gossop & Grant, 1991; Ward et al., 1998). Due in part to the possible HIV epidemic among injecting drug users, a similar expansion has occurred in many other countries (Kreek, 1987), such that approximately 200000 people are in methadone treatment throughout the world at any time (Weddington, 1995). However, it has been estimated that only approximately 30% of Australian heroin users (Hall, 1995) and 20% of opioid dependent individuals in the United States are enrolled on methadone maintenance programs (NIH, 1997; Kreek, 1987; 1992), indicating that there may still be a substantial unmet demand for methadone.

There is also evidence to suggest that individual methadone programs differ in their effectiveness in reducing illicit opioid use and retaining patients in treatment (e.g. Ball et al., 1988, 1989; Caplehorn and Bell, 1991; Fisher & Anglin, 1987; Sells et al., 1978). (A

summary of papers examining program characteristics associated with methadone retention and outcome is provided in Appendix 2). Factors found to be associated with lower program effectiveness include sub-optimal methadone dose levels (e.g. Caplehorn and Bell, 1991; Saxon et al., 1996), poor quality of counsellor care provided (e.g. Ball et al, 1988; McLellan et al., 1988, 1991; NIH, 1997), and a lack of patient participation in decision making about methadone dose level (e.g. Condelli, 1993; Magura et al., 1988; Maddux, 1993). Further, programs that are both punitive in responding to illicit drug use (e.g. Bell et al., 1995; Caplehorn et al., 1993b, 1996; Foy et al., 1989) and impose high expectations that patients gain employment (e.g. Jaffe, 1970; Szapocznik & Ladner, 1977) tend to be less effective. General clinic policy (i.e. an orientation to maintenance as opposed to lower doses and abstinence) (e.g. Bell et al., 1995; D'Ippoliti et al, 1998), optional counselling (e.g. Maddux et al., 1995a), less expensive fees for treatment (e.g. Maddux et al., 1993) and greater accessibility (e.g. Gaughwin et al., 1998; Payte & Khuri, 1993) are also factors associated with greater treatment retention rates.

1.4.3 The South Australian Public Methadone Program

Previous research suggests that traditional methadone maintenance practice is limited in the extent to which it can attract and retain patients. The development of low intervention methadone programs, which incorporate many of the aspects reported to improve treatment efficacy (e.g. Ali et al., 1992; Newman, 1991), appears to be a promising approach in addressing these inadequacies. Low intervention programs encompass the principles of harm minimisation, and recognise that patients may be at more or less advanced stages in the process of change. When incorporated into existing comprehensive programs, along the lines of a hierarchy of intervention, this approach may make services more acceptable to a wider range of individuals. As it encourages patient-centred services which are more

acceptable to those engaging in risk behaviours, this approach may have the advantage of attracting into treatment opioid users not reached by comprehensive methadone programs (e.g. Buning et al., 1990). This may enable these users to have access to other therapeutic resources, and may ultimately result in the retention of a higher percentage of opioid users within the treatment domain (e.g. Dole, 1991; Hartgers et al., 1992; Yancovitz et al., 1991).

Despite the potential of the low intervention approach to increase participation in methadone maintenance, several authors have expressed concern and scepticism regarding its overall effectiveness (e.g. Burgess et al., 1990; Uchtenhagen, 1990). While recognising the need to recruit more opioid users into treatment, especially as a response to the threat of HIV transmission, these authors call for an expansion of comprehensive therapy programs rather than the incorporation of low intervention approaches. Indeed, following on from Ball et al's (1988) finding of a correlation between positive outcome, length of stay and quantity and quality of treatment services, Uchtenhagen (1990) has proposed that methadone maintenance programs without the usual treatment requirements (e.g. clinic control of dose and regular urinalysis) would be less effective in obtaining the intended behavioural changes.

Evidence from controlled and observational studies disputing these postulates is limited. The evidence that is available, however, suggests that low intervention methadone programs can be effective in attracting patients to treatment, reducing illicit opioid use, and retaining patients in treatment. For instance, a successful methadone program that incorporates a low intervention approach is the `Methadone by Bus' project operating in Amsterdam (Buning et al., 1990). This project, based on the principles of harm reduction, was designed and implemented in order to reach populations of opioid users who were not utilising existing helping facilities. The current practice of the project allows patients who are able to refrain

from using illicit drugs to `graduate' to other, more comprehensive methadone programs. Furthermore, a limited service interim methadone maintenance program trialed in New York reduced heroin use among individuals awaiting entry into a more comprehensive treatment program, while also increasing the percentage entering treatment (Yancovitz et al., 1991). These projects have been effective in attracting opioid users into the treatment domain and increasing the number of patients who participate in more comprehensive programs.

In 1993, the South Australian Public Methadone Program developed a treatment structure that includes a hierarchy of intervention (see Table 1.1). A low intervention stream provides methadone with little therapeutic input. Two further streams provide regular counselling, in addition to methadone, but also entail greater patient responsibility. Differences in privileges across streams are designed to provide incentive for movement into the higher intervention streams and complete cessation of illicit opioid use.

This program has been recently evaluated and it was found that the use of illicit opioids declined to less than 10% of baseline levels six months after admission to the program. This was associated with a significant reduction in criminal behaviour and improved health status (Ryan & White, 1996; White & Ryan, 1995). The retention rates in this program were greater than that in the former comprehensive program (White et al., 1996). These results highlight the effectiveness of a hierarchical approach to methadone maintenance in the Australian context.

Table 1.1: The South Australian Public Methadone Program

	STREAM A (low intervention /low supervision)	STREAM B (Available after two months on program)	STREAM C (Available after six months on Stream B)
Daily Methadone Collection	Central clinic pharmacy	Community pharmacy	Community Pharmacy
Take-away methadone doses	None	4 doses per month	16 doses per month
Urinalyses	None *	Monthly	Bimonthly
Counselling	By request	Case management	Case management
Methadone Prescription review	2 months	3 months	3 months

* urine samples may be requested twice per year for program audit purposes

In summary, a variety of patient characteristics and program practices are associated with successful retention and outcome from methadone maintenance. The patient characteristics reviewed in this section appear to be of little predictive value, and many of the program policies and procedures in Australian methadone programs represent best practice. While variables such as those reviewed are important, it appears that methadone dose level is a critical determinant of patient compliance and retention in a program.

1.5 The importance of methadone dose level in relation to treatment outcome

Methadone dose is a critical determinant of patient compliance and retention in a maintenance program (e.g. Banys et al., 1994; Maremmani et al., 1994; Ward et al., 1998). Caplehorn & Bell (1991) reported that oral dose level was significantly associated with retention when controlling for clinic and patient variables. Daily methadone doses of 60mg or less, 60-79 mg, and greater than 80mg were associated with one-year retention rates of 40%, 70% and 85% respectively. In a further paper, Caplehorn and colleagues (1994)

reported that for each 40mg increase in the maximum methadone dose received during treatment, the risk of leaving treatment was almost halved. More recently, Torrens and colleagues (1996) reported that patients maintained on less than 80mg were more than three times as likely to leave treatment than those maintained on over 80mg. These studies indicate that there is a very steep relationship between methadone dose level and treatment retention.

Dole & Nyswander (1965) argued that high doses (greater than 80mg) are required to create the necessary level of cross-tolerance with heroin, known as 'narcotic blockade' (cited in Ward et al., 1998). In general, higher methadone dose levels have been associated with reduced rates of heroin use. Ball & Ross (1991) reported that when other patient and treatment characteristics were controlled for, patients maintained on 45mg or less were approximately five times more likely to have used heroin in the past 30 days than patients on doses greater than 45mg. Swensen and colleagues (1993) showed that illicit drug taking was substantially reduced if the daily methadone dose exceeded 80mg per day. Caplehorn and colleagues (1993) reported a similar relationship to Ball and Ross (1991): after controlling for patient characteristics and time in treatment, the odds of using heroin were reduced by 2% for every 1mg increase in methadone dose. In conjunction with the studies by Strain and colleagues (1993b; 1993c: see section 1.3) it is apparent that there is a very steep methadone dose-response relationship.

In a South Australian study (Dyer et al., 1992; White et al., 1994) methadone maintenance patients who did not inject a drug received higher methadone doses (55.5mg/day compared with 47.5mg/day) than those who had injected a drug in the previous month. This difference remained significant in an analysis of covariance controlling for duration on the program. These findings corroborated earlier studies showing that methadone dose is an important

factor in reducing injecting heroin use (e.g. Ball et al., 1988; Caplehorn et al., 1993), but demonstrated that this relationship held within a single methadone program. In some other studies (e.g. McGlothin & Anglin, 1981) dose has been found to be confounded with other differences between programs, including the level and quality of counselling and philosophy of the service. It has also been argued that dose itself may not be the critical factor, but rather that the methadone doses typically prescribed reflect other characteristics of methadone programs which may be more important determinants of frequency of drug use (e.g. Caplehorn & Bell, 1991; Maddux et al., 1991). In contrast, these South Australian findings suggest that methadone dose is an important influence on injecting drug use independent of treatment duration and program support.

To summarise, the research suggests that doses below 60mg/day are inappropriate for most patients, and are associated with poor retention and program compliance (e.g. Kreek, 1992a; Lowinson et al., 1992, p552; NIH, 1997; Ward et al., 1994). In practice however, many clinicians in methadone maintenance programs prescribe methadone doses at levels known to be inadequate for therapeutic effectiveness (e.g. Gaughwin et al., 1998; Langendam et al., 1988; Maremmani et al., 1993; Newman, 1991).

1.5.1. Factors associated with the prescription of sub-optimal methadone dose levels

The average methadone dose level in Australian methadone programs is generally within the effective range. A study conducted for the World Health Organisation (Gossop & Grant, 1991) compared the policy and procedures of methadone maintenance programs in Australia, Canada, France, the Netherlands, Thailand and the United Kingdom. In Australia, the mean daily methadone dose was approximately 55-60mg per day, although fewer than 10% of patients received more than 100mg per day, and those patients receiving doses

greater than 80mg per day experienced difficulties obtaining take-home doses. However, in many other countries sub-optimal methadone dose levels are frequent. For instance, a review of a random sample of 172 methadone programs in the United States revealed that 25% of these programs enforced an upper methadone dose limit of 60mg (D'Aunno & Vaughn, 1992). In 1992, approximately one-half of American methadone patients received a daily methadone dose of less than 50mg (Cooper, 1992).

There are a number of methadone program policies and procedures that are associated with the prescription of low methadone dose levels (e.g. Bell et al., 1995; Gerstein, 1992). Other factors may include prescriber concerns about overdose risk, and the occurrence of symptoms of intoxication. This is particularly pertinent during the induction of a patient on to a methadone program and achieving a stabilised dose.

The initial dose should be adequate to avoid or minimise withdrawal symptoms, without producing sedation, and with consideration to the patient's tolerance to opioids (e.g. Horns et al., 1975; O'Brien, 1993). There is considerable consensus that the starting dose of methadone should be in the range of 10-40mg, with increases of no more than 10mg every 3-4 days until stabilised (e.g. Aylett, 1982; Drummer et al., 1990; Mattick & Hall, 1994; Ward et al., 1998). Once the initial dose and tolerance have been established, stabilisation can be achieved through gradual increases of 10mg every 2 -3 days until a maintenance dose is reached, without producing significant agonist direct effects (Horns et al., 1975; Lowinson et al., 1992, p553; Olsen, 1996). Once stabilised, patients can tolerate significant changes (approximately 5mg/week) in dose level without experiencing measurable effects (e.g. Aylett, 1982; Horns et al., 1975; Jaffe, 1992).

Some patients are able to be maintained on lower doses (e.g. Bianchi et al., 1992; Craig et al., 1980), but as Ward and colleagues (1994) assert, this should not be taken as evidence that all patients can be stabilised on low methadone dose levels. There is now considerable consensus that the more effective policy is to set methadone dose levels suitable for the individual needs of patients (e.g. Bianchi et al., 1992; Olsen, 1996; Ward et al., 1988). This is consistent with findings that flexible dosage polices are associated with higher retention rates than fixed-dose policies (e.g. Banys et al., 1994).

A study of Swiss methadone maintenance patients (Del Rio et al., 1997) found that the relative risk (RR) of leaving treatment was less if the patient was stabilised on higher doses (65-110 mg/day: RR 1.00) than middle dose ranges (45-60 mg/day: RR 2.37). However, dropouts were least frequent on the lowest doses (15-40mg/day: RR 0.77). Patients in this study received individualised methadone doses, whereby self-reports of drug craving or illicit opioid use resulted in an increased dose. This suggests that the effectiveness of the methadone dose in alleviating craving or subjective withdrawal symptoms are important considerations in predicting retention in maintenance programs.

1.5.2 Patient beliefs regarding the deleterious effect of methadone

Another important factor associated with sub-optimal dosage levels is patient concerns, both realistic and unrealistic, about the adverse effects of high methadone doses. In response to these patient concerns, some clinics now encourage patient involvement in decision making about dosage levels as this has been shown to improve outcomes (Havassey et al., 1981; Maddux et al., 1995). However, when patients are given some control of their dose level, only a small minority of patients will substantially increase their dose (e.g. Goldstein et al., 1975). An explanation may be that patients who are more ambivalent about treatment, more

doubtful of its benefits and who dislike its effects, are less likely to set themselves higher methadone dose levels (Bell, 1992; cited in di Pramo, 1992).

Patients continue to resist adequate dosages based upon beliefs that methadone 'rots the bones', decreases libido and is more difficult to withdraw from than heroin (e.g. Bell et al., 1995; Iguchi & Stitzer, 1991; Johnson, 1994; Lowinson et al., 1992). Such attitudes are prevalent among methadone patients and other heroin users. Hunt and colleagues (1985) examined the images of methadone maintenance reported by 368 current methadone patients and 142 opioid users not in treatment, via structured interviews and ethnographic fieldwork. Methadone was blamed for a list of physical ailments and reputed to have an opioid content 6-10 times that of heroin. Based in part on the perception that methadone was an extremely potent drug in comparison with heroin, there was a widespread belief among all participants that it was virtually impossible to detoxify from methadone and that the detoxification process was physically and psychologically painful.

These findings were consistent with an earlier study that examined the views of patients enrolled in one of first Australian methadone maintenance programs (Reynolds & Magro, 1975). Comparisons were made between those who had left methadone treatment and the patients (approximately 68%) who had remained in treatment for two years. Although methadone was generally regarded as being helpful in removing craving, especially among those still on the program, there remained significant concern about being physically dependent upon an opioid and a dislike of 'side-effects' among both groups.

The belief that there exist numerous methadone 'side-effects' is based in part on misinformation. For instance, no evidence could be found in the literature to support the belief that methadone 'rots the bones'. Such mythology among illicit opioid users may

partly derive from aspects of treatment which directly contradict the image and self-identity of the illicit heroin user, as well as the norms and values of the heroin using subculture which support that identity (e.g. Brown et al., 1975). Beliefs such as these may be detrimental in attracting heroin users into methadone maintenance, and once there, retaining them in treatment. However, there may well be a basis for some of the beliefs that methadone is associated with certain uncomfortable physical symptoms. Judson & Goldstein (1982) suggest that many patients will feel physically and psychologically worse whilst maintained on methadone than when they leave treatment and cease the use of all opioids. Further, complaints such as a reduced libido or a dry mouth might represent direct opioid effects or withdrawal symptoms, and as such might be explained by consideration of methadone pharmacokinetics and pharmacodynamics.

The primary aim of this thesis was to determine the factors that may be associated with symptom complaints among methadone patients. The next section will review the pertinent methadone pharmacokinetics and pharmacodynamics that may be associated with symptom complaints among methadone patients, with particular focus upon those that will be assessed in subsequent chapters.

1.6 Methadone Pharmacokinetics

1.6.1 Chemistry and preparations

Methadone hydrochloride (6-dimethylamino-4,4-diphenyl-3-hepatone) is a racemate of two enantiomers: R-(-) methadone and S-(+) methadone (Jaffe & Martin, 1992; Preston, 1986). There appear to be two separate active sites in the molecule. The nitrogen atom with the bonded hydrochloride is thought to be important in the peripheral nervous system action,

while the two phenyl rings are thought to be necessary for the action on the central nervous system (Preston, 1986). The analgesic activity of the racemate is almost entirely the result of R-(-) methadone, which is approximately 10-50 times more potent at the delta (Opioid I) and mu (Opioid III) receptors than S-(+) methadone (Blum & Holder, 1984; Kristensen et al., 1995; Schall et al., 1996). S-(+) methadone also lacks significant respiratory-depression action and is ineffective in preventing opioid withdrawal symptoms, but does possess antitussive activity (Jaffe & Martin, 1992). However, racemic methadone remains the orthodox preparation in many methadone programs. Unless indicated, the studies reviewed in this section refer to racemic methadone.

Methadone hydrochloride is available in tablets (5 and 10 mg) and in solutions for injectable and oral use. Physeptone tablets contain methadone hydrochloride, starch, magnesium and glycerine (Preston, 1986; Steels et al., 1992). Methadone syrup is the principle preparation used in Australian methadone maintenance programs. Until 1995 most of the methadone mixtures available were made by a single manufacturer, however since then other manufacturers have started producing methadone formulations, meaning that the colour, flavour and consistency may vary between countries and programs (Preston, 1986). The preparation of choice for most Australian methadone programs is methadone mixture (5mg/1mL) (Preston, 1986). The mixture used in the South Australian methadone program contains sorbitol (1.9g/5mL) (DASC, 1997). This reduces the sugar content of the mixture, thought to be associated with tooth decay in long-term patients (Preston, 1986). The injection of sorbitol can result in toxic effects thus the dilution of take-away doses to at least 100mL has been proposed as a strategy to reduce this likelihood. The diluent recommended in South Australia is purified water with the addition of 0.05% sodium benzoate and 0.1% citric acid. Diluted methadone doses are used within five days of preparation (DASC 1997).

Preparations such as this are generally well accepted by methadone patients (Preston, 1986; Steels et al., 1992).

1.6.2 Absorption

Methadone has an oral bioavailability of between 80% and 95% (Benet & Williams, 1992; Meresaar et al., 1981; Nilsson et al., 1982), indicating that it is well absorbed by the gastro-intestinal tract. Methadone can be detected in plasma within 30 minutes after oral ingestion, and reaches peak concentrations in approximately 2 to 4 hours (Blum & Holder, 1984; Inturrisi & Verebely, 1972; Jaffe & Martin, 1992; Nilsson et al., 1982; Meresaar et al., 1981; Wolff et al., 1993b). After subcutaneous or intramuscular administration peak concentrations occur within one or two hours (Jaffe & Martin, 1992).

1.6.3 Distribution and binding

After therapeutic oral doses, about 85 - 90% of methadone is bound to plasma proteins (Blum & Holder, 1983; Horns et al., 1975; Jaffe & Martin, 1992). The volume of distribution of methadone is approximately 4-5 l/kg (Meresaar et al., 1981; Nilsson et al., 1982). After repeated administration there is gradual accumulation in various body tissues, including the brain (e.g. Wolff et al., 1993b). When administration is discontinued, low concentrations are maintained in plasma by slow release from the extramuscular binding sites. This may provide one explanation for the relatively mild but protracted withdrawal syndrome (Blum & Holder, 194; Jaffe & Martin, 1992).

1.6.4 Elimination (metabolism/excretion)

The primary site for biotransformation of methadone is the liver (see below), although metabolism may also occur in the intestinal mucosa and lungs (Blum & Holder, 1984; Ward et al., 1998). In humans, the major metabolic pathway of biotransformation of methadone is initial N-demethylation, followed by immediate cyclisation to form a pyrrolidine. A second N-demethylation may then occur, to transform the pyrrolidine into the major metabolite EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) (Blum & Holder, 1984; Jaffe & Martin, 1992).

Hydroxylated derivatives of both the pyrollidine and pyrroline metabolites are excreted in the urine and the bile along with small amounts of unchanged drug, and account for up to 50% of the oral dose (Blum & Holder, 1984; Inturissi & Verebely, 1972; Pond et al., 1985). Anggard and colleagues (1975) determined the daily excretion of methadone and EDDP in six subjects during a six-week period over which the daily dose increased from 10mg to 80 mg. The net excretion of methadone and EDDP increased in a dose dependent fashion with considerable daily variation. In addition to methadone, seven metabolites were identified in the urine and three metabolites in faeces.

The amount of methadone excreted in the urine is increased when the urine is acidified (Inturrisi & Verebely, 1972; Jaffe & Martin, 1992; Nilsson et al., 1982). However, it is unlikely that this will affect the total rate of elimination as metabolism, rather than renal clearance, appears to be the primary mechanism of clearing the drug from the body (Anggard et al., 1975).

1.6.5 Methadone half-life

The half-life of racemic methadone in maintained patients is approximately 35 hours with substantial inter-individual (e.g. Benet & Williams, 1992; Kreek, 1973b; Wolff et al., 1993b,1997; Sawe, 1986) and intra-individual variability (e.g. Horns et al., 1975; Inturissi & Verebely, 1972; Kell, 1994;)(from 10 hours to 80 hours). There is some difference between enantiomers, with the half-life for the R-(-) enantiomer approximately 50 hours, and for the inactive S-(+) enantiomer approximately 30 hours (Eap et al., 1996, 1998; Kreek, 1992a; Kreek et al., 1977). In non-tolerant individuals the apparent mean half-life of racemic methadone has been reported to be approximately 15 hours. (Blum & Holder, 1984; Inturrisi & Verebely, 1972). However, other studies of single administration of oral methadone have reported longer half-life values ranging from approximately 40 hours (Nilsson et al., 1982) to approximately 55 hours (Verebely et al., 1975).

Methadone is metabolised in the liver by three enzymes: cytochrome P450IA2, cytochrome P450IID6, and cytochrome P450IIIA4. Cytochrome P450IID6 preferentially metabolises R(-) methadone and P450IA2 metabolises both enantiomers (Eap et al., 1996; 1998). A genetic polymorphism for P450IID6, and large inter-individual variability of the activity of P450IA2 and P450IIIA4 has been reported (Ketter et al., 1995). Further, both P450IA2 and P450IIIA4 are inducible by many drugs (Eap et al., 1998; Ketter et al., 1995) (See Section 1.7.2). Hence, the inter-individual variability in the metabolism of methadone may be explained by genetic as well as environmental (i.e. other drug use) factors.

A wide range of clearance rates in methadone maintained patients have been reported including 110mL/min (de Vos et al., 1995), 190 mL/min (Gourlay et al., 1986) and approximately 310mL/min (Wolff et al., 1993). This compares with an acute dose clearance

rate of approximately 95 mL/min (Nilsson et al., 1982). The wide inter-patient variation in methadone half-life and clearance rates, as well as the long half-life make methadone a difficult drug to use, at least for analgesia (Gourlay et al., 1986).

Table 1.2: Summary of Methadone Pharmacokinetics.

oral bioavailablity(%)	> 90
urinary excretion (%)	14-34 (inversely correlated with urinary pH)
Bound in plasma (%)	85-90
Clearance (mL/min)	110-220
Vol. Dist. (l/kg)	4-5
half-life (hours)	35 (with substantial inter-individual variability)

Adapted from Benet & Williams, 1992, p1690; de Vos et al., 1995; Jaffe & Martin, 1992; Meresaar et al., 1981; Nilsson et al., 1982; Wolff et al., 1993; Wolff et al., 1997.

It is unclear whether changes occur in the pharmacokinetics of methadone as a result of chronic dosing. Anggard and colleagues (1974) reported that in five of their six subjects there was evidence of increased methadone metabolism as the levels of the major metabolite were initially low, but then increased gradually over a six week period to exceed the level of unchanged methadone. This finding may have been a result of the accumulation of the major metabolite relative to methadone, or a result of an enhanced metabolism of methadone into the major metabolite.

Holmstrand and colleagues (1978) observed 21 patients during induction onto methadone. Patients received 30mg/day for the first 10 to 24 days, and then 60mg/day for a subsequent 10 to 24 days. Analyses of plasma methadone concentrations collected at 4-day intervals showed that there was accumulation to a peak level after 8-10 days and then a subsequent fall in plasma concentrations of 25% for patients prescribed 30mg/day and 15% among those prescribed 60mg/day. The authors concluded that these results indicated the development of dispositional tolerance. However, this effect was only recorded in 4 of the 12 patients in the 30mg/day group, and 6 of the 16 patients in the 60mg/day group. Further, it was not known whether changes in liver functioning may have moderated this effect, as the authors stated that the serum transminase levels were elevated in 6 of the 21 patients, while 12 of the patients were known to have had previous episodes of hepatitis.

Nilsson and colleagues (1982) investigated the pharmacokinetics of methadone on days 1 and 25 in two groups of subjects. In one group (n=6) subjects received 30 mg per day, in the other group subjects (n=6) received 30mg/day for 10 days followed by 60 mg/day. There were no significant differences between the groups in overall methadone clearance rates or half-life. The authors reported that 4 (33%) of the subjects displayed an increase in clearance rates of between 40% and 165%, suggesting the development of metabolic tolerance in these subjects. However, this conclusion is difficult to interpret as the change in clearance rate was not consistent for all subjects, and other factors such as changes in liver functioning, overall health status and the use of other drugs may have moderated the results.

Finally, Kell (1994) did not find an effect of treatment length upon plasma methadone concentrations among 200 methadone patients observed over a period of 27 months. Results suggested that there was no evidence of hepatic induction by methadone. Any changes in plasma methadone concentration over time were explained by either diversion or

supplementation of methadone, the use or cessation of use of other drugs, or changes in hepatic or renal function. In total, these studies do not provide sufficient evidence to challenge Kreek's (1973a, 1973b) assertion that methadone does not affect its own metabolism.

1.7 Factors affecting the pharmacological effectiveness of methadone

As described above there is substantial inter-patient variation in methadone half-life and clearance rates. Other factors may also influence the action and metabolism of methadone in maintained patients, including health status and the use of other drugs (e.g. Kell & Techman, 1996; Kreek, 1983a). These factors may significantly alter the pharmacological effectiveness of methadone and may therefore reduce the effectiveness of the treatment, at least for some individuals.

1.7.1 Physiological and Pathological Status

1.7.1.1 Hepatic functioning

As the liver is the primary site for biotransformation of methadone in human beings, diseases that affect liver functioning may also affect methadone metabolism (e.g. Schall et al., 1996). Abnormal liver functioning is common among methadone patients. Approximately 50-60% of patients entering methadone maintenance have biochemical evidence of chronic liver disease, and over 50% of patients retained in chronic methadone treatment have persistent liver abnormalities (Kreek, 1986a). Chronic hepatic dysfunction observed in patients is primarily of three etiologic types: 1) the result of acute infection with a hepatitis virus; 2) alcohol induced liver disease including fatty liver, alcoholic hepatitis

and alcohol cirrhosis; or 3) the result of chronic injecting of illicit drugs that may contain contaminants (Kreek, 1986a; Parwatiker et al., 1974; Platt, 1988).

When present, liver disease may slow the rate of methadone elimination (Kreek, 1983) and significantly prolong the mean plasma half-life of methadone (Kreek, 1986a). Novick and colleagues (1981) found that when compared with methadone patients with mild or no liver disease, patients with severe liver disease exhibited a prolonged methadone elimination half-life, but there were no other discernible pharmacokinetic differences.

There is no evidence that methadone is hepato-toxic (Kreek, 1983a, 1986b; Parwatikar et al., 1974; Rettig & Yarmolinsky, 1995). However, in patients with severe and extensive liver damage methadone maintenance may precipitate porto-systemic encephalopathy, a toxic state caused by the liver failing to metabolise a number of products. This may be temporary and reversible or may result in permanent damage (Preston, 1986). While chronic liver disease is not considered a contraindication for methadone maintenance (Novick et al., 1981), very severe liver disease, or abrupt changes in hepatic status, may cause significant alterations in methadone disposition, and as such care in setting the methadone dose level is required to avoid toxicity (Kell, 1994; Kreek, 1986a).

1.7.1.2 Renal Functioning

Renal disease has been reported to be common among heroin users (approximately 25%), and renal failure may occur as a result of bacterial endocarditis (Platt, 1988). There have been no reports of renal damage of any type resulting directly from methadone treatment (Kreek, 1975, 1983a). Pyuria (20%) and proteinuria (10%) have been observed in patients at

treatment entry, with these percentages decreasing with time in treatment, suggesting that methadone is not nephrotoxic (Kreek, 1986b).

The effect of renal dysfunction on the disposition of methadone in humans is unclear. Rettig and Yarmolinsky (1995) state that the presence of chronic renal disease does not result in the systemic accumulation of methadone or its metabolites, as methadone and its metabolites may be exclusively excreted by the hepatobiliary faecal route in the presence of renal disease. However, other authors suggest that this change in excretion route may not occur and suspect that renal dysfunction may affect the disposition and action of methadone in some maintenance patients (e.g. Kreek, 1983a, 1986a; Sawe, 1986).

1.7.1.3 Pregnancy

Methadone metabolism may be altered in late pregnancy due to a predominant effect of progestins on hepatic drug metabolism (Kreek, 1986a). Plasma methadone concentrations are significantly lower, and systemic elimination of methadone more rapid, as pregnancy progresses through the third trimester (Rettig & Yarmolinsky, 1995). As a result, some women may report symptoms of withdrawal during late pregnancy even when the daily dose remains constant.

The only reported adverse effect of methadone on the foetus has been the production of physical dependence, which causes mild to modest withdrawal in the early postnatal period in many babies. No chronic sequelae of maternal methadone treatment have been found, nor have any teratogenic effects been reported (Byrne, 1995; Rettig & Yarmolinsky, 1995).

1.7.2 Drug interactions with methadone

The majority of methadone patients report pre-admission use of one or more illicit drugs in addition to opioids (e.g. Ball et al., 1986; Hoffman et al., 1984) and many continue to use drugs other than methadone during maintenance treatment (e.g. Gaughwin et al., 1998; San et al., 1993). A variety of drugs have been shown to influence the amount of methadone in plasma by either enhancing or inhibiting the microsomal enzyme systems in the liver. A list of the commonly cited methadone and other drug interactions is presented in Table 1.3.

Drugs associated with an increase in methadone plasma concentrations, and therefore the appearance of direct opioid effect symptoms, include chloral hydrate, chlormethiazole, cimetidine, fluvoxamine, lithium, desipramine and other tricyclic antidepressants. Further, methadone has also been shown to alter the disposition of a number of medications including cisapride, cyclizine, desipramine, zidovudine and the anti-psychotics chlorpromazine, thiothexine and haloperidol. These drugs may be used by patients for medical indications, to "boost" the subjective effects of methadone, alleviate opioid withdrawal or to experience a different drug effect (e.g. Bell et al., 1990; Kleber, 1986; Kreek, 1992).

The use of other drugs, however, may produce signs and symptoms of opioid withdrawal in methadone patients maintained on seemingly adequate doses. Biotransformation of most drugs, including methadone, occurs in the liver via the microsomal enzyme systems (e.g. Benet et al, 1985; Ketter et al., 1995)(see Section 1.6.5.). Some drugs may induce the activity of these enzymes, thereby increasing the rate of elimination of methadone (e.g. Schall et al., 1996). These drugs include rifampicin, phenytoin, phenobarbitone, carbamazepine, disulfirum and possibly cocaine.

Table 1.3. Methadone and other drug interactions.

Drug	Principal effect on maintenance patient	Increased methadone metabolism	Mechanism and comment	References
Alcohol (acute use)	Increased sedation	No	Methadone metabolism inhibited when alcohol consumed in large amounts.	Cushman et al., 1978; Kleber, 1986, p136; Kreek, 1986, pp103-4; Preston, 1996, pp60-1; Saunders, 1986.
Alcohol (chronic use)	Opioid withdrawal	Yes	When alcohol levels fall following chronic administration of large amounts, methadone metabolism may be accelerated due to effects on microsomal enzyme activity.	Kreek, 1986, pp103-4; Rettig & Yarmolinsky, 1995, p49; Preston, 1986, pp60-1.
Anti-psychotics (Chlorpromazine, thiothexine, haloperidol)	May potentiate anti-psychotic effects	No	Methadone and these anti-psychotics increase serum prolactin. Lower doses of anti-psychotics may be required as methadone either potentiates their effects or has its own anti-psychotic action.	Gold et al., 1977; Kleber, 1986, pp125-6.
Barbiturates	Opioid withdrawal, increased sedation	Yes	Raised hepatic metabolism resulting in reduced methadone levels. Additive CNS depression resulting in increased sedation also noted.	Bell et al., 1990; Preston, 1996, pp 60-61
Benzodiazepines (Diazepam)	Increased sedation	Possible	Pharmacodynamic interaction between methadone and diazepam has been recorded, but pharmocikentic interaction is less clear. General effect noted is additive CNS depression	Bell et al., 1990; Kleber, 1986, pp125-8; McDuff et al., 1993; Preston et al., 1984; Preston et al., 1986; Preston, 1996, pp 60-61

Table 1.3. Methadone and other drug interactions. (continued)

Drug	Principal effect on maintenance patient	Increased methadone metabolism	Mechanism and comment	References
Buprenorphine	Partial agonist	No	Produces dose-related antagonist-like effect. Can be used safely only in low dose methadone treatment	Preston, 1996, pp 60-61; San et al., 1993; Strain et al., 1992; Walsh et al., 1995
Carbamazepine	Opioid withdrawal	Yes	Reduced methadone levels due to raised hepatic metabolism. Valproic Acid has been suggested as a more appropriate anticonvulsant.	Bell et al., 1988; Bell et al., 1990; MIMS Annual, 1987; Preston, 1996, pp 60-61; Saxon et al., 1989.
Chloral hydrate	Increased sedation	?	Additive CNS depression	Preston, 1996 pp 60-61
Chlormethiazole	Increased sedation	?	Additive CNS depression	Preston, 1996, pp 60-61
Cimetidine	Increased sedation	No	Possible increase in methadone levels as it inhibits hepatic enzymes and may slow methadone metabolism	Preston, 1996, pp 60-61
Cisapride	Increased sedation	?	Morphine has an increased rate of onset of action and increased sedative effect when used with this drug. A similar interaction is likely with methadone.	Preston (1996) pp 60-61
Cocaine	Opioid withdrawal	Possible	Some reports available suggesting that cocaine may interfere with methadone metabolism by accelerating methadone elimination.	Kreek, 1992; Rettig & Yarmolinsky, 1995, p49; Tennant & Shannon, 1992

Table 1.3. Methadone and other drug interactions (continued).

Drug	Principal effect on maintenance patient	Increased methadone metabolism	Mechanism and comment	References
Codeine	Increased sedation	No	Additive CNS depression	Preston, 1996, pp 60-61
Cyclizine	Injection with opioids is associated with hallucinations	No		Preston (1996) pp 60-61
Dextropropoxyphene (structurally related to methadone)	Increased sedation	No?	Additive CNS depression	MIMS Annual, 1987; Preston, 1996, pp 60-61
Disulfiram	Increased sedation possible.	No	Produces an adverse reaction to alcohol. Some methadone preparations contain alcohol. Increased sedation has been observed in some patients. May inhibit microsomal enzymes.	Kleber, 1986, p137; Preston, 1996, pp 60-61; Rettig & Yarmolinsky, 1995, p49.
Domperidone	Increased sedation	?	Morphine has increased rate of onset of action and increased sedative effect. A similar interaction is likely with methadone.	Preston, 1996, pp 60-61
Fluoxetine	Increased sedation and reduced respiration rate	No	Increased methadone levels may result in enhanced sedative effect. Opioid withdrawal may be present when medication discontinued. may have a less marked effect upon plasma methadone concentration than fluvoxamine	Alderman, 1998

Table 1.3. Methadone and other drug interactions (continued).

Drug	Principal effect on maintenance patient	Increased methadone metabolism	Mechanism and comment	References
Fluvoxamine	Increased sedation.	No	Fluvoxamine is a weker inhibitor of cytochrome P450IID6 than other SSRIs, but does inhibit P450IIIA4 and P450IA2. 50-250mg of Fluvoxamine has been associated with an increase of plasma methadone concentrations by between 40-100%.	Alderman, 1998; Bertschy et al., 1996
Lithium	Increased sedation	No	Additive CNS depression.	Kleber, 1986, p134.
Metoclopramide (dopamine antagonist)	Increased sedation		Morphine has an increased rate of onset of action and increased sedative effect when used with this drug. A similar interaction is likely with methadone.	Preston, 1996, pp 60-61
MAOI antidepressants	CNS excitation	No	MAOI anti-depressants have a stimulant like effect in methadone patients. However, respiratory depression ahs also been recorded.	Kleber, 1983; Preston, 1996, pp 60-61
Pentazocine	Partial agonist.	No	At doses greater than 60mg, pentazocine produces primarily antagonist-like effects.	Kreek, 1986b, p461; Strain et al., 1993a
Phenobarbitone (anticonvulsant)	Opioid withdrawal	Yes	Reduced methadone levels due to raised hepatic metabolism	Bell et al., 1988; Preston, 1996, pp 60-61

Table 1.3. Methadone and other drug interactions (continued).

Drug	Principal effect on maintenance patient	Increased methadone metabolism	Mechanism and comment	References
Phenytoin (Dilantin)	Opioid withdrawal	Yes	Reduced methadone levels due to raised hepatic metabolism. Valproic Acid has been suggested as a more appropriate anticonvulsant.	Borg et al., 1992; Kreek, 1986a, p102; Preston, 1996, pp 60-61; Saxon et al., 1989.
Rifampicin	Opioid withdrawal	Yes	Reduced methadone levels due to raised hepatic metabolism and increase urinary excretion.	Kreek, 1986a, p102; Preston 1996, pp 60-61
Tricyclic antidepressants	Increased sedation	?	Raised desipramine plasma levels (by a factor of 2) have been reported when administered during methadone maintenance.	Kolar et al., 1992; Kleber, 1983; Maany et al., 1990; Preston, 1996, pp 60-61
Urine acidifiers (ammonium chloride)	Opioid withdrawal	No	Reduced methadone levels due to raised urinary excretion	Preston, 1996, pp 60-61
Urine alkalinisers (sodium bicarbonate)	Increased sedation possible	No	Raised methadone levels due to reduced urinary excretion	Preston, 1996, pp 60-61
Zidovudine	Raised levels of zidovudine possible.	No	Concurrent administration of methadone and AZT does not alter peak methadone concentrations or the area under the methadone concentration-time curve.	Preston, 1996, pp 60-61; Schwartz et al., 1992; Selwyn et al., 1989.
Zopiclone	Increased sedation	?	Additive CNS depression	Preston, 1996, pp 60-61

Alcohol and benzodiazepines may also influence the therapeutic effectiveness of methadone. However, the mechanism behind these interactions is less clear and will be briefly discussed.

1.7.2.1. Alcohol

Some patients on methadone maintenance steadily increase their alcohol consumption to hazardous and harmful levels (Judson et al., 1980; Kreek, 1986a; Rettig & Yarmolinsky, 1995; Saunders, 1986). The combined syndromes of alcohol and opioid dependence have profound effects on treatment outcome and health, including significant acute and chronic liver impairment (e.g. Barr & Cohen, 1987; Khuri et al. 1984)

In methadone maintained patients, two different anecdotes have been reported with respect to the effects of alcohol: 1) that large amounts of alcohol "boost" the effect of methadone; and 2) that during chronic heavy use of alcohol, there are reports of opioid withdrawal symptoms (Kreek, 1983a, 1986a; Rettig & Yarmolinsky, 1995). It appears that alcohol may have a biphasic effect on methadone metabolism. When ethanol is present in large amounts, drug metabolism is inhibited, yet when ethanol is no longer present, following chronic administration of large amounts, drug metabolism is accelerated, possibly due to the enhancement of hepatic microsomal metabolising enzyme activities (e.g. Kreek, 1986a; Saunders, 1986).

Some evidence for an increase in enzyme activity is available from an in vitro study using cultured human hepatocytes (Jover et al., 1992). It was found that ethanol potentiated opioid-induced hepatotoxicity. Concentrations of heroin and methadone that had little or no effect on hepatocyte metabolism in the absence of ethanol, were associated with a

significant decrease in urea synthesis rate, metabolism of glycogen and depletion of the intracellular GSH pool after ethanol pre-treatment. The increase in toxicity of heroin and methadone produced by ethanol was associated with a 40% increase in cytochrome P-450 levels of the pretreated hepatocytes

Disulfiram is commonly used in the treatment of alcohol dependence. Depending on whether the methadone preparation contains alcohol, the combination of disulfiram and methadone appears to be generally safe (Kleber, 1986). However, methadone may ameliorate some of the adverse consequences of the disulfiram-alcohol reaction (Kleber, 1986). Further, in some patients excess sedation has been noted, possibly due to a disulfiram-induced inhibition of liver microsomal enzyme (Rettig & Yarmolinsky, 1995).

1.7.2.2. Benzodiazepines

A significant proportion of methadone maintenance patients use benzodiazepines (e.g. Darke et al., 1993; San et al., 1993). Possible reasons for use may include therapeutic use, abuse, and self-medication of negative affect or opioid withdrawal symptoms, depending in part on the properties of the particular benzodiazepine. In the USA, methadone patients report a preference for diazepam, lorazepam, and more recently, alprazolam, while chlordiazepoxide and oxazepam are rarely used for non-therapeutic reasons (Iguchi et al., 1989; McDuff et al., 1993). The most common benzodiazepines used by methadone maintenance patients in Australia are temazepam, oxazepam and diazepam (Darke et al., 1993). Patients who regularly use benzodiazepines are more likely to continue the use of other drugs, engage in HIV risk-taking behaviour, and display higher levels of psychopathology and social dysfunction (Darke et al., 1993).

Diazepam, when taken within one hour of the methadone dose, is reported by patients to "boost" the methadone effect (Kleber, 1986; Miller & Gold, 1991; McDuff et al., 1993), while the chronic use of benzodiazepines is suspected to lead to lowered plasma methadone concentrations and opioid withdrawal (Bell et al., 1990; Ward et al., 1998). These reports suggest a possible interaction between methadone and benzodiazepines.

Preston and colleagues (1984) assessed five methadone patients with histories of diazepam abuse, who had been enrolled on a methadone program for over six months and were receiving mean oral doses of 56mg/day. Patients were administered either a single oral dose of placebo, diazepam (20 or 40mg), methadone (100%, 150% or 200% of maintenance dose) or one of four diazepam and methadone combinations (20 and 40mg diazepam in combination with 100% and 150% of methadone dose) under double blind conditions 22 hours after the last methadone dose. Acute subjective effects and physiological measures (heart rate, skin temperature, respiration, blood pressure measured continuously and pupil photographs taken 15 minutes before and 15, 30, 45, 60, 90 and 120 minutes post dose) were recorded. The combination of 150% methadone dose and 40mg diazepam induced pupil constriction and subjective opioid effect scores greater than the effects of those doses of methadone and diazepam alone. Results suggested an interaction in which the opioid effects of methadone were enhanced by methadone. However, patients more frequently identified drug combinations as being sedative like than methadone like, which would have been expected if diazepam was simply boosting the effects of methadone. The overall conclusion was that the direct opioid effects of methadone were enhanced by the concurrent administration of diazepam.

In a follow-up study (Preston et al., 1986), the effects of diazepam on plasma methadone concentrations (which had been recorded 15 minutes before and 15, 30, 45, 60, 90 and 120

minutes post dose) were analysed. Results suggested that the concurrent administration of diazepam did not significantly change the time-course or areas under the plasma concentration-time curve of methadone or diazepam compared with the levels following administration of either drug alone. However, data were collected over a limited time period (120 minutes post-dosing), and it is unlikely that peak plasma methadone concentrations would have been reached. Nonetheless, these results suggest a pharmacodynamic rather than a pharmacokinetic interaction between diazepam and methadone.

The mechanism of this pharmacodynamic interaction is not clear, however one explanation may be that there are commonalties of actions. Some support for this explanation derives from reports that diazepam, by augmenting GABA-ergic transmission in the central nervous system, could augment the effects of methadone on catecholamine pathways, leading to mood, motor and behavioural changes (Kleber, 1986; p128).

In summary, these physiological, pathological and drug interaction factors may account for some of the individual variation in the response to methadone, and therefore dose requirements. However, other factors, predominately of a pharmacodynamic nature, are also involved in patient complaints of 'side-effects'.

1.8 Methadone Pharmacodynamics

1.8.1 Site of action

Methadone exerts its effects by binding to opioid receptors which are present in high numbers in the dorsal horn of the spinal cord, thalamus, midbrain periaqueductal grey, rostral ventral medulla, and other regions of the brain, as well as in neural plexuses in the gastrointestinal tract (Dhawan et al., 1986; Jaffe, 1992; Kreek, 1992). Three classes of opioid receptors have been identified (i.e. delta (Opioid I), kappa (Opioid II) and mu (Opioid III)), which appear to produce different physiological effects (see Table 1.4). It appears that delta and mu receptors are involved in systems that influence mood, reinforcing effects, respiration, pain, blood pressure and endocrine and gastrointestinal function. Kappa receptors, when activated, can produce endocrine changes and analgesia, but in contrast to delta and mu agonists, kappa agonists are not self-administered by animals in experimental conditions, and appear to produce aversive effects and dysphoria (Dhawan et al., 1986; Jaffe, 1992). Methadone acts predominately on the mu receptor where it binds with high affinity (Jaffe & Martin, 1992).

Table 1.4: Summary of the principal locations, associated neurotransmitters and functions of opioid receptors

Receptor	Principal Locations	Neurotransmitter	Primary Function
Opioid I (delta)	neocortex olfactory bulb nucleus accumbens	Enkephalins	analgesia respiratory depression olfaction gastro-intestinal motility cognitive function hallucinations some reinforcing properties
Opioid II (kappa)	nucleus accumbens	Dynorphins	nociception (pain receptor) increased urination feeding endocrine secretion immune function constipation thermoregulation Does not produce positive subjective effects and can produce dysphoria, and therefore is not reinforcing.
Opioid III (mu)	neocortex thalamus nucleus accumbens hippocampus amygdala dorsal horn of spinal cord	Endorphins	analgesia respiration (decreased sensitivity to hypercapnia) cardiovascular function intestinal transit locomotor activity thermoregulation Produces positive subjective effects and is reinforcing.

Adapted from Dhawan et al., 1996; Jaffe & Martin, 1990.

Three distinct families of peptides have been identified: the enkephalins, the endorphins and the dynorphins. Each family is derived from a distinct precursor polypeptide: proenkephalin for the enkephalins; pro-opiomelancortin (POMC) for the endorphins; and, prodynorphin for

the dynorphins (Jaffe & Martin, 1992; Kreek, 1992a). A number of biologically active peptides are derived from these precursors. With respect to POMC, these peptides include melanocyte-stimulating hormone, adrenocorticotropin (ACTH) and beta-lipotropin (Jaffe & Martin, 1992).

There have been some suggestions that chronic administration of opioids may lead to a decrease in the synthesis and release of endorphins (Gold et al., 1981; Simon, 1992). However, the general consensus is that the effect of opioids on the endogenous opioid system remain uncertain (e.g. Fishman, 1978; O'Brien, 1993). O'Brien (1993) compared the results of five comparable studies, of which four found plasma beta-endorphin to be normal during periods of opioid use, and three of these studies also found beta-endorphin elevated during opioid withdrawal. He concluded that as a result of the available assay methods, there are few consistent and significant relationships between measures of exogenous opioid use and measures of endogenous opioid activity. Regarding methadone patients, his own work suggested that neither methadone dose nor methadone plasma levels correlate with plasma endogenous opioid levels (O'Brien, 1993).

1.8.2. Symptom complaints among methadone maintenance patients

During the early phases of methadone maintenance, when the patient is being stabilised, multiple so-called 'side-effects' are observed. Many of these are direct opioid effects to which full tolerance has not developed. These include the primary direct effects of euphoria, drowsiness, somnolence, nausea and vomiting, difficulty in urination, oedema of the lower extremities, menstrual irregularities, sexual function problems, insomnia, constipation and excessive sweating (Kreek, 1986b).

Most of the initial opioid effects, predominantly somnolence, can be avoided by starting methadone maintenance treatment at relatively low dose levels, and increasing the dose gradually so that oral doses given do not exceed the degree of tolerance (Kreek, 1986b). Physiological functions that are reportedly deranged during cycles of heroin use include: 1) CNS stress responses that are mediated by the hypothalamic-pituitary-adrenal axis; 2) reproductive hormones of the hypothalamic-pituitary-gonadal axis with resultant abnormal function; 3) various indices of immune function that are linked to or modulated by neuro-endocrine function. These altered functions are reported to normalise during long-term steady-dose methadone treatment (Kreek, 1986a; Rettig & Yarmolinsky, 1995).

A review of the prevalence of specific symptom complaints among methadone patients will be presented in Chapter Two. The following section will review the mechanisms associated with common symptom complaints reported among methadone patients, particularly those that will be assessed in subsequent chapters. A summary of symptom complaints reported by methadone maintenance patients, mechanisms of action for these symptoms and the degree of tolerance development is provided in Table 1.5.

1.9 Methadone effects on the central nervous system

1.9.1 Analgesia

Opioids produce analgesia by binding to mu receptors in the peripheral and central nervous systems, both spinally and supraspinally, and inhibit nociceptive activity (Burks, 1989; Codd et al., 1995; Fields, 1993; Foley, 1993; Lehofer et al., 1997; Olsen, 1996). Opioids inhibit pain transmission neurones directly and indirectly through pain modulating systems. Direct inhibition of nociceptive transmission pathway neurones is most apparent at the

spinal level, where opioids reduce transmitter release from primary afferent neurones and directly hyperpolarise nociceptive dorsal horn neurones. Similar direct actions by opioids may also inhibit supraspinal nociceptive transmission neurones at the thalamic and cortical levels (Fields, 1993; Melzack, 1990).

Indirect mechanisms for opioid analgesia involve the action of opioids upon the modulatory network incorporating the periaquaductal gray and the rostral ventromedial medulla, which in turn controls nociceptive transmission neurones (Fields, 1989; 1993; Liebmann et al., 1994; Millan, 1993; Porreca & Burks, 1993). Thus in addition to their direct inhibitory action on nociceptive transmission at the spinal level, an indirect inhibition is produced by opioids through an action on a brainstem modulatory pathway that projects to the spinal cord.

Methadone has an analgesic potency comparable to morphine (10mg i.m. morphine is equivalent to 10mg i.m. methadone and 20mg oral methadone) (Blum & Holder, 1984; Jaffe & Martin, 1992). Analgesia is increased in a dose-related manner, to a point beyond which larger doses lead to greater direct effects but no greater analgesia (Jaffe, 1992). The average minimum effective blood plasma concentration for analgesia is approximately 30 ng/mL (Gourlay et al., 1986; Jaffe & Martin, 1992). The onset of analgesia occurs 10-20 minutes after parenteral administration and 30-60 minutes after oral medication (Jaffe & Martin, 1992). Despite the relatively long plasma half-life of methadone, the duration of analgesia is often only 4-8 hours. Repeated analgesic doses of methadone lead to drug accumulation because of the discrepancy between the plasma half-life and the duration of analgesia (Foley, 1993; Jaffe & Martin, 1992; Portenoy & Payne, 1992). During chronic methadone treatment, tolerance is thought to develop rapidly to most analgesic effects of methadone (Kreek, 1986b).

Table 1.5. Methadone pharmacodynamics: Summary of common symptom complaints and other opioid effects reported among methadone patients, mechanisms of action and tolerance development.

Symptom	Mechanism of action	Degree and rate of tolerance development	Reference
Analgesia	Binds to opioid receptors at spinal, supraspinal and peripheral sites, where pain transmission neurones are inhibited directly and indirectly.	Develops quickly and is almost complete. However, tolerance may be partial and develop more slowly in the neural system associated with chronic pain.	Fields, 1993, p3; Foley, 1993, p696; Melzack, 1990; Rettig & Yarmolinsky, 1995, p48; Thomason & Dilts, 1991; p110
Cardiovascular			
a)ECG Abnormalities	Mechanism unknown, but may be due in part to pre-existing medical conditions	Unknown	Kreek, 1986b, p464; Platt, 1988, p90.
b)Swelling arms/legs	Mechanism unknown, but may be due in part to increased blood flow to peripheral blood vessels	May develop quickly as patients reports primarily occur during the early stages of maintenance treatment.	Preston, 1986, p44.
c)Heavy arms/legs	Mechanism unknown, but may be due in part to increased blood flow to peripheral blood vessels. Muscle rigidity is a direct opioid effect that also may be involved.	Unknown	Jaffe & Martin, 1992, p493; Preston, 1986, p47.
d) Hypotension	Methadone may produce peripheral vasodilation, reduced peripheral resistance and inhibited baroreceptor reflexes in the supine patient. Therefore, abnormally low blood pressure may occur when the individual assumes the standing position, possibly resulting in fainting.	Partial tolerance may develop.	Jaffe & Martin, 1992, p493; Thomason & Dilts, 1991, p110

Table 1.5. Methadone pharmacodynamics: Summary of common symptom complaints reported among methadone patients, mechanisms of action and tolerance development. (continued)

Symptom	Mechanism of action	Degree and rate of tolerance development	Reference
Constipation	Methadone direct effects diminish bilary, pancreatic and intestinal secretions and also decreases propulsive peristaltic waves. Poor diet and lifestyle may also be contributing factors.	Partial tolerance may develop slowly to the effects on gastromotility. Constipation will continue to be a problem for the majority of methadone maintenance patients.	Byrne, 1995; Foley, 1993, p732; Jaffe & Martin, 1992, p494-495; Kromer, 1993, p 163-181; Platt, 1988, p93; Thomason & Dilts, 1991, p109.
Decreased Respiration	Direct opioid effect on brainstem respiratory centres. Primary effect is a reduction in the stimulatory response to carbon dioxide.	Tolerance develops slowly, and some degree of respiratory depression may be recorded after five months in methadone treatment.	Florez & Hurle, 1993, pp263-9; Gritz et al., 1975; Jaffe & Martin, 1992, p492; Santiago & Edelman, 1985.
Increased Appetite (Weight Gain)	While increased appetite may be a direct agonist effect, weight gain in methadone patients is more likely to be a result of health and lifestyle improvements	Unknown	Byrne, 1995; Kreek, 1986b, p454; Preston, 1986, p59
Increased sweating	Methadone may alter the equilibrium point of hypothalamic heat-regulation mechanisms leading to increased body temperature. Opioid induced histamine release may also be important.	Tolerance develops slowly and does not remit in all methadone patients. Small dose reductions may be beneficial.	Byrne, 1995, p49; Faden, 1993, p228; Jaffe & Martin, 1992, p492; Rettig & Yarmolinsky, 1995, p48; Thomason & Dilts, 1991, p110.
Insomnia	Initial methadone treatment is associated with increased awakenings, and decreased REM and Stage 3 & 4 sleep.	Tolerance is rapidly developed in most methadone patients.	Kay, 1973; Kreek, 1975, p179.

Table 1.5. Methadone pharmacodynamics: Summary of common symptom complaints reported among methadone patients, mechanisms of action and tolerance development. (continued)

Symptom	Mechanism of action	Degree and rate of tolerance development	Reference
Miosis	Due to action on the autonomic segment of the nucleus of the oculomotor nerve.	Although partial tolerance may develop, miosis can be measured in maintenance clients during enrolment on the program.	Jaffe & Martin, 1992, p492; Platt, 1988, p93; Rogers & Spector, 1980; Rosse et al., 1998; Thomason & Dilts, 1991, p110; Weinhold & Bigelow, 1993.
Nausea/Vomiting	Occurs as a direct effect and during opioid withdrawal. Primary mechanism is direct stimulation of the chemoreceptor trigger zone located in the medullary reticular formation.	Tolerance is rapidly developed.	Byrne, 1995, p49; Florez & Hurle, 1993, p282, Jaffe & Martin, 1992, p493; Thomason & Dilts, 1991, p109.
Reduced saliva flow (xerostomia)	Reduced saliva flow is a direct opioid effect. Dental caries, which may be worsened by this effect, can be also attributed to poor dental hygiene and dental problems that pre-date methadone treatment. In addition, opioid users demonstrate a desire for foods high in refined sugar, possibly due to a direct opioid effect.	A dry mouth will be reported by long-term maintenance patients, suggesting that tolerance develops very slowly to this effect.	Byrne, 1995, p50.; Jaffe & Martin, 1992; Zador et al., 1996
Sexual Problems (reduced libido and sexual performance)	Opioids act in the hypothalamus to inhibit GnRH and CRF, thereby decreasing LH, FSH, ACTH and B-endorphin levels. The function of the secondary sexual organs are also depressed.	Tolerance is developed during methadone treatment. Increased libido and sexual performance may also be influenced by health and lifestyle factors.	Cicero et al., 1975; Fishman, 1978; Jaffe & Martin, 1992; p492.

Table 1.5. Methadone pharmacodynamics: Summary of common symptom complaints reported among methadone patients, mechanisms of action and tolerance development. (continued)

Symptom	Mechanism of action	Degree and rate of tolerance development	Reference
Skin disorders (pruritis, urticaria, flushing)	Primarily related to opioid induced histamine release. Anxiety, stress, poor diet or lifestyle may exacerbate symptoms.	Unknown	Jaffe & Martin, 1992, p495; Keegan, 1976; Lee et al., 1994; Rogers & Spector, 1980; Thomason & Dilts, 1991, p110.
Urinary Effects a) Increased urinary retention	Methadone decreases voiding reflexes and increases the tone of sphincter muscles thereby making it difficult to relax them sufficiently to pass urine.	Tolerance develops rapidly.	Jaffe, 1992, p187; Jaffe & Martin, 1992, p495
b) Increased urinary urgency	Smooth muscle is stimulated making the bladder contract more strongly.	Tolerance develops rapidly.	Jaffe & Martin, 1992, p495; Preston, 1986, p45; Thomason & Dilts, 1991, p109.

1.9.2 Insomnia and other sleep effects

Opioids such as heroin and methadone have been reported to produce a dose-related decrease in sleep efficiency, delta sleep and REM sleep, and have twice the potency of morphine in producing insomnia of this type (Kay, 1973; Platt, 1988). Chronic opioid administration results in observable effects upon sleep patterns. During early methadone treatment there is a decrease in REM and Stages 3 and 4 sleep and an increase in awakenings (Kreek, 1975). Tolerance develops to the initial decreases in REM sleep and delta sleep after the methadone stabilisation period. However, in some patients the increase in awakenings persists, although to a lesser degree (Kreek, 1975). Vocalisations during REM sleep and nocturnal delta bursts increase during methadone treatment (Kay, 1973). Waking EEG shows a marked increase in slow wave activity. Specifically, during the early weeks of methadone, EEG tracing of patients show increased alpha abundance, slowing of alpha frequency, and theta and delta bursts. However, after two to three months, tolerance will develop to this effect and the EEG tracings will return to pre-treatment patterns (Kreek, 1975). The effects of chronic methadone appear to be a combination of varying degrees of tolerance to the arousal effects and the emergence or exaggeration of slow-wave activity.

Insomnia is a symptom of early opioid withdrawal. Withdrawal from methadone is associated with an initial increase in dreaming and then several weeks of insomnia, with a decrease in slow wave activity in the waking EEG (Kay, 1973). Prolonged withdrawal effects include an increase in REM sleep episodes, which peaks at 13 weeks after withdrawal, and a later increase in delta sleep (Kay, 1973). Reports of insomnia by methadone maintenance patients may also be associated with the experience of other opioid withdrawal symptoms (to be discussed in section 1.13).

1.9.3 Miosis

Opioid miosis is frequently used as an objective index of opioid effect (e.g. Inturrisi & Verebely, 1972; Martin et al., 1970). Miosis results from an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve (Jaffe & Martin, 1992). The dilator muscle of the pupil is innervated by noradrenergic nerve fibres, whereas the constrictor muscles are innervated by cholinergic nerves (Rosse et al., 1998). Increases in central noradrenergic activity are believed to be responsible for the increase in pupil size observed during opioid withdrawal (Gold et al., 1979).

Although partial tolerance to the opioid induced miotic effect may develop, methadone patients will continue to have constricted pupils whilst enrolled on a methadone program (Jaffe & Martin, 1992; McCaul et al., 1982; Platt, 1988). Weinhold & Bigelow (1993) examined the quantitative characterisation of the effects of lighting intensity and exposure on opioid miosis. Seven methadone patients received their usual daily dose (50-60 mg). Pupil photographs were obtained 15 minutes before methadone and 5,15,30,45,60,90,120 and 180 minutes after the oral dose. Methadone miosis was detected after 30 minutes, increased at 60 minutes and peaked at 90 minutes. Pupil diameter decreased 1.0 mm with each log unit increase in lighting intensity and peak methadone miosis was best detected under moderately dim interior lighting. The use of benzodiazepines did not affect opioid miosis.

1.9.4 Nausea and vomiting

Nausea and vomiting are common in the early stages of methadone maintenance treatment (Byrne, 1995; Thomason & Dilts, 1991). Nausea and vomiting are likely to result from direct stimulation of the chemo-receptor trigger zone for emesis, located in the medullary reticular formation (Jaffe & Martin, 1992). These symptoms are dose dependent and tolerance develops rapidly (Florez & Hurle, 1993).

Interestingly, nausea and vomiting are also associated with opioid withdrawal, suggesting that opioids may induce emetic and anti-emetic activities simultaneously. Opioid receptors are involved in both of these activities but the antemetic action is more sensitive to antagonism by naloxone than the emetic action (Florez & Hurle, 1993). Presence of either nausea or vomiting may also depend upon patient variables, such as other drug use, health status and the degree of tolerance.

1.9.5 Neuroendocrine effects and sexual behaviour

Methadone maintenance patients report that a decreased interest in sex, impotence, amenorrhea and delayed ejaculation are common problems during opioid use (Lafiska et al., 1981; Platt, 1988), while opioid withdrawal has been associated with renewed sexual interest and premature ejaculation (Mirin et al., 1980). A link has been shown between these observations and opioid induced changes in the hypothalamic-pituitary-gonadal axis (e.g. Dobrin & Mares, 1974; Jaffe & Martin, 1992; Mirin et al., 1980). This section will review the effects of opioids, including methadone, on the neuroendocrine system.

1.9.5.1. Opioid effects on the hypothalamic-pituitary-gonadal axis

Research on opioid effects on the hypothalamic-pituitary-gonadal axis has been difficult as the pituitary gonadotropins and testosterone are secreted in a pulsatile fashion, so that in non-drug using controls there is considerable variation in the mean plasma concentrations of these hormones (Mirin, 1980). Nevertheless, there is now consensus on the nature of these effects. It is generally accepted that opioids act in the hypothalamus to inhibit the release of gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF), thus decreasing circulating concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH), ACTH and beta-endorphin (Cella et al., 1993; Jaffe & Martin, 1992; Kreek, 1986b; Mirin et al., 1980).

Chronic opioid use is associated with low plasma testosterone levels in men (Fishman, 1978; Jaffe & Martin, 1992; Lafiska et al., 1981; Mendelson et al., 1975). The function of the secondary sex organs appears to be suppressed by methadone administration. The ejaculate volume, seminal vascular and prostatic secretions, serum testosterone levels and sperm motility have all been shown to be reduced in methadone maintenance patients compared with heroin users and non-opioid using controls (Cicero et al., 1975). Gynaecomastia is a rare side effect in males, and may be unilateral or bilateral, and is probably related to these hormonal effects (Byrne, 1995).

Sexual dysfunction persists in many methadone patients, with almost a quarter of patients reporting impotence, an increased time to ejaculation, a decreased quality of orgasm and a low libido (Byrne, 1995; Espejo et al., 1973; Kreek, 1973, 1975; Platt, 1988; Winnick, 1992). Methadone may lead to an increased tone in the sphincter muscles that close the urethra, having the effect, in men, of delaying orgasm (Preston, 1986). Some patients report

that their libido and sexual capacity have increased after enrolling in a methadone maintenance program. This may be due in part to changes in health and lifestyle (Winick, 1992).

Chronic female heroin users report a reduction of sexual desire and performance, presumably as a result of the depressive effects of opioids on pituitary hormones (Platt, 1988). As many as 60-90% (Finnegan, 1979 in Platt, 1988, p95) of female heroin users have menstrual irregularities, with amenorrhoea the most frequently reported. Factors that may contribute to this include polydrug abuse, malnutrition, hepatitis, pelvic infection and the stress of involvement in a user lifestyle. Methadone maintenance is associated with a reduction of menstrual problems for many of these women (Byrne, 1995; Finnegan 1979 cited in Platt, 1988, p95; Byrne, 1995; Jaffe & Martin, 1992).

With chronic administration, tolerance is thought to develop to the effects of opioids, including methadone, on neuroendocrine function (Jaffe & Martin, 1992; Kreek, 1986b; Fishman, 1978). Kreek (1992a & 1992b) asserts that chronic administration of methadone allows normalisation of neuroendocrine function. She reports a number of her studies indicating that the basal levels and circadian rhythm of hormones of the hypothalamic-pituitary-adrenal axis become normalised in stabilised long-term methadone clients, while the hypothalamic-pituitary-gonadal function also becomes indistinguishable from normals after long-term methadone maintenance. As such, persistent sexual problems reported by long-term methadone patients may be a result of incomplete tolerance to the direct effects of methadone, although health and lifestyle factors may also be important.

1.9.6. Respiration

Opioids such as methadone produce significant effects on respiration. In general, mu receptor activation in the brainstem and at peripheral chemoreceptors produces a dose dependent reduction in tidal volume, and a diminished sensitivity to the rising concentrations of carbon dioxide. With increasing doses opioids reduce the frequency of breathing as well as tidal volume (Jaffe & Martin, 1992; Florez & Hurle, 1993; Santiago & Edelman, 1985; Thomason & Dilts, 1991; White, 1998). Natural sleep may also produce a decrease in the sensitivity of the medullary centre to carbon dioxide, and the effects of mu agonists and sleep might be additive (Jaffe & Martin, 1992).

Alterations in normal respiratory function observed during the early stages of methadone treatment are thought to decrease slowly as a function of time (Kreek, 1986b). However, some degree of respiratory depression has been recorded in patients stabilised on methadone for several months (Gritz et al., 1975). For example, it has been found that after 5 months of methadone treatment, the carbon dioxide response was fully recovered, but tolerance to the hypoxia-sensitive reflex action was not complete (Kreek, 1986b). While resting parameters may appear normal in methadone patients, chemosensitivity of the respiratory centre may remain blunted for a longer period of time (Florez & Hurle, 1993; Kreek, 1986b; Santiago & Edelman, 1985).

1.9.7. Excessive sweating and increased skin temperature

Opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanisms, such that body temperatures may decrease, although it has been reported that chronic and high doses may increase body temperature (Gritz et al., 1975; Jaffe & Martin, 1992). While

further research is required, animal studies suggest that mu receptor agonists result in heat gain, while kappa receptor activation results in heat loss (Faden, 1993). Clinical reports suggest that excessive sweating and raised skin temperature can occur at any methadone dose level (Byrne, 1995). Excessive sweating is also a commonly reported opioid withdrawal symptom (Handelsman et al., 1987; Gossop, 1990). Tolerance develops rapidly to the hyperthermic effects of morphine in the rat (Adler & Geller, 1993), whereas clinical reports suggest that tolerance to excessive sweating and increased temperature develops slowly, and the symptoms do not remit in all methadone patients (Rettig & Yarmolinsky, 1995; Thomason & Dilts, 1991).

1.10 Cardiovascular effects

Opioids exert actions on the cardiovascular system. Endogenous opioid peptides and receptors have been identified at sites within the CNS associated with central cardiovascular regulation, including the hypothalamus, nucleus tractis solitarius and intermediolateral nucleus (Faden, 1993).

The literature is unclear with respect to the direct effect of methadone on a patient's blood pressure. Competing reports have been located: 1) Opioids may depress central vasomotor control resulting in decreased blood pressure (Gritz et al., 1975; Platt, 1988; Rogers & Spector, 1980); 2) stimulation of mu receptors may be associated with increased blood pressure (Faden, 1993); and 3) mu agonists have no major effect on blood pressure (Jaffe & Martin, 1992). The absence of consensus may be explained in part by a report that the cardiovascular system has many transmitter systems involved in its homeostatic control (Faden, 1993). Thus, activation of non-opioid systems may mask the effects upon blood pressure of opioid-controlled systems. However, therapeutic doses of opioids have been

reported to produce peripheral vasodilation, reduce peripheral resistance and inhibit baroreceptor reflexes. Therefore, abnormally low blood pressure may occur when a supine individual assumes the standing position (Jaffe & Martin, 1992; Thomason & Dilts, 1991).

Decreased and irregular heart rate are rarely reported methadone effects that may occur at peak plasma methadone concentrations (e.g. Gritz et al., 1975). The mechanism of these effects is not known (Olsen, 1996; Preston, 1986). Some abnormalities of electrocardiogram (ECG) patterns have been observed in methadone maintenance patients (Lipski, Stimmel and Donoso, 1973 cited in Platt, 1988, p90). However, these effects may also result from general health and lifestyle or cardiac insults sustained during heroin use (Kreek, 1986b).

1.11. Weight Gain

Maintenance patients who experience weight gain may attribute this to the actions of methadone. Animal studies have shown that opioid antagonists reduce food consumption (Cooper & Kirkham, 1993). Appetite increase has been noticed in methadone maintenance, but very few cases of morbid obesity have been found within chronic methadone maintenance patients (Byrne, 1995; Kreek, 1986b). A nutritional assessment of female methadone maintenance patients (Zador et al., 1996) demonstrated a diet characterised by high sugar content and low amounts of dietary fibre. A predilection for foods high in refined sugars, possibly due to an opioid mediated effect on the neuro-regulatory appetite centres, was also noted. Such an effect may contribute to the poor dental health of methadone patients, although other factors may include the opioid effect on inhibiting saliva secretion (Jaffe & Martin, 1992) and the financial expense associated with routine dental care.

1.12 Gastrointestinal effects

Constipation is a frequent complaint reported by methadone patients. Although diet and lifestyle may be contributing factors (e.g. Zador et al., 1996), it is apparent that opioids exert direct effects on gastrointestinal motility and intestinal chloride and gastric acid secretion (Byrne, 1995; Kromer, 1993; Olsen, 1996; Platt, 1988). These effects are primarily mediated by delta and mu receptors in the gastrointestinal tract and spinal cord (Foley, 1993; Olsen, 1996). Opioids reduce acetylcholine release in the gut producing a net inhibition of gastrointestinal motility. During opioid withdrawal acetylcholine-mediated responses are increased (Culpepper-Morgan et al., 1989; Foy, 1991).

Yuan and colleagues (1998) used the lactulose hydrogen breath test to evaluate gut motility and transit among 19 long-term methadone maintenance patients. It was found that the mean oral-cecal transit time for methadone patients (159 minutes.) was significantly longer than the transit time recorded among non-opioid users (109 minutes). Although partial tolerance may develop to the effects on smooth muscle and gastromotility, the majority of methadone patients will remain chronically constipated (Foley, 1993; Jaffe & Martin, 1992; Yuan et al., 1998). There has been one reported death of a methadone maintenance patient due to complications of severe chronic constipation (Kreek, 1986).

Methadone and other opioids are also reported to increase the tone of the sphincter muscles that allow urine to pass from the bladder and decrease the voiding reflexes, and in this way increase the likelihood of urinary retention (Jaffe, 1992; Jaffe & Martin, 1992). Smooth muscle in the bladder is also stimulated by opioids, sometimes resulting in an unpleasant sensation of nearly constant urinary urgency. (Olsen, 1996; Preston, 1986; Thomason &

Dilts, 1991). Tolerance is reported to develop quickly to these effects (Jaffe & Martin, 1992).

1.13. Opioid Withdrawal

In general, the signs and symptoms of opioid withdrawal are the opposite of the direct opioid effects (O'Brien, 1993; Way, 1993). Opioid withdrawal has been described as similar to a flu-like illness, which is subjectively severe but objectively mild (Farrell 1994; Handelsman et al., 1987; Loimer et al., 1991; Turkington & Drummond, 1989).

The character and severity of opioid withdrawal that appears when an opioid is discontinued is influenced by a variety of factors, including the amount of the drug used, the duration of use and the health and psychological functioning of the user (Jaffe, 1992). In the earliest phase of withdrawal from a short acting agonist (e.g. heroin), the majority of symptoms are of a subjective nature and may include craving, anxiety, irritability and nausea (Emmett-Oglesby, 1989; Farrel, 1994; Jaffe, 1992; Handelsman et al., 1987; Swift & Stout, 1992). If no further opioids are consumed increasing physical discomfort will occur at about 8-12 hours after the last dose (Jaffe, 1992). This is associated with increased anxiety, agitation, sweating, yawning, rhinorrhea and lacrimation. Subsequently, physical symptoms including muscle and bone aches, hot and cold flushes, mydriasis, piloerection, vomiting, tremors and increases in bowel motility, blood pressure, pulse, temperature and respiratory rate may occur (Farrell, 1994; Handelsman et al., 1987; Jaffe, 1992). These opioid withdrawal signs and symptoms peak at 48 to 72 hours after the last dose, and most of the observable signs will disappear after 7 to 10 days (Jaffe, 1992). A protracted withdrawal syndrome, including subtle signs and symptoms, can be measured for at least 6 months after cessation of short acting opioids (Jaffe, 1992; Kreek, 1992).

The locus coeruleus in the anterior pons in the central nervous system is a primary site for the centrally mediated elements of opioid withdrawal (Foy, 1991; Gold, 1993; Kreek, 1992). This nucleus has almost exclusively adrenergic neurones that project to other parts of the brain including the limbic system and the cortex. Opioids bind to receptors located on the locus coeruleus neurones producing hyperpolarisation and inhibition. During withdrawal the direct effects of opioids on the adrenergic system are reversed, so that the excitability of adrenergic neurones is increased, there is augmented activity of the second messenger system, and there is stimulation of most of the post-synaptic sites of action (Foy, 1991; Gold, 1993).

Symptoms such as dysphoria, pain, nausea, restlessness and cramps are centrally mediated for the most part by this adapted adrenergic system (Foy, 1991; Gold, 1993). This is consistent with the ability of clonidine, an alpha-2 noradrenergic agonist, to ameliorate many withdrawal signs and symptoms (Kreek, 1992; NIH, 1997; Olsen, 1996), although others such as restlessness, irritability, inability to concentrate and sleep disturbances will persist (Kreek, 1992; Krystal et al., 1992).

Hormonal changes in chronic opioid users may include increased prolactin and reduced luteinising hormone levels due to the direct effect on the hypothalamic-pituitary-gonadal feedback loop (see section 1.9.5.1). Upon withdrawal, the patient may experience a hormonal surge precipitated by a change in the hypothalamic catecholamine levels. This may account for some of the aggressive behaviour manifested by a patient undergoing withdrawal (Dobrin & Mares, 1974).

Many of the withdrawal signs and symptoms involving the gastrointestinal tract may be mediated through acetylcholine and substance P which are linked through a feedback loop (Foy, 1991). Opioids inhibit acetylcholine release and substance P release, and also inhibit the substance P releasing neurone by interfering with the feedback loop. Opioids also produce a degree of denervation sensitivity of substance P receptors. When levels of opioid fall, or the drug is withdrawn, contraction of the longitudinal smooth muscle will occur and this reaction is largely substance P mediated, although other mechanisms (e.g. adrenergic) may also be involved (Foy, 1991; Gold, 1993).

The abrupt withdrawal of methadone produces a withdrawal syndrome that is qualitatively similar to that of the short acting agonists, with the exception that it develops more slowly, is less intense and will last for a longer period of time (Jaffe, 1992; O'Brien, 1993; Sorenson et al., 1992; Stitzer et al., 1991). Symptoms will generally appear between 24 and 48 hours after the last dose, will peak at the third day, and will begin to decrease after three weeks, returning to normal levels after approximately 6 or 7 weeks (Jaffe, 1992). A secondary or protracted withdrawal syndrome, including subnormal physiological parameters and psychological disturbance may occur for as long as 24 weeks after the acute withdrawal phase (Jaffe, 1992).

Withdrawal symptoms can be elicited after very limited exposure to an opioid. Physical dependence effects from a single morphine dose can be observed by antagonist challenge at intervals from 45 minutes to 24 hours post-morphine. (Heishman et al., 1990; Higgins et al., 1992; Kirby et al., 1989). Wright and colleagues (1989; 1991) established that a single dose of methadone in subjects with a previous history of opioid use but abstinent during testing, can experience withdrawal induced by low doses of naloxone (0.01-0.02 mg/kg) lasting at least 54 hours. Stitzer and colleagues (1991) examined naloxone precipitated withdrawal 24

to 168 hours after pre-treatment with a single 30mg im dose of methadone in 6 male subjects (experienced opioid users but abstinent at time of testing). Their study found that withdrawal symptoms could be precipitated for as long as 96 hours. The withdrawal intensity declined slowly, as the intensity at 24 hours and 96 hours post-methadone was similar. Agonist effects (pupil size and subjective effects) were detectable at 24 hours, but not 96 hours. These results suggested that methadone withdrawal could be detected beyond the end of acute agonist effects. In total, these studies suggest that the pre-conditions for development of physical dependence and withdrawal reactions to opioids, including methadone, are developed very quickly.

1.13.1. Factors associated with withdrawal symptoms experienced by methadone maintenance patients.

Opioid withdrawal symptoms such as sweating, anxiety, lack of energy and insomnia are reported by many patients to continue during methadone maintenance (Cohen et al., 1983). As many as 80% of methadone clients may experience withdrawal symptoms at some stage during methadone treatment (e.g. Whitehead, 1974). This section will briefly review possible factors associated with withdrawal symptoms reported by methadone maintenance patients. This issue will also be discussed in Chapter Five.

1.13.1.1. Methadone dose level

Withdrawal symptoms that appear toward the end of the inter-dosing interval are often accompanied by claims by patients that the dose is inadequate (i.e. the methadone dose is 'not holding') (e.g. Bell et al., 1988; Havassey & Tschann, 1984). It is generally assumed that for any individual there is an adequate methadone dose level to block withdrawal

symptoms (Bell et al., 1990). The effective methadone dose range is reported to be between 30 and 100mg/day for most patients (Bell et al., 1988; Goldstein, 1991; Schuster, 1989 in Banys et al., 1994). However, a clear relationship between methadone dose level and withdrawal severity has not been found in studies of methadone detoxification procedures (e.g. Banys et al., 1994; Gossop et al., 1987, 1989, 1991). Further, some patients will report withdrawal symptoms in the latter part of the dosage interval despite high daily doses (e.g. Tennant, 1987). Finally, considerable fluctuations in methadone plasma levels are generally well tolerated, and patients are often unable to detect relatively large variations in their daily dose (Horns et al., 1975; Stitzer et al., 1984). Therefore, methadone dose level is a crude measure in determining the likelihood of subjective withdrawal and other factors, such as the interpersonal variability in methadone metabolism (see section 1.6), may be important.

1.13.1.2. Plasma methadone concentration

Opioid withdrawal may also appear in methadone maintenance patients due to a decrease in methadone plasma concentrations (Walton et al., 1978). (see Chapter Five for a review of the relationship between methadone plasma concentration and opioid withdrawal signs and symptoms).

There appears to be plasma threshold level below which clients will experience withdrawal symptoms. Although a range of minimum plasma levels have been suggested (Kreek, 1973; Bell et al., 1988), one can conclude from the literature that a methadone plasma concentration of at least 100 ng/mL (Bell et al., 1988; Dole, 1980; Loimer and Schmid, 1992) is required for effective maintenance treatment.

The plasma levels of clients with low doses may fall below this plasma threshold toward the end of the dosage interval (Bell et al., 1988). For a small number of clients with enhanced metabolism, plasma levels may fall below this threshold even at relatively high doses (e.g. Tennant, 1987). Goldstein and Judson (1973) postulated that approximately 10% of methadone maintenance clients would be unable to maintain the necessary minimally effective methadone levels in plasma and tissues for 24-hours. Other factors associated with reduced plasma concentrations and the occurrence of withdrawal may include the interaction with enzyme inducing drugs such as phenytoin and barbiturates (e.g. Bell et al., 1998; see section 1.7).

However, previous studies (e.g. Angaard et al., 1974; Horns et al., 1975; Kreek, 1973) have shown a remarkably large variation in methadone plasma levels between subjects maintained on the same dose, and within subjects sampled at different times. Furthermore, above this plasma threshold, plasma and dose levels do not appear to correlate with the occurrence of withdrawal symptoms (e.g. Holmstrand et al., 1987). The relationship between methadone plasma concentration and the occurrence of withdrawal symptoms will be studied and discussed in more detail in Chapter Five.

1.13.1.3. Other possible factors

A number of individual characteristics have also been associated with reports of opiod withdrawal among methadone patients. These include personality types, mood, learned behaviours and attempts to deceive clinic staff in order to gain a dose increase.

Previous studies have indicated that methadone dose, age, length of opioid dependence or the number of substances found in urine are less important in affecting withdrawal severity

than psychological factors (e.g. Havassey & Tschann, 1984; Jeanomond et al., 1991; Phillips et al., 1986). Factors such as personality and mental state at the time of withdrawal (Kleber, 1981 cited in Lowinson et al., 1992), expectation of the degree of distress (e.g. Gossop, 1987), and information of what to expect (Phillips et al, 1986) may influence withdrawal severity during detoxification situations.

The impact of psychological variables on the severity of opioid withdrawal symptoms was examined in a group of 32 admissions to an in-patient drug dependence unit. Neuroticism and the degree of distress expected by the patient were related to the subsequent subjective severity of symptoms. This suggests that anxiety may serve to amplify withdrawal symptoms (Phillips et al., 1986).

Withdrawal complaints are fewer in programs with explicit and enforced guidelines for dosage increases (Bell et al., 1988; Havassey & Tschann, 1984), suggesting that some complaints may be associated with attempts for a dose increase. A study by Goldstein et al (1975) indicated that when methadone patients complain of an inadequate dose, the complaints stop if negotiations result in a higher dose, but will persist if the dose increase is given without the clients' knowledge. These studies suggest that giving clients some control over their dose level may increase their well being.

Whitehead (1974) described methadone maintenance patients, stabilised on a high oral methadone dose, who exhibited signs and symptoms of withdrawal when certain social and psychological situations were encountered. He labelled this effect 'pseudo-withdrawal' and suggested complaints of withdrawal, especially during the first year of treatment, were psychosomatic and learned behaviours. However, as this study did not measure methadone plasma concentrations or other physiological or pharmacological factors, such a causative

argument is unwarranted. Nevertheless, the possibility that many of the withdrawal complaints of methadone patients are associated with anxiety or social situations remains a valid hypothesis. A number of authors have observed conditioned withdrawal symptoms in methadone maintenance patients (e.g. Childress et al., 1986; Farrell, 1994; Mucha et al., 1991; Newlin et al., 1989). These observations may be explained by classical conditioning, whereby withdrawal like symptoms are produced in the presence of stimuli previously paired with opioid use or opioid withdrawal (e.g. O'Brien, 1986). This potential mechanism of opioid withdrawal symptoms in methadone patients will be discussed in Chapter 4.

In summary, pharmacological and psychological factors are likely to have considerable influence on the presence and severity of opioid withdrawal among methadone patients. Pharmacological factors may include variability in methadone metabolism, pathological status or the use of enzyme inducing drugs. Personality, state of mind at time of withdrawal, setting in which withdrawal takes place, expectations as to the severity of symptoms and the possibility of obtaining relief from them have all been suggested to have a marked effect on the severity of withdrawal. The occurrence of significant opioid withdrawal symptoms in methadone patients may have considerable clinical implications, increasing the likelihood of poor treatment outcome (e.g. Krystal et al., 1992), poor retention (e.g. Reynolds and Magro, 1975) and patient self-medication will illicit drugs.

1.14. The present research

Methadone maintenance is the primary effective intervention in reducing heroin-related harm. Participants in methadone programs reduce heroin use and associated criminal activities, and their health and social functioning improves during enrolment on a program. However, a number of patient and program characteristics can influence the rate at which heroin users are attracted to, and retained in, methadone treatment. Many programs have modified their clinical practice and procedures to increase these rates. Nevertheless, an important predictor of treatment retention and outcome is the magnitude of the daily dose. It is important that the methadone dose alleviates the discomfort of opioid withdrawal without producing significant direct opioid effects. Previous research suggests that dose levels below 60mg/day are inappropriate for many patients, and are associated with poor retention and program compliance. However, patients may resist the setting of higher dose levels due in part to beliefs that methadone produces a number of uncomfortable 'side-effects', and is therefore a drug to be avoided.

The published studies reviewed in this chapter have indicated that patients may experience methadone-related symptoms. Many of the symptoms reported by methadone patients are likely to be direct opioid effects to which tolerance has not developed. Other symptoms may represent the occurrence of opioid withdrawal. Withdrawal symptoms that occur toward the end of an inter-dosing interval are often accompanied by patient claims that the methadone dose is inadequate (i.e. the methadone is 'not holding'). Although many programs have adopted a policy of setting individualised methadone dose levels, designed to cover an individual's opioid withdrawal without producing significant direct effects, complaints of withdrawal persist. Possible factors associated with these complaints may include variations in methadone metabolism, and physiological characteristics and concurrent drug use that

alter methadone disposition and therefore action. The discomfort of these symptoms may lead patients to leave methadone treatment or engage in illicit drug use. Clearly, determining the factors associated with symptom complaints reported by methadone maintenance patients warrants further investigation.

1.14.1 Aims and objectives

The principal aim of this research project was to determine the factors associated with the occurrence of symptom complaints in methadone maintained patients. Specifically, the objectives were:

- To determine the prevalence of symptom complaints in methadone maintained patients;

- To determine the patient characteristics and treatment variables associated with the occurrence of direct opioid effect and withdrawal symptoms;

- To examine the nature and extent of conditioned withdrawal among methadone maintenance patients;

- To determine the factors that might explain why some patients report withdrawal symptoms toward the end of the inter-dosing interval (ie the methadone is 'not holding') and others do not;

Objectives (continued)

- To determine the subjective and physiological changes in methadone patients during an inter-dosing interval ;

- To characterise the relationship between plasma racemic methadone concentration and pharmacodynamic resposnses;

- To determine the pharmacokinetic and pharmacodynamic factors that influence withdrawal severity.

1.14.2. Expected outcomes

It was anticipated that this research would provide a detailed description of patients' response to the pharmacological effects of methadone. Determining the pharmacological, patient and program characteristics associated with the occurrence of symptom complaints would have significant clinical relevance. In addition, examining the methadone pharmacokinetics and pharmacodynamics in patients who report insufficient coverage of methadone may have significant theoretical and clinical implications.

CHAPTER TWO

THE PREVALENCE OF SYMPTOM COMPLAINTS AMONG METHADONE MAINTENANCE PATIENTS

2.1 Introduction

At steady state levels, methadone stabilises the pharmacological condition of patients and by so doing provides an opportunity to normalise health and social functioning. However, not all patients respond to methadone in the same manner, and many will report persistent physical and psychological complaints that they attribute to methadone treatment. The discomfort of these symptoms may well jeopardise the likelihood of a positive treatment outcome. The primary aims of the present study were to determine the frequency of symptom complaints among methadone patients, and to identify possible patient and treatment characteristics that may be associated with these complaints.

2.1.1. Prevalence of symptom complaints

A number of published studies (see Table 2.1) attest to the persistence of symptom complaints during methadone treatment. A study by Goldstein and Judson (1973) found little difference in the prevalence of symptom complaints between patients maintained on methadone doses of 40, 80 and 160 mg/day. The most common complaints, even after six months on a stabilised dose, were insomnia, sweating, painful joints and bones, constipation, general malaise and craving. All of these complaints were experienced, to some extent, by more than 40% of the sample, and the majority of these complaints were experienced to a severe degree by approximately 20% of patients. Similar findings were reported by Kreek (1973) who found that increased sweating was reported by 48% and

Table 2.1: Published reports of the percentage of methadone maintenance patients reporting symptom complaints at different stages of methadone treatment. Values represent percentage (%).

	Pre-methadone treatment	Short-term enrolment (less than 6 months)		Intermediate enrolment (6 months or more)		Long-term enrolment
Length of Enrolment Methadone Dose n	n=51 [1*]	3 months > 90mg/day n=51 [1*]	27 weeks 80mg/day n=120 [2]	6 months or more 40-80 mg/day n=150 [3]	9 months > 90mg/day n=51 [1*]	3 years or more 80-120 mg/day n=129 [4]
Direct Opioid Effects						
Constipation	60	52	68	57	48	17
Dry Mouth	57	26	-	-	25	-
Itchy Skin	37	18	22	-	17	-
Urinary Retention	51	31	-	-	23	-
Opioid Withdrawal						
Excessive Sweating	75	63	64	47	64	48
Insomnia	75	35	48	23	43	16
Muscle Pain	67	37	26	11	41	-
Bone/Joint Pain	71	37	48	-	50	-
Nausea	68	46	30	25	32	-
Mixed/Other						
Lethargy	72	45	18	23	35	-
Reduced Libido	50	44	15	26	53	22
Increased Appetite	-	-	-	19	-	4
Sexual Problems	64	38	40	-	45	14
Irreg.Menstrual Cycle	-	-	46	-	-	-
Vomiting	55	18	-	-	14	-
Weight Gain	74	32	-	-	41	-

Adapted from: 1* Data from Longwell et al., 1979 was collected retrospectively from methadone patients enrolled for at least 9 months. Mean (s.d.) of enrolment length and methadone dose not provided. 2. Goldstein & Judson,1973. 3. Yaffe et al., 1973. 4. Kreek, 1973

persistent constipation by 17% of patients maintained on high methadone doses for three or more years, while insomnia and sexual dysfunction were also reported by a significant proportion.

In another study, 51 methadone patients, maintained on a daily dose of greater than 90mg/day and retained in treatment for over 9 months, were asked to rate their current symptom complaints, and retrospectively, those experienced prior to treatment entry and after three months of treatment (Longwell et al., 1979). It was found that all of the current symptom complaints had been present prior to treatment entry. Symptom complaints reduced in severity after methadone stabilisation for the majority of patients. However, excessive sweating (64%), reduced libido (53%), bone/joint pain (50%) and constipation (48%) persisted during methadone treatment. Other studies have consistently found similar results (e.g. Bloom & Butcher, 1970; Judson et al., 1980; Judson & Goldstein, 1982; Langrod et al., 1981; Reynolds & Magro, 1975), although no studies using large representative samples of methadone patients that had been conducted within the last decade could be located.

2.1.2. Possible factors underlying methadone symptom complaints

As presented in Chapter One, factors relating to the pharmacology of methadone may explain many of these symptoms. First, some of the complaints may represent direct opioid effects (see Sections 1.9 through 1.12). Some examples are constipation and a dry mouth. Many of the direct opioid effects reported during the initial phases of treatment should gradually diminish as patients reach steady state levels and develop tolerance to the acute opioid effects. However, tolerance develops at varying rates to the various opioid effects, and many of the persistent complaints may be attributed to a lack of tolerance (Kreek, 1979; 1992). For instance, it is well known that constipation, dry

mouth, constricted pupils and excessive sweating are common opioid effects to which tolerance develops slowly (see Table 1.4 in Chapter One).

Secondly, opioid withdrawal may be a factor in symptom presentation (see Section 1.13). Symptoms such as insomnia and muscle or joint pain have been shown to persist during methadone treatment (e.g. Longwell et al., 1979). It has been suggested that a daily oral methadone dose of at least 60mg will be required to alleviate withdrawal symptoms in many patients (see Section 1.13.2). The published studies presented in Table 2.1. were conducted with patients maintained on fixed dosage regimens. The South Australian Public Methadone Program has a policy of setting methadone dose levels to meet the individual needs of patients. As such, a reduced prevalence of withdrawal type symptoms in this program might be expected.

Even when the daily methadone dose appears to be adequate, many patients report withdrawal symptoms toward the end of the inter-dosing interval (i.e. the methadone dose does not 'hold') (e.g. Bell et al., 1988; Tennant, 1987). One possible explanation is that although patients are maintained on methadone, withdrawal symptoms may appear if there is a significant decrease in the blood levels of the drug (e.g. Dole, 1994; Holmstrand et al., 1978; Loimer & Schmid, 1992; Tennant & Shannon, 1992). Illness or the concurrent use of other drugs (see Section 1.7) may be important factors in the reduced effectiveness of the methadone dose. The repeated failure of the methadone dose to 'hold' over the 24-hour inter-dosing interval may result in elevated drug use and poor psychosocial outcome (e.g. Holmstrand et al., 1978) and with it the associated risk of blood borne diseases. As a result, patients who report significant and frequent withdrawal symptoms are a clinically important sub-sample of the methadone population.

Although it is likely that some complaints are most likely due to the pharmacological effect of methadone, while others will include a variety of withdrawal symptoms, other factors cannot be ruled out. Thus, pre-existing or unrelated medical conditions, such as influenza (e.g. Borg et al., 1992; Kreek, 1979; Longwell et al., 1979) and psychological influences (e.g. Bell et al., 1988; Childress et al., 1986) should also be considered as potential factors. Further, some reported complaints may be an attempt to gain a dose increase (e.g. Goldstein et al., 1975) or conditioned responses to drug-related stimuli (e.g. O'Brien, 1986; Whitehead, 1974)(Conditioned withdrawal will be described in Chapter Four).

In summary, a clinically significant proportion of methadone patients will report a number of symptoms that they attribute to their daily methadone dose. These may take the form of withdrawal symptoms or direct opioid effects. Many of the acute opioid effects may gradually diminish as tolerance is developed. However, complaints of withdrawal symptoms may persist and the discomfort of these symptoms may well jeopardise the likelihood of a positive treatment outcome. In order to identify potential precipitating factors, it is first necessary to establish the prevalence of symptom complaints in the study population. The present study examined the overall symptom frequency reported by a representative sample of patients enrolled in the South Australian Public Methadone Program. Secondly, comparisons were made with methadone maintenance patients who reported experiencing withdrawal symptoms (i.e. the dose does not 'hold') with a group who did not, to determine whether they differed in the presentation of other symptom complaints and to describe possible identifying characteristics.

2.1.3. The present study

In the present study the frequency of symptom complaints were assessed among a representative sample of methadone maintenance patients. The aims were:

1. To determine the frequency of symptom complaints among methadone maintenance patients.

2. To determine patient characteristics, drug use and treatment variables associated with the occurrence of direct opioid effect and withdrawal symptoms.

3. To compare patients who reported significant withdrawal symptoms with a group who did not, in order to determine whether they differed in the presentation of other symptom complaints and to determine possible identifying characteristics.

Hypotheses:

1. That patients maintained on lower methadone dose levels will report a higher frequency of withdrawal symptoms.

2. That longer enrolment on the methadone program will be associated with a reduced frequency of symptom complaints consistent with the development of tolerance to these effects.

2.2. Method

2.2.1 Participants

Ethical approval for this study was obtained from the Social Science Ethics Committee at the University of Adelaide. The Research Review Committee of the Drug & Alcohol Services Council (DASC) approved access to the methadone patients of South Australia. DASC is an incorporated health centre of the South Australian Health Commission (State Government of South Australia), and operates the public methadone program at a large specialised drug abuse clinic in an inner city suburb. Data were collected from 114 patients enrolled in the South Australian Public Methadone Maintenance Program. Participants were recruited by being approached in the waiting rooms of the methadone dispensing area. The study was advertised as examining the nature of methadone symptom complaints, as such the sample may have included a higher proportion of patients experiencing symptom complaints than would have occurred via purely random sampling. Participants were assured that all information provided was anonymous and confidential, that the Methadone Program did not employ the researcher, and that the decision to participate would not affect their treatment program. Data were collected in private rooms attached to the waiting area, and generally took about five minutes to complete. The researcher was present to answer any questions from the participants.

Comparisons were also made with a control group of 55 honours level and postgraduate students from the Psychology Department at the University of Adelaide. Controls gender ratio, age and weight ranges were within the range of the methadone patients. None of the controls had taken any other psychoactive drug (other than alcohol, nicotine or caffeine) within one month of the study. All participants were volunteers and were given a lottery ticket with a prize of $20.00 for participation.

2.2. Procedure and Measures

All participants provided general demographic details, information regarding their drug use and pre-existing chronic complaints, and details of their current methadone treatment. For the present study the Methadone Symptoms Checklist (MSC-version 1 - see Appendix 3) was developed to provide a means of recording the symptom complaints associated with methadone maintenance treatment. The checklist was derived from a list of commonly reported symptom complaints presented in the literature (Bloom & Butcher, 1970; Goldstein & Judson, 1973; Kreek, 1973, 1979; Longwell et al., 1979; Reynolds and Magro, 1975; Yaffe et al., 1973). A five-category Likert scale, ranging between 'never'(0) and 'always'(4), was used to measure the frequency of specific symptom complaints within the prior six months, or since enrolling in the program if this had been for less than six months. A list of 23 items was prepared. It included five symptoms attributed to direct opioid effect (constipation, dry mouth, itchy skin, itchy nose, urinary retention) and five opioid withdrawal symptoms (insomnia, muscle pain, bone/joint pain, excessive sweating). Nine symptoms could not be attributed to either a direct opioid effect or withdrawal symptom and so were categorised as 'mixed' (lethargy, reduced libido, teeth problems, increased appetite, sexual problems, trouble thinking clearly, confusion, dizziness and vomiting). Patients were also asked whether they had experienced menstrual irregularities (females only), changes in body weight, and whether they had experienced significant opioid withdrawal in the latter part of the inter-dosing interval (i.e. does the methadone 'hold'). An additional open question for any other symptom not mentioned was also included.

For the following statistical analyses the Likert response scale was collapsed to form two categories: 1) 'ever experienced', defined as a symptom experienced at least sometimes during the prior six months; and, 2) 'always experienced', defined as symptoms occurring either frequently or all of the time in the prior six months. Differences

between groups were analysed using chi-square, Student t-tests, and analyses of covariance. All data were analysed using SPSS-PC+.

2.3. Results

2.3.1. Demographics

A total of 114 methadone patients participated in this study. Methadone patients had a mean age of 30.5 years (s.d. 6.2, 18-47) and 57% (n=65) were male. Participants had been enrolled in the methadone program for a mean of 350.3 days (s.d. 241.5, 30-730). The mean daily methadone dose was 60.1 mg (s.d. 28.5, 5-130). Measurement of current body weight was recorded for 70 (61.4%) participants, allowing computation of the ratio of methadone dose to weight (Mean: 0.98 mg/kg, s.d. 0.47, 0.2 - 2.35).

Alcohol was consumed by 33% (n=37) of participants in the previous month, while 78% (n=89) smoked tobacco. Unsanctioned drug use was self-reported by 55% (n=63) of participants, with 70% (n=44) of these reporting the use of heroin, and 32% (n=20) reporting the unsanctioned use of benzodiazepines.

The sample was representative of the population of South Australian methadone program patients with respect to gender ratio, age, and daily methadone dose (DASC, 1993; Faulkner, 1994).

The mean age of the control group (n=55) was 29.1 years (s.d. 6.2, 23-47) and 54% (n=30) were male. Alcohol was consumed by 20% (n=11) of controls in the previous month, while approximately 15% (n=8) smoked tobacco. No control participant reported the use of illicit drugs or benzodiazepines in the preceding month.

2.3.2. The frequency of symptom complaints

The frequency of specific symptom complaints ever experienced during methadone treatment is presented in Table 2.2. Of the 20 symptoms, 15 (75%) were reported with a frequency of 30% or greater. The most frequent opioid effect symptoms ever experienced during methadone treatment were constipation (68%) and dry mouth (65%). The withdrawal symptoms most commonly reported were excessive sweating (85%), insomnia (43%) and muscle pain (43%). Approximately 53% of the patients self-reported that they experienced significant opioid withdrawal toward the end of the 24-hour inter-dosing interval (i.e. their daily methadone dose did not 'hold') during some stage of their treatment. Approximately 34% of the sample reported that this occurred either frequently or all of the time (see Table 2.3.).

Some symptoms could not be attributed completely to either a direct opioid effect or withdrawal. Indeed, they may be characteristic of both direct opioid effect and withdrawal. As such, these symptoms were categorised as 'mixed'. The most frequently reported of these symptoms were lethargy (67%) and reduced libido (64%). Menstrual irregularities were reported by 49% of the female patients (n=49).

Approximately 46% (n=52) of patients reported increased body weight, 11% (n=13) reported decreased body weight, with the remainder reporting that their weight had remained stable during the previous six months. All controls reported stable weight during the preceding six months.

Approximately 84% (n=96) of the methadone patients reported no other symptoms that they attributed to methadone. For the remainder, irritability and difficulty waking in the morning were each reported by 4% (n=4), a decreased appetite was reported by 2%

(n=2), while depression, noisy and irregular breathing while asleep, poor circulation, swollen extremities, headaches, slow healing from injuries, body odour and carpel tunnel were each reported by 1% (n=1) of patients.

Table 2.2: Percentage of methadone patients (n=114) and controls (n=55) reporting specific symptoms ever experienced in the preceding six months.

Symptom Complaint	Methadone (%) (n=114)	Controls (%) (n=55)	Symptom Complaint	Methadone (%) (n=114)	Controls (%) (n=55)
Direct Opioid Effects			**Mixed/Unclear**		
Constipation	68	1***	Lethargy	67	33***
Dry Mouth	65	4***	Reduced Libido	64	4***
Itchy Skin	26	7***	Teeth Problems	49	0***
Itchy Nose	18	4***	Increased Appetite	40	0***
Urinary Retention	18	0***	Sexual Problems	33	0***
			Confusion	28	4***
Opioid Withdrawal			Trouble Thinking Clearly	33	4***
Excessive Sweating	85	11***	Dizzy	20	0***
Insomnia	43	4***	Vomiting	14	0***
Muscle Pain	43	7***			
Bone/Joint Pain	36	0***	Menstrual Irregularities	49 (n=49)	0*** (n=25)
Nausea	35	4***	Not Hold	53	-

$\chi 2$ * $p<0.05$; ** $p<0.01$; ***$p<0.0001$

Comparisons were also made between the patients and controls for the symptoms experienced either frequently or all of the time during methadone treatment (see Table 2.3.). The pattern of patients reporting chronic symptom complaints was similar to those in Table 2.1. The most common direct opioid effect symptoms chronically experienced during methadone treatment were constipation (40%) and dry mouth (41%). The withdrawal symptom most commonly reported was excessive sweating (59%), while insomnia (43%), lethargy (38%) and a reduced libido (37%) were other common chronic complaints. None of the symptoms were reported by the control group to occur either frequently or all of the time.

Table 2.3.: Percentage of methadone patients (n=114) and controls (n=55) reporting specific symptoms frequently or always experienced in the preceding six months.

Symptom Complaint	Methadone (%) (n=114)	Controls (%) (n=55)	Symptom Complaint	Methadone (%) (n=114)	Controls (%) (n=55)
Direct Opioid Effects			**Mixed/Unclear**		
Constipation	40	0***	Lethargy	38	0***
Dry Mouth	41	0***	Reduced Libido	37	0***
Itchy Skin	15	0***	Teeth Problems	34	0***
Itchy Nose	8	0***	Increased Appetite	25	0***
Urinary Retention	7	0***	Sexual Problems	33	0***
			Confusion	11	0***
Opioid Withdrawal			Trouble Thinking Clearly	16	0***
Excessive Sweating	59	0***	Dizzy	6	0***
Insomnia	25	0***	Vomiting	4	0***
Muscle Pain	21	0***			
Bone/Joint Pain	21	0***	Menstrual Irregularities	18 (n=49)	0***
Nausea	13	0***	Not Hold	34	-

Fisher's Exact * $p<0.05$; ** $p<0.01$; ***$p<0.0001$

2.3.3. Comparisons based on the length of time enrolled on the methadone program.

Participants who had been enrolled on the methadone program for less than 12 months (n=61) were compared with those who had been enrolled for 12 months or more (n=53). There were no significant differences between these groups regarding gender ratio (63% male compared with 51%), methadone dose (mean (s.d.) of 55.93 (26.32)mg compared with 64.87 (30.31)mg; t=-1.68, n.s.) or the methadone dose to body weight ratio (0.92 (0.46) mg/kg compared with 1.01 (0.47) mg/kg, t=-0.86, n.s.). Those who had been enrolled on the program for less than 12 months were significantly younger than the other patients (mean of 28.82 (6.56) years compared with 32.34 (5.19) years; t=-3.14, $p<0.01$). There were no significant differences between the groups regarding the proportion reporting any illicit drug use (63% of the participants enrolled less than 12 months compared with 47%), the use of heroin (46% compared with 32%) or the use of benzodiazepines (15% compared with 21%).

Table 2.4. presents the proportion of each group experiencing the symptoms either frequently or all of the time. In general there were relatively few differences between the groups, with sweating (67% compared with 49%) and an increased appetite (36% compared with 13%) being the only symptoms reported by significantly fewer patients enrolled on the program for 12 months or more. The proportion of patients reporting that their dose did 'not hold' for either frequently or all the time were similar for both groups (33% compared with 36%). There was a trend for more of the patients enrolled on the program for less than 12 months to report dizziness (12% compared with 2%, Fisher's Exact = 0.08), and for more of the patients enrolled for 12 months or more to report weight gain (55% compared with 38%; Fisher's Exact = 0.07). There were also no significant differences between the groups regarding the mean number of symptoms reported (4.33 (2.97) symptoms compared with 3.75 (2.63) symptoms; t=1.09, n.s.).

Table 2.4.: Percentage of methadone patients enrolled on the program for less than 12 months (n= 61) and greater than or equal to 12 months (n=53) reporting symptoms frequently or always experienced in the preceding six months.

Symptom Complaint	Less than 12 months (%) (n=61)	12 months or more (%) (n=53)	Symptom Complaint	Less than 12 months (%) (n=61)	12 months or more (%) (n=53)
Direct Opioid Effects			**Mixed/Unclear**		
Constipation	39	40	Lethargy	39	36
Dry Mouth	46	36	Reduced Libido	30	45
Itchy Skin	18	11	Teeth Problems	30	38
Itchy Nose	8	8	Increased Appetite	36	13**
Urinary Retention	7	8	Sexual Problems	20	21
			Confusion	10	13
Opioid Withdrawal			Trouble Thinking Clearly	12	21
Excessive Sweating	67	49 *	Dizzy	12	2 (p=0.08)
Insomnia	26	25	Vomiting	3	2
Muscle Pain	25	17			
Bone/Joint Pain	21	21	Weight Gain	38	55 (p=0.07)
Nausea	16	9	Not Hold	33	36

$\chi 2$ * $p<0.05$; ** $p<0.01$; ***$p<0.0001$

2.3.4. Comparisons based on the total number of symptom complaints

All subjects reported having 'ever experienced' at least one symptom. Of the 19 possible the sample reported a mean of 8.4 (s.d. 3.83, 1-18) symptoms[1]. The total number of symptoms reported were moderately correlated with the level of methadone dose, with a Pearson Product Moment correlation coefficient of r=.29(P<0.001; n=114), and with the methadone dose to weight ratio (r=.39, p<0.001; n=54). There were no significant correlations with length of time on the program (r=.14, n.s.) or age (r=.10, n.s.).

Significantly more symptoms were reported by subjects who had used benzodiazepines (Mean: 10.5 compared with 7.93; t=2.53; p<0.02). It was found that these subjects had a significantly higher daily methadone dose (Mean 81.55 compared with 55.52, t=3.10; p<0.05). However, the difference in the number of symptoms reported remained significant in analyses of covariance which adjusted for methadone dose (F(1,111)=3.43; p<0.05) and the methadone dose to weight ratio (F (1,111) = 21.66, p<0.001). There were no significant group differences in the number of symptoms reported with respect to gender (mean (s.d.) of 8.17 (3.72) for men compared with 8.67 (4.00) for women; t=-0.69, n.s.), heroin use (7.70 (3.35) for heroin users compared with 8.81 (4.07); t=0.172, n.s.) or the use of any illicit drug (8.33(3.60) for drug users compared with 8.45 (4.14); t=-0.16, n.s.).

Analyses were also conducted separately for the composite number of withdrawal symptoms (maximum of 5), direct opioid effects (maximum of 5) and mixed symptoms (maximum of 9). The patients reported having 'ever experienced' a mean of 2.42 (s.d. 1.61, 0-5) withdrawal symptoms; 1.96 (s.d. 1.27, 0-5) direct opioid effect symptoms, and 3.48 (s.d. 1.85, 1-7) mixed symptoms. The total number of withdrawal symptoms

[1] As the response scale for weight changes was different and menstrual irregularities applied only to females, these symptoms were not included in these analyses.

reported were not correlated with the level of methadone dose (r = .21, n.s.) or with the methadone dose to weight ratio (r=.26, n.s.; n=54). There were no significant correlations with length of time on the program (r=.03, n.s.) or age (r=.10, n.s.). There were no significant group differences in the number of withdrawal symptoms reported with respect to gender (mean (s.d.) of 2.37 (1.56) for women compared with 2.49 (1.70) for men; t=-0.39, n.s.), heroin use (2.36 (1.46) for heroin users compared with 2.46 (1.71); t=0.31, n.s.), benzodiazepine use (3.05(1.54) for benzodiazepine users compared with 2.29(1.59); t=2.00, p=0.06) or the use of any other drug (2.46(1.46) for drug users compared with 2.37 (1.80); t=-0.28, n.s.).

The total number of direct opioid effects were significantly correlated with the methadone dose level (r=.39, p<0.001; n=114) and with the methadone dose to weight ratio (r=.44, p<0.001; n=54). There were no significant correlations with length of time on the program (r=.01, n.s.) or age (r=.10, n.s.). Significantly more direct opioid effects were reported by patients who had used benzodiazepines (3.00(1.41) compared with 1.73(1.13); t=3.76; p<0.001). The difference remained significant in analyses of covariance which adjusted for methadone dose (F (1,111) = 9.70; p<0.001) and the methadone dose to weight ratio (F (1,111) = 6.98, p<0.01). There were no significant group differences in the number of direct opioid effects respect to gender (1.98(1.11) for women compared with 1.94(1.39); t=-0.18, n.s.), heroin use (1.68(1.14) for heroin users compared with 2.13(1.33); t=-1.11, n.s.), or the use of any drug (2.00(1.32) for drug users compared with 1.90(1.22); t=0.41, n.s.).

The remaining 'mixed' symptoms were moderately correlated with the methadone dose level (r=.21, p<0.05; n=114) and with the methadone dose to weight ratio(r=.27, p<0.05; n=54). There were no significant correlations with length of time on the program (r=.19, n.s.) or age (r=.10, n.s.). There were no significant group differences in the number of 'mixed' symptoms reported with respect to gender (3.69(1.76) for women compared

with 3.32(1.92) for men; t=-1.07, n.s.), heroin use (3.11(1.73) for heroin users compared with 3.71(1.91); t=-1.74, n.s.), benzodiazepine use (3.80(1.96) for benzodiazepine users compared with 3.41(1.83); t=0.81, n.s.) or the use of any other drug (3.35(1.79) for drug users compared with 3.65(1.94); t=-0.84, n.s.).

2.3.5. Test-retest reliability of symptom complaints

In order to assess the test-retest reliability of the questionnaire and the stability of symptom reporting, approximately one-third (n=38) of the participants were randomly selected to complete the symptom questionnaire a second time one week after the initial testing. A total of 30 (79%) of these participants subsequently completed the second questionnaire. The average age (mean 30.2, s.d. 6.19, 19-45), gender ratio (57% male), methadone dose levels (mean 60.10, s.d. 0.37, 30-130) and length of time enrolled on the program (mean 320.92 days, s.d. 238.21, 30-700) of these participants were within the ranges of the larger sample.

Pearson correlation coefficients (Table 2.5.) calculated for each reported symptom at the two time points indicated a significant degree of stability in responses to this symptom questionnaire. There was also a high degree of correlation between the total number of symptoms reported at each time period ($r=0.76$, $p<0.001$).

Table 2.5.: Seven day test re-test reliability for each symptom experienced by methadone patients in the preceding six months (n=30).

Symptom Complaint	Pearson correlation coefficients (r) (n=30)	Symptom Complaint	Pearson correlation coefficients (r) (n=30)
Direct Opioid Effects		**Mixed/Unclear**	
Constipation	.92 ***	Lethargy	.64 ***
Dry Mouth	.68 ***	Reduced Libido	.85 ***
Itchy Skin	.73 ***	Teeth Problems	.88 ***
Itchy Nose	.86 ***	Increased Appetite	.84 ***
Urinary Retention	.83 ***	Sexual Problems	.83 ***
		Confusion	.95 ***
Opioid Withdrawal		Trouble Thinking Clearly	.86 ***
Excessive Sweating	.86 ***	Dizzy	.94 ***
Insomnia	.73 ***	Vomiting	.88 ***
Muscle Pain	.93 ***		
Bone/Joint Pain	.90 ***	Menstrual Irregularities	.98 *** (n=13)
Nausea	.61 ***	Not Hold	.96 ***

* p<0.05; ** p<0.01; ***p<0.0001

2.3.6. Comparison between the holder and non-holder groups

Participants who reported that their daily methadone dose did not 'hold' either frequently or all of the time (n=39) (designated the non-holders) were compared with those who reported never experiencing such a problem (n=54) (designated the holders). There were no significant differences between the groups with respect to gender ratio (not hold 59% males compared with 56%) or age (mean(s.d.) for non-holders 31.46 (5.38) years compared with 29.31 (6.91)years; t=-1.62, n.s.). There were no significant differences in the number of patients reporting unsanctioned drug use (54% of non-holders compared with 56% of the holders), including the use of heroin (44% of non-holders compared

with 37%) or benzodiazepine use (21% of non-holders compared with 13%). Nor was there a significant difference between the groups in terms of the length of time enrolled on the methadone program (mean(s.d.) of 330.82 (267.83) days for the non-holders compared with 305.57 (254.05)). The mean daily methadone dose, although higher, was not significantly different for the non-holders (mean (s.d.) 65.10 (32.56) mg compared with 55.39 (24.26) mg; n.s.). However, the mean methadone dose to weight ratio was significantly higher for the non-holders (Mean (s.d.) 1.24 (0.61) mg/kg (n=21) compared with 0.87 (0.33) mg/kg (n=33), $t=-2.52$; $p<0.05$).

A comparison of the frequency of specific symptoms experienced by these two groups is presented in Table 2.6. The non-holders reported all of the withdrawal symptoms significantly more frequently. Conversely, only one direct opioid effect, dry mouth, was reported by significantly more non-holders. Of the mixed symptoms, significantly more non-holders consistently experienced excessive sweating, reduced libido, trouble thinking clearly and confusion.

The non-holders reported a significantly greater total number of symptoms (mean (s.d.) 10.64 (3.47) compared with 6.89 (3.73), $t=-4.99$; $p<0.0001$). This difference remained significant in an Analysis of Covariance which adjusted for the methadone dose to weight ratio ($F(1,51)=40.7$; $p<0.0001$). Regarding the type of symptoms, non-holders reported a significantly greater number of withdrawal symptoms (3.36(1.42) compared with 1.83(1.56); $t=4.88$, $p<0.0001$), which remained significant in an Analysis of Covariance controlling for the methadone dose to weight ratio ($F(1,51)=16.95$, $p<0.001$). Non-holders also reported significantly more direct opioid effects (2.39(1.21) compared with 1.78(1.33), $t=2.30$, $p<05$), although this difference did not remain significant when controlling for the methadone dose to weight ratio ($F(1,51)=1.54$, n.s.).

Table 2.6.: Phase One - Percentage of Holders and Non-holders reporting specific symptoms in the preceding six months (n=114).

	Symptoms Ever Experienced		Symptoms Always Experienced	
	Holders (%) (n=54)	Non-holders (%) (n=39)	Holders (%) (n=54)	Non-holders (%) (n=39)
Direct Opioid Effects				
Constipation	69	69	41	39
Dry Mouth	52	85*	28	56***
Itchy Skin	22	36	13	21
Itchy Nose	19	23	6	15
Urinary Retention	17	26	6	10
Opioid Withdrawal				
Excessive Sweating	76	95*	56	69*
Insomnia	30	69***	17	46***
Muscle Pain	28	64***	13	36***
Bone/Joint Pain	24	59***	15	39***
Nausea	26	49*	9	23***
Mixed/Unclear				
Lethargy	69	72	32	54
Reduced Libido	57	69	26	54*
Teeth Problems	48	51	30	36
Increased Appetite	52	33	35	21
Sexual Problems	32	36	19	23
Trouble Thinking Clearly	26	41	7	26*
Confusion	20	36	4	23**
Dizzy	15	28	6	10
Vomiting	9	23	2	5
Menstrual Irregularities	22	23	42	44

$\chi 2$ * $p<0.05$; ** $p<0.01$; ***$p<0.0001$

2.4. Discussion

To benefit the patient, a methadone dose must be prescribed that maximises the beneficial effects of methadone treatment yet minimises undesirable symptom complaints. In turn, such methadone dose levels can benefit the community by increasing treatment retention and improving treatment outcome. In this study, methadone patients who had participated in the methadone program for an average of approximately 11 months reported an average of 8 symptom complaints that they attributed to methadone treatment, with all patients reporting at least one symptom. The majority of specific symptoms surveyed were experienced by nearly one third of the sample. The most frequently reported direct opioid effect symptoms were constipation and a dry mouth. Frequently reported opioid withdrawal symptoms were excessive sweating and muscle pain, while insomnia and reduced libido were also common. These findings are largely in accord with the reports of other authors (e.g. Goldstein & Judson, 1973; Kreek, 1973; Longwell et al., 1979). Comparisons with controls were also consistent with previous research indicating that methadone patients will report these symptoms to a far greater extent than non-opioid using controls (Judson & Goldstein, 1982).

It is possible that pre-existing physical and psychological factors inherent in this population that were not reported may explain many of the reported symptoms. To determine this, longitudinal prospective studies are required. However, the results of this study, along with those of Judson and Goldstein (1982), are consistent with anecdotal reports from methadone patients that the number and severity of symptom complaints experienced whilst on methadone are not the norm for this population.

It was hypothesised that longer enrolment would be associated with a reduced frequency of symptoms, consistent with the development of tolerance to many of the opioid effects.

Tolerance has been reported to develop rapidly to insomnia, nausea/vomiting, reduced libido and urinary retention, while constipation, dry mouth and excessive sweating persist in many patients (see sections 1.9 through 1.12, and Table 1.5). In the present study the total number of symptoms reported was not correlated with time enrolled on the methadone program or other background or drug use variables. Regarding specific symptoms, comparisons based on the time enrolled on the program were consistent with previously published figures (see Table 2.1.). However, only increased appetite and excessive sweating were reported by significantly fewer patients enrolled for 12 months or more, although excessive sweating persisted in approximately 50% of patients. It is possible that the development of tolerance to many of these opioid effects takes place over a longer period of time than the time period measured in this study.

A minority of patients reported a number of additional symptoms that they attributed to methadone treatment. It is likely that some of these symptoms, such as depression and irritability, may represent opioid withdrawal, while other symptoms, such as body odour and carpel tunnel, are unlikely to be related to methadone pharmacology. This suggests that a minority of patients may attribute symptom complaints to methadone rather than lifestyle or other factors. However, despite the reliance on subjective reports without objective validity tests, all patients reported symptom complaints, and these reports had reliability over a seven-day period. Thus, irrespective of the aetiology of these symptoms, patients hold the belief that methadone has adverse effects and this has clinical relevance.

It was hypothesised that lower methadone dose levels would be associated with a higher frequency of opioid withdrawal symptoms. It was found that the total number of symptoms reported was only moderately correlated with methadone dose. Specifically, lower dose levels were not associated with more withdrawal symptoms, but were moderately associated with direct opioid effect symptoms and symptoms attributed to

both direct effect and withdrawal. Goldstein and Judson (1973) found little difference in the prevalence of symptom complaints between patients maintained on 40, 80 and 160mg/day. They postulated that a slow rate of tolerance development for these symptoms might explain this finding. In the present study it may have been that there was an insufficient number of withdrawal symptoms measured to demonstrate a correlation with dose level. Further, the methadone program in which these patients were enrolled has a policy of individualised dosing, whereby self-reports of craving or opioid withdrawal result in a methadone dose increase. The mean methadone dose among study participants was consistent with the level required to alleviate withdrawal symptoms in many patients (see section 1.13.2). These clinical practices may explain the lack of a correlation between low methadone doses and opioid withdrawal. It may also be the case that factors other than the level of oral methadone dose are important in symptom presentation.

Two subsets of patients reported an elevated level of symptom complaints. The finding that, after controlling for methadone dose level, benzodiazepine use was associated with increased symptom complaints, including higher levels of direct opioid effect but not opioid withdrawal symptoms, has clinical significance. It has been reported that when taken within one hour of dosing, benzodiazepines enhance the methadone effect, while chronic use is suspected to lower plasma methadone concentrations and produce withdrawal (see section 1.7.2.2.). The findings from the present study were in accord with those of Preston and colleagues (1984), who concluded that the direct opioid effects of methadone were enhanced by concurrent administration of benzodiazepines. However, the possibility that patients used benzodiazepines to self-medicate opioid withdrawal symptoms cannot be ruled out at this point. The use of benzodiazepines is frequent amongst methadone patients (e.g. Dyer et al., 1992; Iguchi et al., 1989), and attention must be directed to limiting their use, as this might decrease the prevalence of symptom complaints for at least this subset of methadone patients.

Over half of the sample reported having the experience of their methadone dose not 'holding' for the entire inter-dosage interval. It was of further concern to note that over one-third of patients reported that their methadone dose was consistently ineffective in suppressing withdrawal symptoms despite the finding that these patients had a higher oral methadone dose than other patients. Previous authors have maintained that self-reports of not-holding are merely an attempt to gain an increase in oral methadone dose (e.g. Bell et al., 1988; Whitehead, 1974). In the present study, reports of 'not-holding' persisted despite higher mean methadone dose levels. It was possible that these patients had received an increase in their methadone dose level in response to the reported opioid withdrawal, consistent with the clinical practice of this methadone program. The findings of this study suggest that, except in cases of very low methadone dose levels, dose increases may not be sufficient to alleviate opioid withdrawal in some methadone patients.

Furthermore, the finding that one-third of patients indicated that their methadone dose was consistently ineffective in suppressing withdrawal symptoms is in accord with recently published studies. Schall and colleagues (1996) reported that approximately 36% of patients enrolled in a German levo-methadone maintenance program reported withdrawal symptoms. These patients did not have significantly lower dose levels (mean of 0.7mg/kg) than other patients. More recently, a Spanish study (Torrens et al., 1998) reported that 38% of patients, stabilised on a mean daily methadone dose of approximately 87mg, reported five or more symptoms on the Short Opiate Withdrawal Scale (SOWS; Gossop, 1990), indicating significant opioid withdrawal. When considered in conjunction with the findings from the present study, it appears that even when methadone dose levels appear appropriate, as many as one-third of patients will complain of reduced methadone efficacy and opioid withdrawal during part of the inter-dosing interval.

In the present study, the non-holders reported a higher overall level of symptom complaints, including symptoms not associated with opioid withdrawal, although the significance of the higher frequency of the sum of direct opioid effects was removed when controlling for the higher methadone dose of these patients. These patients could not be differentiated by demographic, health or drug use characteristics. Further, the use of benzodiazepines or other drugs were not more frequent in this group. The onset of withdrawal symptoms in the latter part of the 24-hour inter-dosing interval (i.e. the dose does not hold) may suggest that these patients experience a decline in plasma methadone concentrations toward the end of the inter-dosing interval (Bell et al., 1988). This might result from an enhanced metabolism of methadone (Tennant, 1987). These issues will be explored in Chapter Three and Chapter Five.

2.4.1. Summary

This study charted the prevalence of symptom complaints reported by methadone maintenance patients. More than half of the patients reported experiencing their methadone dose not 'holding' for the entire 24-hour inter-dosing interval. Despite receiving a higher oral methadone dose, over one-third of the patients reported that the methadone dose was consistently ineffective in suppressing withdrawal symptoms. This group of non-holders reported a higher overall level of symptom complaints, including symptoms not associated with opioid withdrawal. They could not be differentiated by demographic, other drug use or treatment characteristics. In total, these findings suggest that other factors, possibly related to changes in plasma methadone concentration levels, may play a role in overall symptom frequency. The first step in addressing this issue would be to chart the temporal pattern of symptom complaints, and this will be explored in Chapter Three.

CHAPTER THREE

THE PATTERN OF SYMPTOM PRESENTATION DURING THE 24-HOUR INTER-DOSING INTERVAL.

3.1 Introduction

An important finding from the first study was that approximately one-third of methadone patients reported that their daily methadone dose failed to prevent withdrawal symptoms for the entire dosage interval (i.e. the dose is 'not holding'), despite higher methadone dose levels. This suggested that opioid withdrawal intensity, at least for these patients, would change throughout the course of the 24-hour inter-dosing interval. It was not known whether other symptoms also change in intensity during the inter-dosing interval. The first study charted frequency of symptom complaints, but not the subjective intensity of these symptoms. The present study was designed to measure the intensity of methadone symptom complaints throughout an inter-dosing interval.

3.1.1. The methadone does 'not hold'.

While it is often difficult to determine the exact nature of complaints of 'not holding' it is probable that the level of methadone in the plasma is important. There may be a plasma methadone concentration threshold below which patients will experience withdrawal symptoms. A range of minimum plasma methadone concentration levels have been suggested including 100ng/mL (Bell et al., 1988; Dole, 1980), 150ng/mL (Dole, 1988; 1994) and 200ng/mL (Holmstrand et al., 1978; Hiltunen et al., 1995; Loimer & Schmidt, 1992). One can conclude that a methadone plasma concentration of at least 200 ng/mL

and a daily oral dose of no less than 60 mg (see section 1.13) are essential for effective maintenance treatment.

There are a number of possible reasons why methadone patients may have low methadone plasma concentrations. For instance, patients maintained on low methadone doses may fall below this threshold toward the end of the dosage interval (Bell et al., 1988). In these cases a dose increase may rectify the problem. Secondly, for a small number of patients with an enhanced metabolism, plasma levels may fall below this threshold even at relatively high doses (e.g. Tennant, 1987). Other reasons may include the use of enzyme-inducing drugs and environmental factors (e.g. Bell et al., 1990). Furthermore, fluctuations in the measured plasma levels of outpatients may also be accounted for by obtaining illicit methadone or by diverting the prescribed dose. A further review of published papers on the relationship between methadone plasma concentration and symptom complaints will be presented in Chapter 5.

3.1.2. The present study

It is likely that the intensity of withdrawal symptoms will change throughout the dosage interval with patients who complain that their methadone dose does 'not hold'. The aim of the present study was to determine whether this was also the case with other methadone patients, and also whether other chronic symptom complaints vary throughout the dosage interval. This study also compared patients who experienced subjectively uncomfortable withdrawal symptoms in the period prior to each methadone dose (i.e. non-holders) with a group who did not (i.e. holders), in order to determine the nature of any temporal pattern in the presentation of these and other symptom complaints. It was hypothesised that the intensity of opioid withdrawal symptoms should increase in the period immediately prior to the daily methadone dose for the group of

'Not Hold' patients. This information may provide the basis for assessing the role of methadone plasma concentration in reports of withdrawal symptoms.

The aims were:

1. To determine the subjective changes in direct opioid effect and withdrawal symptoms among methadone maintenance patients during a single 24-hour inter-dosing interval.

2. To compare methadone maintenance patients who reported significant withdrawal symptoms (non-holders) with a group who did not (holders), in order to determine whether the magnitude and temporal pattern of their subjective response to methadone also differed.

3.2. Method

3.2.1. Participants

Ethical approval for this study was obtained from the Social Science Ethics Committee at the University of Adelaide. The Research Review Committee of the Drug & Alcohol Services Council (DASC) approved access to the methadone patients.

Participants in this study were enrolled in the South Australian Public Methadone Program, and were recruited by being approached in the methadone dispensing area. The study was advertised as examining the characteristics of patients who reported that their methadone dose did 'not hold', as such the sample included a higher proportion of these

patients than would have occurred via purely random sampling. Participants were instructed to complete the questionnaires at home, and then paid $20.00 on their return.

3.2.2. Procedure and measures

For this study, the Methadone Symptoms Checklist (MSC) was modified to record temporal patterns in symptom presentation over the 24-hour inter-dosing interval. The response scale was changed to record the intensity of symptoms rather than the frequency and additional items were included to create three sub-groups of items. Items included 10 direct opioid effects and 21 symptoms that could be characteristic of both direct effect and withdrawal. In addition, 16 opioid withdrawal symptoms, derived from the Short Opiate Withdrawal Scale (SOWS)(Gossop, 1990) and the Subjective Opiate Withdrawal Scale (Handelsman et al., 1987) was also included in the MSC-version2. A four category Likert type scale was used from none (0) to extreme (3). The maximum score for the number of withdrawal symptoms was 16, and withdrawal severity was 64.

An additional question for patients to self-identify as non-holders was also included in the MSC-version2. Thus, a total of 48 items were included in this version of the checklist (see Appendix 4).

Data were also collected using the Morphine Benzedrine Group scale (MBG) of the Addiction Research Centre Inventory (Haertzen & Hickey, 1987) (see Appendix 5). The MBG includes 16 items, each of which require a yes (1) or no (0) response, producing a maximum possible score of 16. It has been found to be a valid and reliable self-report measure of positive opioid effect (Haertzen & Hickey, 1987).

Patients in this study arrived at the methadone clinic 30 minutes before their daily methadone dose was due. Information was collected on current treatment regimen

(methadone dose level and time enrolled on the program) and general demographic factors. Patients then completed the MSC-version2 and the MBG, before receiving their normal daily methadone dose. The patients were then free to leave the clinic and were instructed to complete the questionnaires every 2 hours for the next 12 hours, and then once again immediately prior to the next methadone dose. Thus measures were recorded before the daily methadone dose and at the following times after dosing: 2, 4, 6, 8, 10, 12 and 24, resulting in a total of 8 measurement times.

Self-identification as either a holder or non-holder was used as the independent variable. Differences between the patient groups were analysed using student t-tests and chi-squares. Analyses of the temporal pattern of symptom complaints were conducted using repeated measures multivariate analyses of variance (MANOVA) and repeated measures multivariate analyses of covariance (MANCOVA). All data were analysed using SPSS for Windows (version 6.0) (Norussis, 1993).

3.3. Results

3.3.1. Demographics

A total of 51 methadone patients participated in this study. Participants had a mean age of 33.9 years (s.d. 6.2, 22-45) and 55% (n=28) were male. Participants had been enrolled in the methadone program for a mean of 703.9 days (s.d. 741.2, 120 days - 10 years). The mean daily methadone dose was 53.6 mg (s.d. 32.7, 15-140). Measurement of body weight was recorded for all participants allowing computation of the ratio of methadone dose to weight (Mean 0.73 mg/kg, s.d. 0.5, 0.25-2.0).

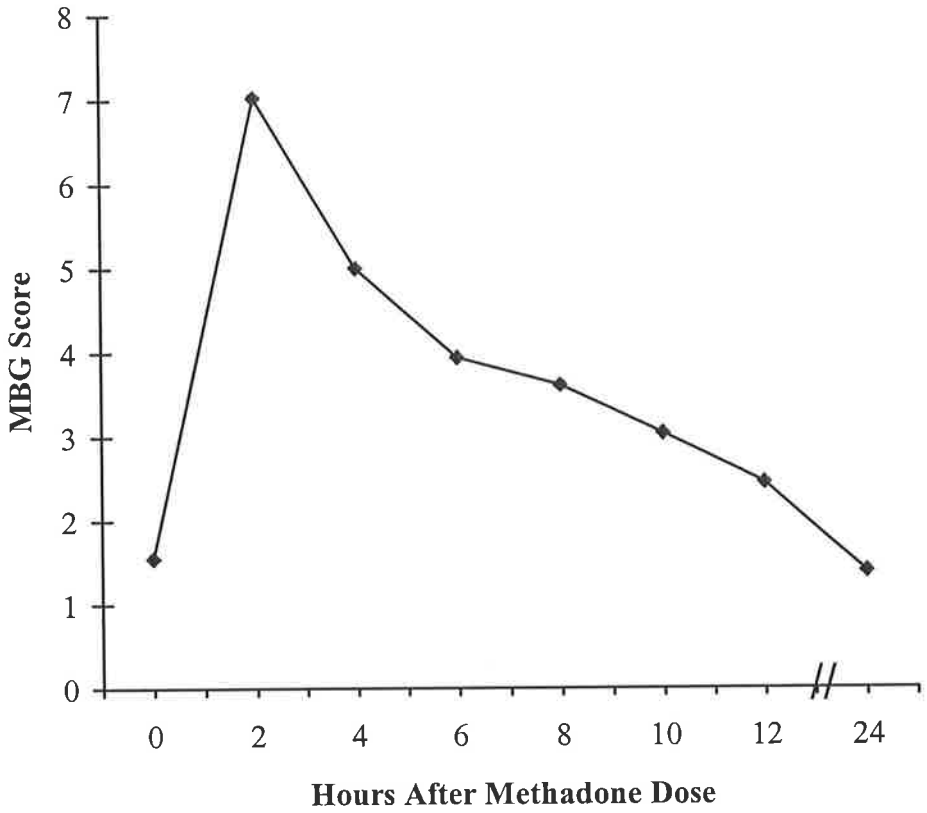
Alcohol was consumed by 31% (n=16) of participants in the previous month, and they consumed a mean of 6.24 (s.d. 7.18, 1-24) standard drinks per typical week. Approximately 94% (n=48) of patients smoked tobacco, with a mean of 26.25 (s.d. 7.68, 10-50) cigarettes per day. Unsanctioned drug use was reported by 49% (n=25) of participants, with 28% (n=7) of these reporting heroin use. These patients injected heroin a mean of 4.0 (s.d. 2.23, 2-7) times in a typical week in the previous month. Approximately 24% (n=6) reported the non-therapeutic use of benzodiazepines, on a mean of 16.40 (s.d. 13.06, 4-30) occasions in a typical week in the previous month. None of the participants reported significant illness at the time of data collection (i.e. colds or influenza etc) and none were HIV sero-positive.

3.3.2. Direct opioid effects

Changes in MBG score throughout the dosage interval for all participants are presented in Figure 3.1. The maximum possible score for the MBG was 16. Mean scores on the MBG varied considerably throughout the 24-hour period, peaking at 7.02 (s.d. 3.89, 0-15) two hours after oral administration of methadone and declining in the remainder of

the 24-hour period, dropping to 1.39 (s.d. 1.83, 0-7) immediately prior to the methadone dose. This change over time was found to be significant in a one-way repeated measures analysis of variance ($F(7, 350) = 29.85$; $p<0.0001$).

Figure 3.1: Mean MBG scores throughout the inter-dosing interval for all patients (n=51). Maximum possible score is 16.



Some of the direct opioid effect symptoms followed a similar pattern. The percentage of participants reporting itchy skin, itchy nose, a pleasant feeling in the stomach and feeling 'high' exhibited this pattern (Table 3.1). Other symptoms however, such as constipation and a dry mouth, remained relatively stable throughout the dosage interval.

Table 3.1. Percentage (%) of methadone patients reporting symptoms attributed to methadone throughout the inter-dosing interval (n=51).

	Time (hours) after oral methadone dose							
	Before dose	2 hrs.	4 hrs.	6 hrs.	8 hrs.	10 hrs.	12 hrs.	24 hrs.
<u>Opioid Withdrawal</u>								
Anxiety	69	22	30	28	43	49	59	84
Bone/Joint Pain	16	10	4	2	2	6	14	16
Cold Flushes	48	28	18	33	28	45	57	65
Crave Opioids	37	8	8	18	10	31	28	43
Diarrhoea	6	10	0	4	2	4	4	8
Goose Pimples	45	8	10	14	16	18	37	53
Heart Pounding	24	10	8	8	16	20	33	20
Muscle Aches	51	20	18	14	28	28	35	51
Muscle Spasms	31	9	20	12	26	24	31	41
Nausea	55	31	22	16	22	14	26	61
Runny Nose	51	31	35	43	26	31	41	59
Stomach Cramps	37	8	12	16	26	22	26	43
Sweating	53	45	49	53	47	51	57	65
Teary Eyes	41	16	16	12	22	16	33	49
Tense Muscles	35	18	20	18	28	49	43	41
Yawning	45	10	28	31	33	59	65	59
Dose Not Holding	29	12	14	22	23	26	25	29
<u>Direct Opioid Effects</u>								
Constipation	69	53	57	53	55	49	45	71
Dry Mouth	48	67	60	57	51	59	37	55
Feel Energetic	47	61	65	67	53	37	45	45
Feeling High	0	17	16	8	2	4	2	0
Itchy Nose	8	43	61	35	23	20	12	4
Itchy Skin	22	60	59	53	33	33	31	8
Pleasant Feeling in Stomach	4	47	57	14	12	16	6	0
Swollen Feet	23	14	16	8	18	25	14	20
Urinary Retention	23	20	23	12	16	10	23	25
Urinary Urgency	29	25	23	37	45	39	63	57

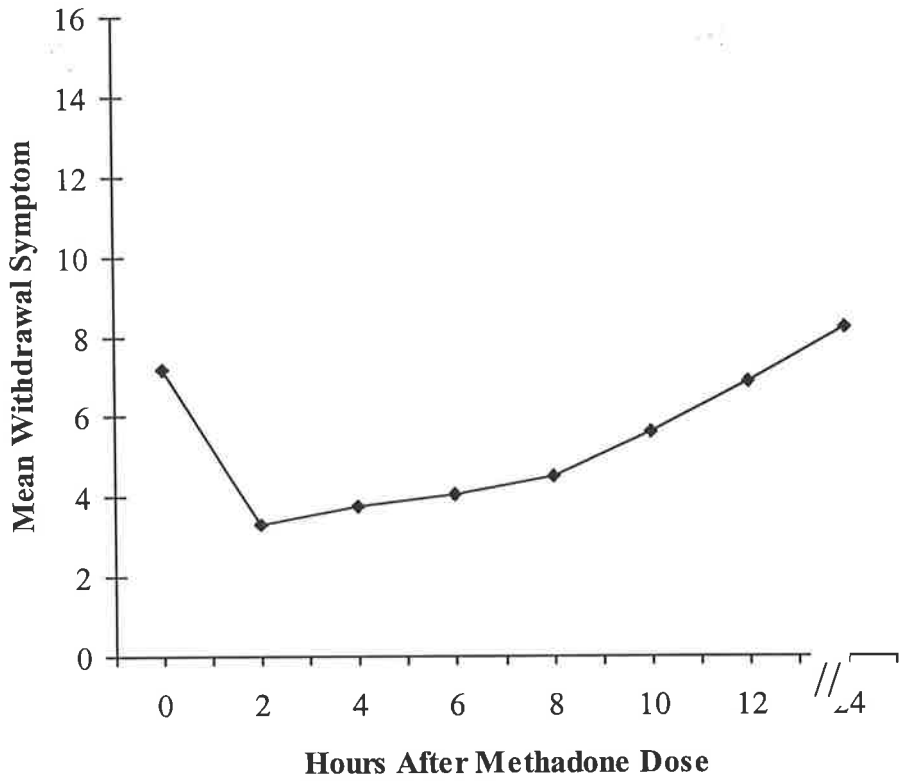
Table 3.1. Percentage (%) of methadone patients reporting symptoms attributed to methadone throughout the inter-dosing interval (n=51) -continued.

	Time (hours) after oral methadone dose							
	Before dose	2 hrs.	4 hrs.	6 hrs.	8 hrs.	10 hrs.	12 hrs.	24 hrs.
<u>Mixed</u>								
Bleeding Gums	10	8	4	2	0	0	0	2
Blurred Vision	24	10	24	22	22	12	26	26
Chest Pains	16	6	16	6	12	18	16	12
Confusion	26	18	20	20	26	30	30	41
Crave Alcohol	4	6	4	12	10	8	2	2
Dec. Appetite	67	51	55	45	49	45	59	65
Depression	74	17	27	39	27	49	63	59
Dizziness	30	18	22	12	18	20	28	28
Hallucinations	2	2	4	2	4	4	6	2
Headache	28	20	30	26	33	43	41	43
Heartburn	20	8	8	8	8	14	18	18
Inc. Appetite	6	18	20	20	31	39	27	14
Inc. Libido	8	12	28	6	8	20	8	0
Irritable/Angry	55	25	22	45	49	57	51	69
Lethargy	78	47	67	65	71	78	90	73
Nervousness	57	22	18	31	26	33	41	61
Numbness	23	22	22	14	14	16	14	30
Reduced Libido	60	49	51	51	51	53	67	57
Thirsty	67	61	59	78	53	53	65	84
Trouble Thinking Clearly	63	25	25	43	45	47	53	59
Vomiting	8	8	6	6	8	6	8	8

3.3.3. Opioid withdrawal symptoms

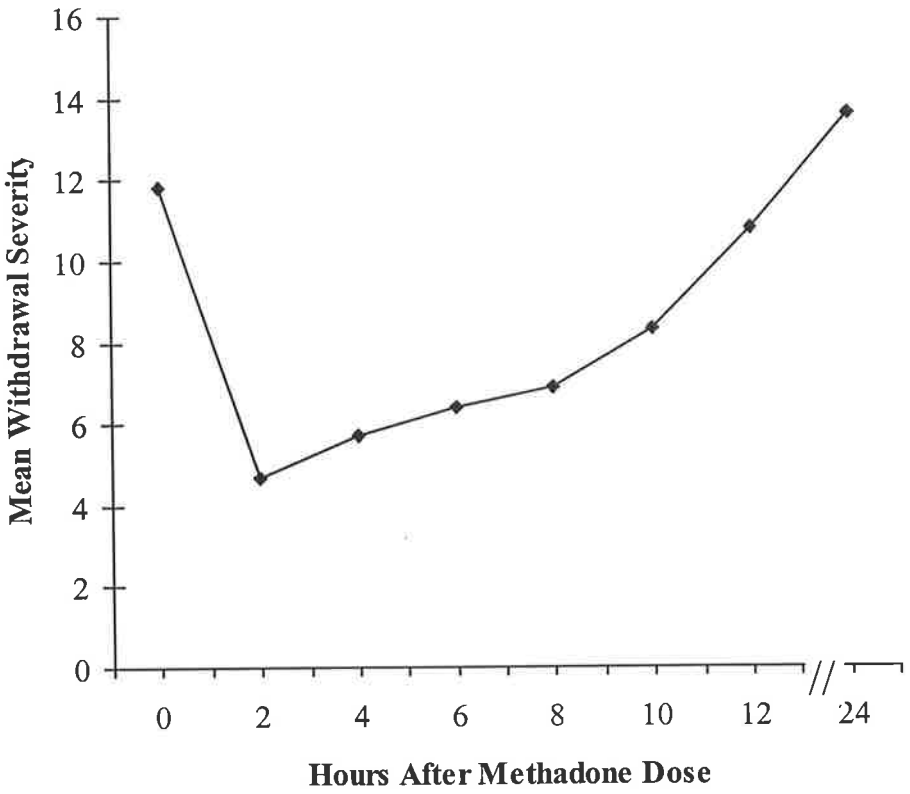
A total of 16 symptoms commonly associated with opioid withdrawal were combined to form an index of withdrawal (see Table 3.1 for items). The number of withdrawal symptoms peaked in the period immediately prior to the methadone dose with a mean rating of 7.16 (s.d. 5.31, 0-16). The mean number of symptoms then dropped to 3.29 (s.d. 3.55, 0-15) two hours after the dose, before climbing to 6.84 (s.d. 4.53, 1-16) 12-hours after the dose and 8.25 (s.d. 5.05, -16) immediately prior to the next dose (Figure 3.2). This change over time was found to be significant in a one-way repeated measures analysis of variance ($F(7, 350)=25.26$; $p<0.0001$).

Figure 3.2: Temporal pattern of the mean number of withdrawal symptoms throughout the inter-dosing interval for all patients (n=51). Maximum possible score is 16.



The maximum possible score for the intensity of withdrawal was 64. The severity of withdrawal symptoms peaked in the period immediately prior to the methadone dose with a mean rating of 11.76 (s.d. 11.78, 0-49). The mean rating then dropped to 4.70 (s.d. 7.68, 0-48) two hours after the dose, before climbing to 10.76 (s.d. 10.62, 1-60) 12-hours after the dose and 13.58 (s.d. 11.96, 2-60) immediately prior to the next dose (Figure 3.3). This change over time was found to be significant in a one-way repeated measures analysis of variance ($F(7, 350)=25.79$; $p<0.0001$).

Figure 3.3: Temporal pattern of mean withdrawal severity throughout the inter-dosing interval for all patients (n=51). Maximum possible score is 64.



The mean ratings of the MBG were compared with the mean number of withdrawal symptoms reported by the subjects. Two-way repeated measures analyses of variance showed significant main effects for symptom type ($F(1, 50) = 8.78$; $p<0.001$) and time($F(7, 350) = 2.96$; $p<0.001$), as well as a significant interaction effect ($F(7, 350) = 44.31$; $p<0.0001$). These results confirmed that the total number of withdrawal symptoms were more likely to peak immediately prior to each methadone dose and then gradually diminish throughout the dosage interval, while opioid effect showed an inverse relation.

3.3.4. Comparison between the holder and non-holder groups

A total of 29 (57%) participants reported that their methadone dose had not 'held' them for the entire inter-dosing interval. There were no significant differences between the groups with respect to gender ratio (48% male non-holders compared with 64% of holders), age (mean (s.d.) 22.86 (6.29) years for non-holders compared with 35.32 (5.87); t=0.16, n.s.), or time enrolled on the methadone program (776.11 (641.83) days for non-holders compared with 754.89 (721.46); t=0.54, n.s.). There were no significant differences between the groups regarding the proportions using alcohol (31% (n=9) of non-holders compared with 32%(n=7)), benzodiazepines (10% (n=3) of non-holders compared with 14%(n=3)), heroin (55% (n=16) of non-holders compared with 41%(n=9)), or other illicit drugs (20%(n=6) non-holders compared with 5%(n=1)). The mean daily methadone dose was significantly greater for the non-holders (mean 65.5 mg compared with 42.2mg, t=-2.71; $p<0.001$), as was the mean methadone dose to weight ratio (mean 0.88 mg/kg compared with 0.57 mg/kg, t=-2.62, $p<0.01$).

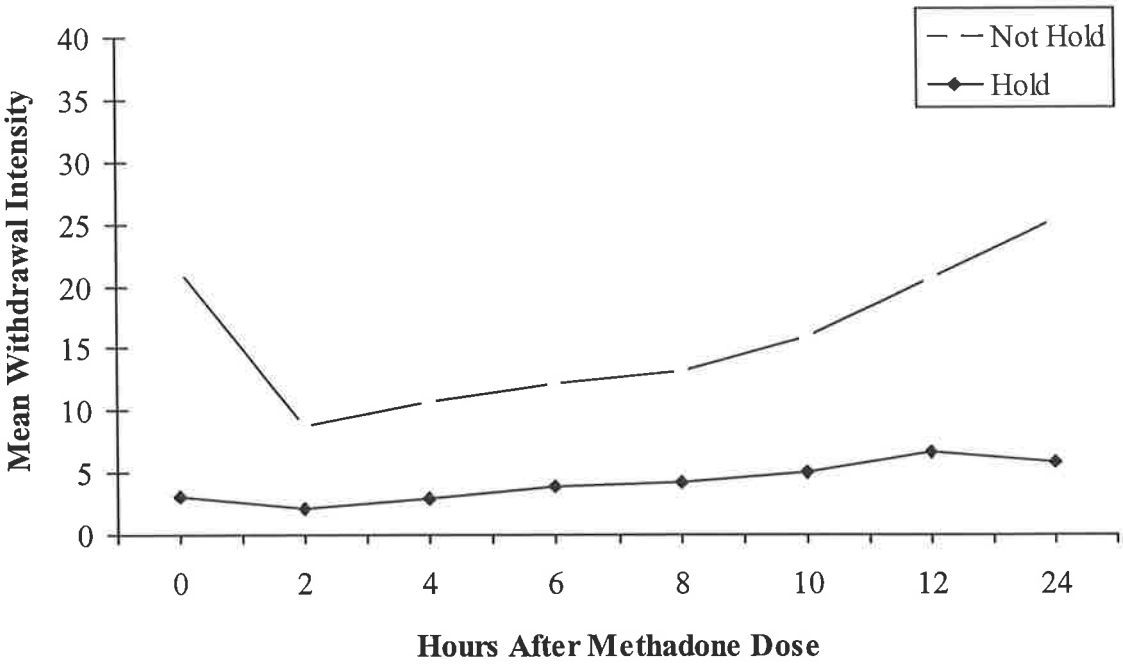
The non-holders reported a consistently greater intensity of withdrawal symptoms throughout the inter-dosing interval (Figure 3.4 - upper panel). This was most apparent immediately prior to each methadone dose (20.4 compared with 3.5 before first dose,

and 22.9 compared with 4.6 before second dose). A repeated-measures MANOVA was performed, with group (Hold, Not Hold) as the between-subject independent variable, intensity of withdrawal as the within subjects dependent variable, and time from methadone dose as the within subjects independent variable. There was a significant main effect for group ($F(1, 49) = 23.71$; $p<0.0001$) suggesting that there was a significant difference in withdrawal intensity experienced between the groups. There was a significant main effect for time from dose ($F(7, 343) = 39.03$; $p<0.0001$). There was also a significant interaction effect between group and time ($F(7, 343) = 24.44$; $p<0.0001$) indicating that the there was a significant difference between the 'hold' and 'not hold' participants in the manner that withdrawal intensity changed throughout the inter-dosing interval.

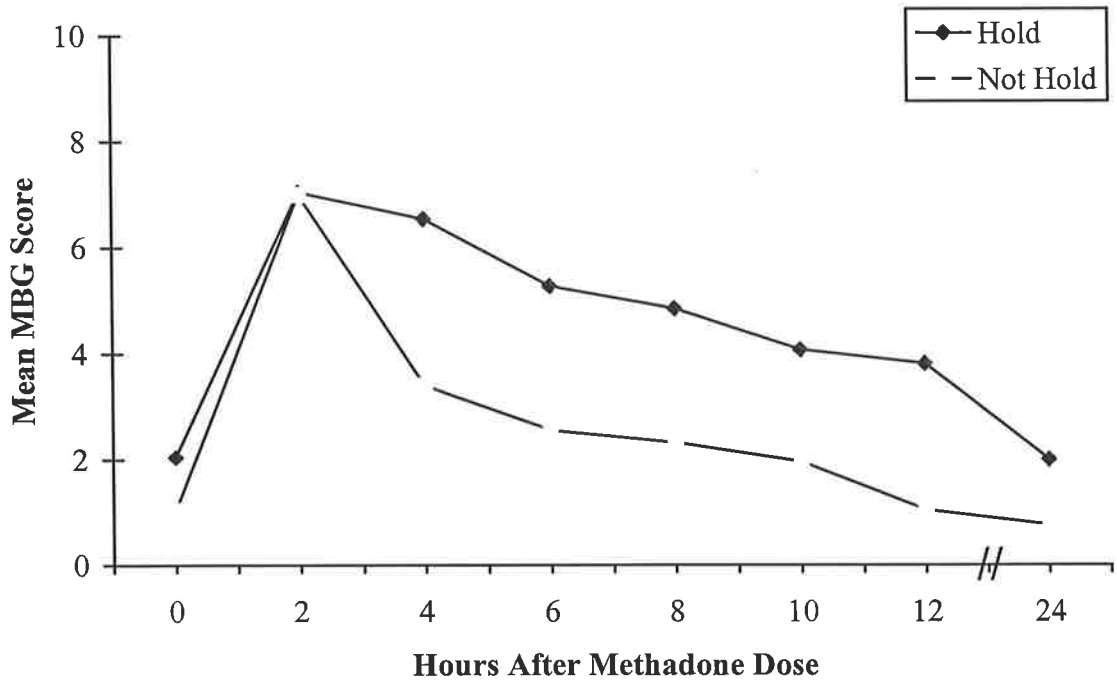
As the groups had a significantly different mean daily methadone dose, two repeated-measures MANCOVAs were conducted, with mean daily dose (mg/day) and mean dose to weight ratio (mg/kg) as the covariates. Results from these analyses are presented in Table 3.2. These results suggest that the difference between the groups could not be accounted for by the differences in daily methadone dose (mg/day) or the dose to weight ratio (mg/kg).

Figure 3.4: Mean withdrawal severity and mean MBG score comparisons between holders (n=22) and non-holders (n=29) groups.

Upper Panel



Lower Panel



The non-holders also reported a consistently lower intensity of opioid effect, as measured by the MBG, throughout the inter-dosing interval (Figure 3.4 - lower panel). A repeated-measures multivariate analysis of variance (MANOVA) was performed, with group (hold, not hold) as the between-subject independent variable, MBG score as the within subjects dependent variable, and time from methadone dose as the within subjects independent variable. There was a significant main effect for group ($F(1,49) = 15.78$; $p<0.0001$) suggesting that there was a significant difference in scores on the MBG between the holders and non-holders. Further there was a significant main effect for time from dose ($F(7, 343) = 30.82$; $p<0.0001$). There was also a significant interaction between group and time from dose ($F(7, 343) = 2.55$; $p<0.01$) suggesting that there was a significant difference between the groups in the temporal variation in MBG score.

Two repeated-measures multivariate analyses of covariance (MANCOVAs) were conducted, with mean daily dose (mg/day) and mean dose to weight ratio (mg/kg) as the covariates. Results from these analyses can be found in Table 3.3. These results suggest that the difference between the groups could not be accounted for by the differences in daily methadone dose (mg/day) or the dose to weight ratio (mg/kg).

Table 3.2: Results from repeated measures multivariate analyses of covariance for group differences in withdrawal intensity with methadone dose as covariate (n=51)

Covariate	Effect	F	DF	p
Dose (mg/day)				
	Group	15.00	1,48	<0.0001
	Time from dose	39.03	7,343	<0.0001
	Group X Time from dose	24.44	7,343	<0.0001
Dose Ratio (mg/kg)				
	Group	15.26	1,48	<0.0001
	Time from dose	39.03	7,343	<0.0001
	Group X Time from dose	24.44	7,343	<0.0001

Table 3.3: Results from repeated measures multivariate analyses of covariance for group differences in MBG score with methadone dose as covariate (n=51)

Covariate	Effect	F	DF	p
Dose (mg/day)				
	Group	13.22	1,48	<0.001
	Time from dose	30.82	7,343	<0.0001
	Group X Time from dose	2.55	7,343	<0.01
Dose Ratio (mg/kg)				
	Group	11.50	1,48	<0.001
	Time from dose	30.82	7,343	<0.0001
	Group X Time from dose	2.55	7,343	<0.01

3.4. Discussion

Results from the first study (Chapter 2) showed that a high prevalence of symptom complaints among methadone maintenance patients could not be accounted for by oral methadone dose or time enrolled on the program. The group of 'not holding' patients reported a higher overall level of symptom complaints, including symptoms not associated with opioid withdrawal. They could not be differentiated by demographic, health, other drug use or treatment characteristics. In total, these findings suggested that other factors, possibly of a pharmacokinetic nature, might play a role in overall symptom frequency. The first step in addressing this issue was to chart the temporal pattern of symptom complaints throughout a 24-hour inter-dosing interval.

The first important finding from this study was that the majority of symptom complaints varied in intensity throughout the inter-dosing interval. Direct opioid effects peaked several hours after oral administration of methadone and declined in the remainder of the 24-hour period, while withdrawal symptoms showed an inverse relation, peaking in the period immediately prior to each dose. These data demonstrate that there is a change in pharmacodynamic response over the 24-hour period that may be associated with changes in methadone plasma concentration.

It was also found that patients complaining of an inadequate dose (i.e. non-holders) experienced a smaller degree of opioid effect, and a greater intensity of opioid withdrawal, throughout the 24-hour period than other patients. Further, while changes in opioid effect intensity were similar between the two groups, changes in withdrawal intensity throughout the dosage interval were different. These differences could not be accounted for by differences in oral methadone dose. Furthermore, patients complaining of the dose 'not holding' were not more likely to use benzodiazepines, and could not be differentiated by any other drug use, health or treatment variable. Although these

patients were consuming a significantly higher oral methadone dose, and had a higher dose to body weight ratio, withdrawal complaints persisted. These findings suggest that there is a difference between patients in their response to methadone.

The standard clinical practice when responding to patients reporting subjectively uncomfortable opioid withdrawal is to increase the level of the methadone dose. However, this study suggests that except in cases of abnormally low methadone plasma concentrations and daily dose, attempts to treat the intensity or temporal variation of symptom complaints by increasing the single oral dose may be ineffective.

Clearly there are limitations to the present study that must be addressed before interpreting these results. Important caveats include the reliance on self-report data, the self-selection of the sample and the absence of an external assessment of drug use and symptom complaints. While there is evidence indicating acceptable reliability and validity of self-report data among injecting drug users in circumstances of assured confidentiality (Bale et al., 1979; Winters et al., 1991) these caveats seriously reduce the power of the findings.

Especially relevant for this study are reports that the number and intensity of physical complaints will increase in normal subjects when attention is focussed upon the body (Pennebaker & Skelton; 1978). Obviously, to address these caveats the collection of physiological and objective data is required. Therefore, analysis of the symptom complaints of methadone patients utilising data from plasma methadone concentrations and physiological and objective indices of physical symptoms was conducted, and will be discussed in Chapter Five. Nevertheless, the data collected in self-report quasi-experimental studies as described in this chapter are necessary and valid precursors to more detailed and expensive pharmacological studies. Furthermore, that the prevalence of symptom complaints reported in this study were consistent with previously published

data (e.g. Goldstein & Judson, 1973; Judson & Goldstein, 1982; Kreek, 1973; Longwell et al., 1979).

The non-holder patients in this study had not been enrolled in the methadone program for a significantly shorter period of time than the other patients. However, this finding does not rule out the possibility that withdrawal symptoms may affect treatment retention. Reynolds and Magro (1975) reported that 'side-effects' are an important reason cited by patients leaving a methadone program. It is possible that many non-holders had departed from the program before this study was conducted. Further, the study sought approximately equivalent numbers of non-holders and holders, and therefore the sample could not be considered as representative of the large methadone population. As such, prospective studies, including the follow-up of former methadone patients, may be required.

3.4.1. Summary

The studies reported in Chapters One and Two have found that a significant proportion of methadone patients will report a variety of chronic symptom complaints. Methadone maintenance patients will report these symptoms to a far greater degree than non-opioid using controls. Many of these complaints were shown to vary in intensity throughout the dosage interval. Direct opioid effects were maximal approximately 2-3 hours after dosing and opioid withdrawal was maximal immediately prior to dosing. The time course of direct opioid effects and opioid withdrawal symptoms suggests a relationship with changing plasma methadone concentration during the 24-hour inter-dosing interval. There were also differences in the way that patients who complained of an inadequate dose experienced these symptoms as compared with other patients. As such, charting symptom presentation throughout the dosage interval can aid in identifying those patients who are experiencing difficulties with their treatment regime.

CHAPTER FOUR

CONDITIONED OPIOID WITHDRAWAL AMONG METHADONE MAINTENANCE PATIENTS

4.1. Introduction

By the time heroin users enter treatment they display significant tolerance to the positive effects (e.g. euphoria) of opioid use, and much of their use of heroin is to avoid or alleviate uncomfortable opioid withdrawal symptoms (O'Brien et al., 1986). For many patients enrolled in a methadone maintenance program, an appropriate dose of methadone can alleviate the discomfort of opioid withdrawal, and in this way provide an opportunity to normalise health and social functioning. However, in Chapter Two it was reported that over one-third of methadone patients consistently experienced withdrawal symptoms despite seemingly adequate methadone dose levels. These patients could not be differentiated by demographic, other drug use or treatment characteristics.

In Chapter Three it was reported that many symptom complaints vary in intensity throughout the dosage interval. Direct opioid effects were maximal approximately 2-3 hours after dosing and opioid withdrawal was maximal immediately prior to dosing: a time course suggesting a relationship with changing plasma methadone concentrations. Patients reporting significant opioid withdrawal toward the end of the inter-dosing interval demonstrated a smaller degree of opioid effect and a greater intensity of withdrawal throughout the entire inter-dosing interval. The study presented in Chapter Three involved symptom reporting by patients outside of the clinic setting (ie patients completed the questionnaire at home). Outside of the clinic patients may come into contact with people and places previously associated with the use of heroin. It has been

reported that withdrawal symptoms may be produced indirectly by the presence of stimuli previously paired with opioid use and opioid withdrawal (conditioned withdrawal) (Childress et al., 1986a, 1986b; O'Brien et al., 1986; Powell et al., 1992: also see Section 1.13.1.3.). In the present study, conditioned responses to heroin-related stimuli were assessed among a small sample of methadone maintenance patients, in order to demonstrate classical conditioning as another potential mechanism for producing opioid withdrawal.

4.1. Conditioned withdrawal among methadone maintenance patients

Wikler (1948; 1965 cited in O'Brien et al., 1986) observed that abstinent opioid users displayed opioid withdrawal signs and symptoms (e.g. yawning, tearing) during group therapy sessions involving explicit discussion of the circumstances surrounding drug use. From these observations he hypothesised that repeated episodes of withdrawal (unconditioned response) might be paired with environmental stimuli (conditioned stimuli) so that eventually those environmental stimuli could provoke a conditioned withdrawal-like response. Following Wikler's observations, numerous experimental and observational studies have demonstrated conditioned withdrawal in opioid users (e.g. Heather et al., 1991; Laberg, 1990; O'Brien, 1977, 1990: see Heather & Greeley, 1990 and O'Brien, 1986 for comprehensive reviews). Cue exposure techniques, whereby patients are repeatedly exposed to stimuli previously associated with drug taking without subsequent drug taking, have been demonstrated to extinguish these conditioned responses among many patients (e.g. Hammersly, 1992; Heather & Greeley, 1990; Marlatt, 1990).

Conditioned withdrawal has been demonstrated to persist after extended periods of abstinence (e.g. Heather & Greeley, 1990). Childress and colleagues (1986b) reported that abstinent opiate users who had recently completed a 30-day Therapeutic

Community treatment experienced subjective withdrawal when exposed to drug-related stimuli. Extinction procedures were effective in eliminating these conditioned responses within 20 hour-long treatment sessions. Conditioned withdrawal responses, as demonstrated by Childress & colleagues (1986b) may contribute to the chronicity of opioid use and to relapse after cessation of use (e.g. Ehrman et al., 1992, Heather et al., 1991).

Conditioned withdrawal responses have also been demonstrated among current methadone maintenance patients. O'Brien and colleagues (1977) demonstrated conditioned withdrawal responses among 8 methadone patients maintained on a mean dose of 43mg/day (range: 25 to 70mg). Conditioned withdrawal responses included increased heart rate and decreased skin temperature. The data suggested that both objective and subjective elements of opioid withdrawal could be conditioned experimentally among methadone patients. However, these authors did not present analyses of the strength of association between the daily methadone dose and the intensity of the conditioned responses.

Childress and colleagues (1986a) examined the prevalence of conditioned withdrawal among male methadone patients in three different settings: 1) research laboratory, 2) clinic; and, 3) the patients' home environment. In the laboratory setting, 25 male methadone patients received a 90-minute stimulus exposure session in a sound and temperature controlled chamber. The experimental session involved exposure to neutral (nature video) and drug-related (video of drug injecting) stimuli. Physiological and subjective measures were recorded. It was found that 25% of the sample reported increased subjective withdrawal in response to drug-related stimuli as compared to the neutral stimulus. A further 48% reported craving that included withdrawal like descriptions. Compared to the neutral stimulus, approximately 34% of the patients showed greater physiological reactions to the drug stimulus. A significant decrease in

skin temperature (average of 2.2C) was recorded, although there was considerable inter-patient variation in this response. There were also no significant differences for other physiological measures, and there were low correlations between the physiological and subjective measures (Childress et al., 1986a).

In the clinical setting, 22 male patients either maintained on, or detoxifying from, methadone participated in a cue exposure trial[1]. Approximately 41% of the patients demonstrated subjective withdrawal symptoms in response to drug-related stimuli. Physiological measures were not recorded in this study. However, this study demonstrated that a higher prevalence of conditioned withdrawal among patients could be elicited in the less artificial clinic setting than in a laboratory. In the final study, 17 male methadone patients reported their experiences of withdrawal feelings during weekly structured interviews. It was found that 94% of the patients reported at least one episode of withdrawal-like feelings outside of the clinic. The factors most frequently reported as contributing to these withdrawal episodes were physical discomfort (e.g. fatigue, flu 38%) and the methadone not holding (31%) (Childress et al., 1986a). These studies suggest that methadone maintenance patients experience withdrawal-like responses, even though, as these authors state (Childress et al., 1986a), these responses are likely to be suppressed by an adequate dose of methadone.

The studies conducted by Childress and colleagues (1986a; 1986b) demonstrate that a significant proportion of methadone maintenance patients will exhibit conditioned withdrawal, and this has been demonstrated in a variety of settings. The authors reasoned that the prevalence and intensity of conditioned withdrawal responses among methadone patients would be a conservative estimate of the frequency of these responses in an abstinent population, as the conditioned responses would be weaker among

[1] Data for methadone dose levels and treatment length were not provided.

methadone patients (Childress et al., 1986a). However, analyses of a methadone dose-conditioned response relationship were not reported. One aim of the present study was to document the relationship between conditioned responses to drug-related stimuli and the daily methadone dose level, among a group of stabilised methadone patients.

4.1.1. The present study

In the present study, stabilised methadone maintenance patients were exposed to drug-related stimuli and subjective and objective responses were recorded. The aims were:

1. To demonstrate the nature and extent of conditioned withdrawal among patients receiving methadone maintenance treatment.

2. To examine the relationship between conditioned withdrawal and methadone dose.

Hypothesis:

1. That higher methadone dose levels will be associated with a reduced conditioned response to drug-related stimuli.

4.2. Method

4.2.1. Participants

Ethical approval for this study was obtained from the Social Science Ethics Committee at the University of Adelaide. The Research Review Committee of the Drug & Alcohol Services Council (DASC) approved access to the methadone patients.

Data were collected from 15 patients enrolled in the South Australian Public Methadone Maintenance Program. Participants were recruited by advertisements placed in the waiting room of the methadone dispensing area of the primary agency. Patients who agreed to participate in the study were assured that all information provided was anonymous and confidential, that the Methadone Program did not employ the researcher, and that the decision to participate would not affect their treatment program. Data were collected in private rooms attached to the waiting areas immediately prior to the daily methadone dose, and generally took about 30 minutes to complete. All participants were volunteers and received $20.00 for participation.

4.2.2. Measures

Data for the subjective responses were collected using an Opiate Withdrawal Scale and the Morphine-Benzedrine-Group Scale of the Addiction Research Center Inventory. The Opiate Withdrawal Scale (OWS) included 16 opioid withdrawal symptoms that were extracted from The Short Opiate Withdrawal Scale (Gossop, 1990) and The Subjective Opiate Withdrawal Scale (Handelsman et al., 1987) (see Appendix 6). Symptoms in the checklist were: nausea, stomach cramps, muscle spasms, cold flushes, heart pounding, tense muscles, bone/joint aches and pains, yawning, teary eyes, runny nose, gooseflesh, sweating, hot flushes, restlessness, feelings of weakness and salivation. A four category

Likert type scale was used from none (0) to severe (3), and the maximum possible score on this questionnaire was 48.

The Morphine Benzedrine Group Scale of the Addiction Research Centre Inventory (MBG)(Heartzen et al., 1987) included 16 items, each of which requires a yes/no response (Appendix 5). It has been found to be a valid and reliable self-report measure of positive opioid effects.

The physiological responses of heart rate, blood pressure, skin temperature and the degree of sweating were also recorded. Heart rate and blood pressure (BP) were measured via an Automatic Digital Blood Pressure and Heart Rate Monitor (OMRON model HEM-703c). Skin temperature and sweating were measured via an ambulatory device incorporating solid state temperature (°C) and humidity (% relative humidity) sensors, designed by the Department of Clinical and Experimental Pharmacology, University of Adelaide.

Stimulus Materials

The Neutral stimulus (NEUT) consisted of a line drawing of sufficient complexity to hold the participants' interest during the 2-minute presentation. The drawing did not contain drug-related imagery.

The Drug stimulus (DRUG) consisted of a 3-dimensional array of drug using paraphernalia including a simulated packet of heroin, together with a needle, syringe and other injecting equipment. The stimulus package was developed in consultation with active heroin users accessed via the South Australian Voice for Intravenous Education (SAVIVE). SAVIVE is the primary heroin users support group in South Australia, and operates the largest needle and syringe exchange program in the state.

4.2.3. Procedure

Patients arrived at the clinic 30 minutes before the daily methadone dose was due. All patients provided general demographic details, information regarding their drug use and details of their current methadone treatment. Patients then participated in a test of conditioned withdrawal (Table 1). This comprised sequential two-minute exposures to the neutral stimulus (NEUT) and the drug-related stimulus (DRUG). In order to ensure that subjects attended to the stimuli, they were asked to describe the stimuli throughout the presentations. The OWS and MBG were recorded immediately before and 360 seconds after the initial presentation of each stimulus. Blood pressure and heart rate were recorded immediately before and after stimuli presentation. Skin temperature and sweating were recorded immediately before and 120, 240 and 360 seconds after the presentation of each stimulus. At the conclusion of the testing period patients received their daily methadone dose.

4.2.4. Analyses

Responses recorded before presentation of the neutral stimulus (NEUT) were used as the baseline measures. The mean values for skin temperature and sweating recorded after each stimulus were calculated and used in the statistical analyses. Repeated measures t-tests were used to detect differences in the responses between baseline and after presentation of the neutral stimulus (NEUT), and between NEUT and the responses after presentation of the drug-related stimulus (DRUG). The relationships among the conditioned responses, and between the intensity of the conditioned withdrawal and methadone dose were determined by Pearson product-moment correlation coefficients. All data were analysed using SPSS for Windows (version 6.0.)(Norussis, 1993).

Table 4.1. Conditioned withdrawal protocol utilised in the present study.

Time (Seconds)	Conditioned Withdrawal Protocol
Baseline	OWS, MBG, BP, Heart Rate, Skin Temperature and Sweating
0-120	**2 minute exposure to NEUT**
120	OWS, MBG, BP, Heart Rate, Skin Temperature and Sweating
240	Skin Temperature and Sweating
360	Skin Temperature and Sweating
0-120	**2 minute exposure to DRUG**
120	OWS, MBG, BP, Heart Rate, Skin Temperature and Sweating
240	Skin Temperature and Sweating
360	Skin Temperature and Sweating

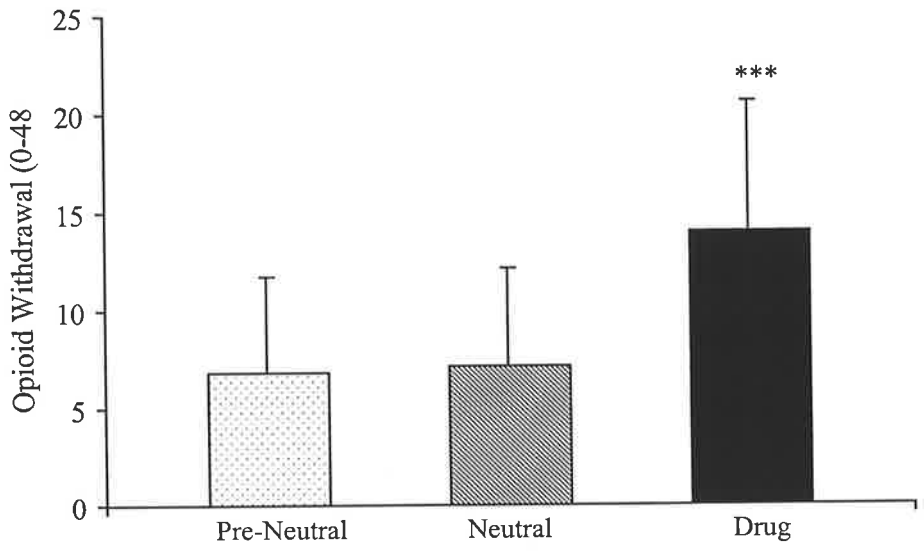
4.3. Results

A total of 15 methadone patients participated in the study. Participants had been enrolled in the methadone program for a mean of 218.67 days (s.d. 34.19, 180-300) and 67% (n=10) were male. The mean daily methadone dose was 64.67 mg (s.d. 12.74, 45-85). Measurement of current body weight was recorded for all participants, allowing computation of the ratio of methadone dose to weight (Mean 0.99 mg/kg, s.d. 0.24, 0.56-1.34). All participants in the previous month consumed alcohol, tobacco and heroin. Heroin was injected a mean of 1.87 times per day (s.d. 0.64, 1-3). None of the participants reported significant illness at the time of data collection (i.e. colds or influenza etc) and none were HIV sero-positive.

4.3.1. Comparison of subjective responses before and after stimuli presentation

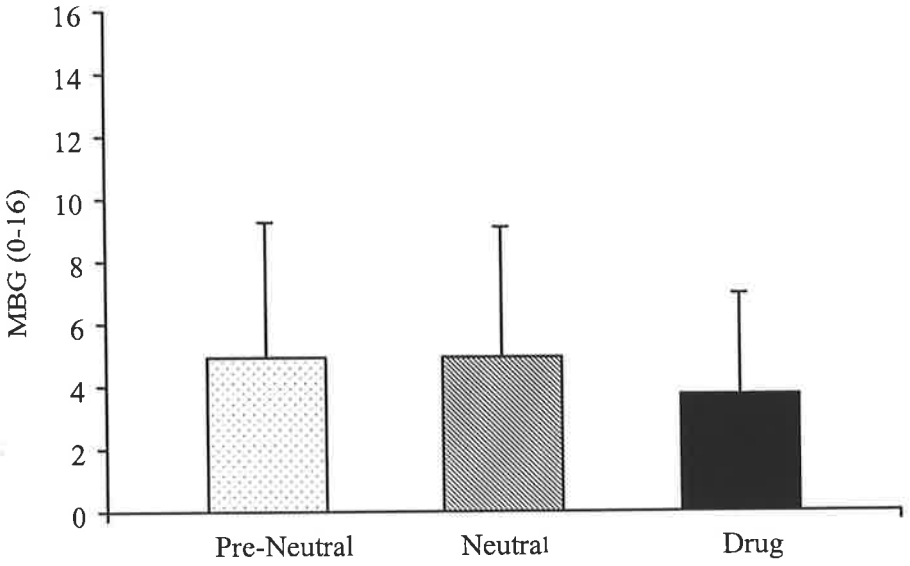
Figure 4.1 presents the mean subjective opioid withdrawal severity of participants. Opioid withdrawal did not change significantly from baseline after presentation of the neutral stimulus (NEUT) (mean (s.d.) of 6.87 (4.87) at baseline compared with 7.13 (4.98) after NEUT, t=1.74, n.s.). However, withdrawal severity did significantly increase from NEUT after presentation of the drug stimulus (DRUG) (13.93 (6.64), t=5.63, p<0.001). There were no significant differences in positive opioid effect (Figure 4.2) after presentation of either the neutral stimulus (4.93 (4.32) at baseline compared with 4.93 (4.15) after NEUT, t=0.0, n.s.) or drug (3.73 (3.22), t=1.57, n.s.) stimulus. There were no significant correlation's between the baseline reports of opioid withdrawal and opioid effect (r= -0.31, n.s.) or between these responses after presentation of either the neutral stimulus (r= -0.30, n.s.) or the drug stimulus (r= -0.28, n.s.).

Figure 4.1: Comparison of mean opioid withdrawal severity among methadone patients (n=15) recorded before presentation of a neutral stimulus, after a neutral stimulus and after a drug-related stimulus. Values are mean and s.d., maximum possible score is 48.



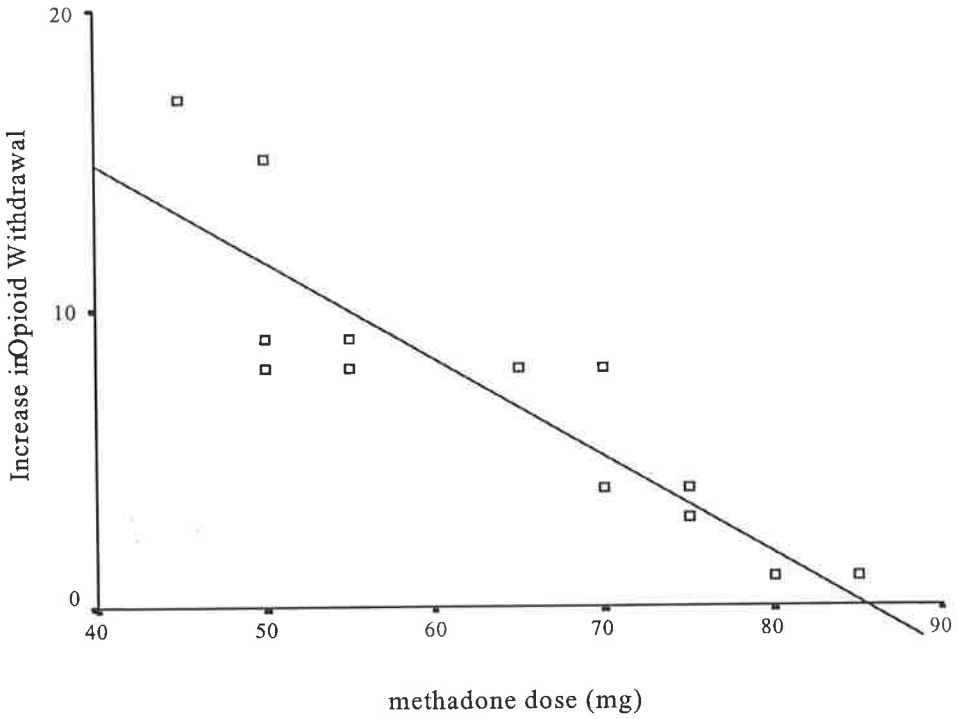
*** p<0.001 vs. neutral

Figure 4.2: Comparison of mean direct opioid effect scores, as measured by the Morphine Benzedrine Group Scale among methadone patients (n=15) recorded before presentation of a neutral stimulus, after a neutral stimulus and after a drug-related stimulus. Values are mean and s.d., maximum possible score is 16.



All participants exhibited a cue specific increase in subjective withdrawal intensity (mean increase of 6.80 (4.68), 1-17). Approximately 53% (n=8) of the patients exhibited an increase in subjective withdrawal of 8 points or more. There were no significant correlations between withdrawal severity after the DRUG stimulus and the frequency of injecting heroin (r=0.18, Rho=0.14, n.s.) or the length of time enrolled on the program (r=0.12, Rho=0.18, n.s.). Nor were there any gender differences (mean increase in withdrawal severity for males =5.90 (3.28) compared with 8.60 (6.80) for females: t=1.06, n.s.). The degree of increase in withdrawal severity from NEUT to after presentation of the DRUG stimulus was significantly associated with a lower oral methadone dose level (Pearson r=0.89, $p<0.01$; Spearman Rho=0.94, $p<0.01$: Figure 4.3.) and a lower methadone dose to body weight ratio (r=0.43, $p<0.05$; Rho=0.60, $p<0.01$).

Figure 4.3. Correlation between the change in subjective withdrawal severity after presentation of a drug-related stimulus and methadone dose among methadone patients (n=15).



4.3.2. Comparison of physiological responses before and after stimuli presentation

In comparison with the baseline, there were no significant differences in systolic blood pressure immediately after presentation of the NEUT stimulus (112.79(13.69) compared with baseline of 113.43 (12.83) mmHg; t=1.15, n.s.). Nor was there a significant difference between systolic blood pressure recorded after the NEUT and DRUG stimuli (115.15(9.17) mmHg, t=-1.2, n.s.). Nor were there any significant changes in diastolic blood pressure between baseline and NEUT, (72.57(16.28) at baseline compared with 73.9(15.11) after NEUT; t=1.42, n.s.), or between NEUT and DRUG (78.29 (12.97), t=1.87, p=0.08).

There were no significant differences among the remainder of the objective measures. Specifically, there were no differences in heart rate (Figure 4.4.) after presentation of NEUT (71.93(10.61) b.p.m. at baseline compared with 72.30(10.73) b.p.m. after NEUT; t=0.63, n.s.), or after presentation of DRUG (71.60(9.10) b.p.m.; t=0.63, n.s.). There were no differences in the degree of sweating (Figure 4.5.) after presentation of NEUT (49.73(12.74) % at baseline compared with 47.22(11.68) % after NEUT; t=1.99, n.s.), or after presentation of DRUG (47.28(12.89) %; t=0.18, n.s.). Nor were there differences in Skin Temperature (Figure 4.6.) after presentation of NEUT (29.80(3.43) °C at baseline compared with 31.20(3.16) °C after NEUT; t=1.21, n.s.) or between NEUT and DRUG levels (32.32(3.07) °C for DRUG; t=0.63, n.s.).

Figure 4.4.: Comparison of mean heart rate among methadone patients (n=15) recorded before presentation of a neutral stimulus, after a neutral stimulus and after a drug-related stimulus. Values are mean and s.d., beats per minute.

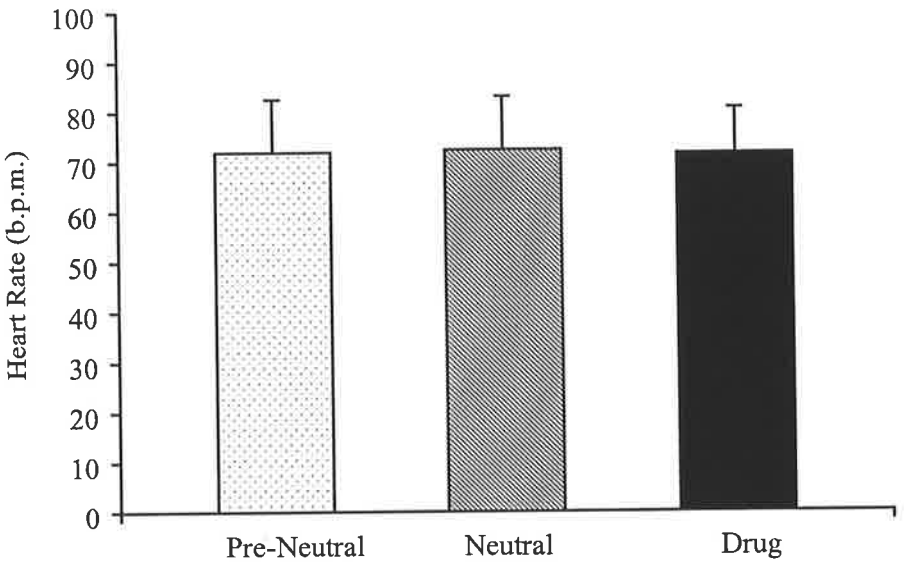


Figure 4.5.: Comparison of mean sweating (%) among methadone patients (n=15) recorded before presentation of a neutral stimulus, after a neutral stimulus and after a drug-related stimulus. Values are mean and s.d.

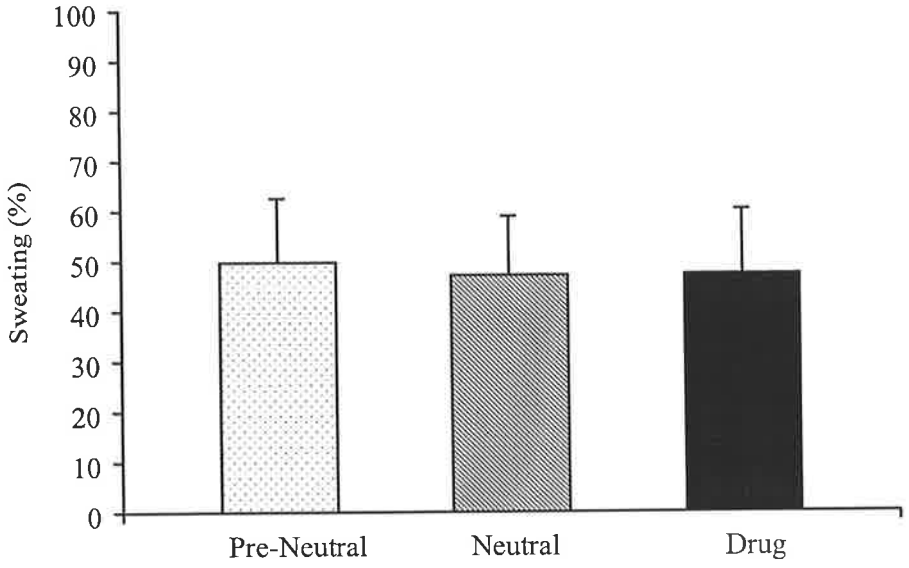
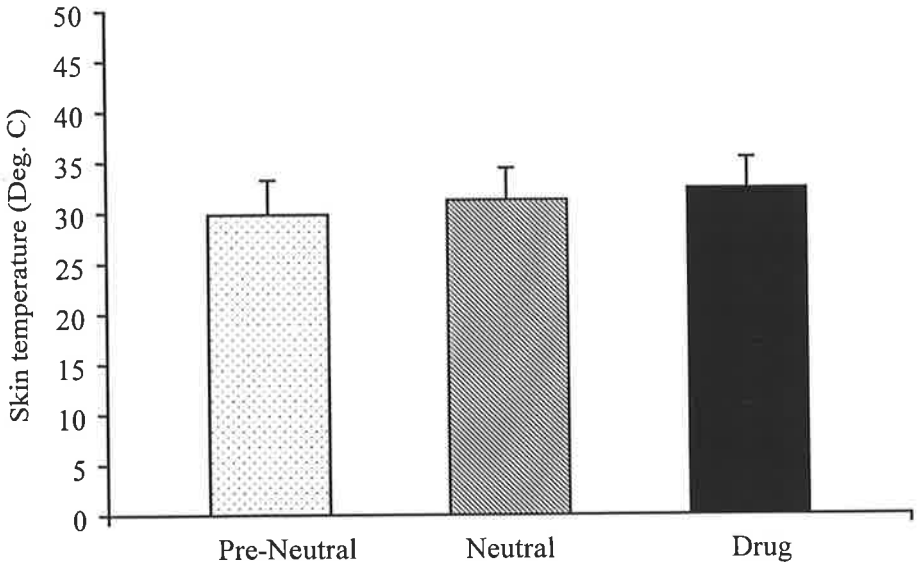


Figure 4.6.: Comparison of mean skin temperature among methadone patients (n=15) recorded before presentation of a neutral stimulus, after a neutral stimulus and after a drug-related stimulus. Values are mean and s.d. (°C).



4.4. Discussion

In the present study, the nature of conditioned withdrawal among a small sample of stabilised methadone maintenance patients, and the relationship between conditioned withdrawal and methadone dose were examined. It was found that the intensity of subjective opioid withdrawal reported by these patients increased after presentation of a drug-related stimulus by an average of 6.80 on a 48-point scale. Approximately one-half of the patients exhibited an increase of 8.00 points or more on the subjective withdrawal scale.

In studies of conditioned responses among opioid users, conditioned stimuli have often been slides, videos or three-dimensional objects related to injection practices. The differential effectiveness in producing conditioned responses among these cues has yet to be systematically examined (Heather & Greeley, 1990). However, it is generally agreed that cue salience is important, as patients' responses may vary depending upon the individual relevance of the drug-related stimuli (Childress et al., 1986c). It has also been suggested that the patient should remain focussed upon the stimuli if the conditioned response is to be maximised (eg Dawe et al., 1993). The drug-related stimulus utilised in the present study was developed in conjunction with active heroin users, who were accessed via a large heroin support group. Patients were also instructed to describe the stimuli during presentation. The results from the present study suggest that these procedures were effective in facilitating a conditioned response.

Higher methadone dose levels have been associated with reduced signs and symptoms of opioid withdrawal among many patients (see section 1.13). Childress and colleagues (1986a; 1986b) postulated that methadone would also generally attenuate the incidence and intensity of conditioned withdrawal responses among methadone patients, although statistics demonstrating such a dose-response relationship were not reported. As such, it

was hypothesised that higher methadone dose levels would be associated with a reduced conditioned response to the drug-related stimulus among the patients in the present study. This hypothesis was confirmed in that the size of the increment in subjective withdrawal was negatively associated with the methadone dose level, such that patients prescribed higher methadone doses exhibited smaller changes in conditioned withdrawal severity.

The program in which these patients were enrolled has a policy of allowing patients considerable control over dose level (DASC, 1997), and the average daily methadone dose of 65mg demonstrated in the present study is consistent with recommended clinical practice (see section 1.13.2). It is unlikely that the subjective withdrawal severity reported by the patients after presentation of the drug-related stimulus, which were almost double baseline levels, was the result of inadequate dosing. Rather, it appears that the methadone dose levels in the present study were sufficient to alleviate daily opioid withdrawal in many patients, while higher dose levels also reduced the severity of the conditioned opioid withdrawal response.

Classical conditioning models postulate that former heroin users may experience renewed motivation to use drugs due to conditioned responses to stimuli formerly associated with the onset of drug effects. The conditioned responses may be withdrawal (Wikler, 1948; 1965 cited in O'Brien et al., 1986), opponent processes (Siegel, 1990) or drug agonistic effects (Stewart et al., 1984; Stewart & Wise, 1992). Although not designed to compare these different models, the results from the present study offer some support to the theories of conditioned withdrawal and conditioned opponent processes, while providing less support for a drug agonist effect.

In the present study there were no correlations between the measures of conditioned withdrawal and direct opioid effect. That is, withdrawal responses occurred in the

absence of any conditioned drug effect. This finding is consistent with the work of O'Brien and colleagues (1986) and Childress and colleagues (1986a) who demonstrated the relative independence of conditioned withdrawal and conditioned drug effect. However, the small and self-selected nature of the sample in the present study are important caveats that should be considered before conclusions are made regarding the conditioned responses that may be reliably demonstrated among methadone maintenance patients. Further, the specific parameters that determine whether drug-like or drug-opposite conditioned responses will be elicited have not yet been experimentally identified (Ehrman et al., 1992). O'Brien and colleagues (1990) concluded from human and animal data that stimulants (eg amphetamines and cocaine) are more likely to produce drug-like conditioned responses whereas opioids are more likely to produce drug-opposite effects. It is uncertain whether this would be a result of the pharmacological nature of these drugs or of the social or individual characteristics associated with their use. Finally, Staiger & White (1988) demonstrated that either a drug-like or drug-opposite response could be elicited depending upon the context in which-alcohol related cues were presented. This was not directly assessed in the present study.

In the present study, there was no evidence of a physiological element of conditioned withdrawal. Mean blood pressure, heart rate, skin temperature and the degree of sweating were not significantly different from baseline levels after presentation of the drug-related stimulus. Previous research has documented a physiological conditioned response among opioid users. Sideroff & Jarvik (1980) presented heroin users with a video-tape of heroin related stimuli. Compared with controls, heroin users displayed significant increases in heart rate (a drug-opposite response). O'Brien and colleagues (1977) demonstrated conditioned withdrawal responses among 8 methadone patients maintained on a mean dose of 43mg/day (range: 25 to 70mg). Conditioned withdrawal responses included increased heart rate and decreased skin temperature. These data

suggest that both objective and subjective elements of opioid withdrawal might be conditioned experimentally. However, physiological elements of conditioned responses are often not recorded. McLellan and colleagues (1986) reported low correlations between physiological responses (heart rate, galvanic skin response, skin temperature) and subjective conditioned responses among former heroin users. Subjective craving without physiological responses was common and vice versa. Childress and colleagues (1986a) reported that skin temperature significantly decreased, but there were no significant differences in heart rate after presentation of a drug-related stimulus in a laboratory setting. Substantial inter-patient variability among the physiological measures was also recorded. The authors did not measure physiological responses in the less artificial clinical setting. These studies have highlighted the generally poor relation between physiological and subjective measures of conditioned withdrawal among opioid users. Furthermore, there are a number of physiological opioid withdrawal signs (see section 1.13) that might be amenable to measurement. It may be possible that the physiological changes resulting from exposure to a drug-related stimulus were not measurable by the gross autonomic measures utilised in the present study.

Craving and withdrawal are partly a conditioned response to drug-related stimuli that have been encountered frequently during the drug-using career. Such conditioned responses are thought to play an important role in the maintenance of drug taking, and have been shown to persist after extended periods of abstinence (see Heather & Greeley, 1990). As such, such conditioned responses may contribute to relapse to drug use (Heather & Greeley, 1990, O'Brien et al., 1977; 1990), although a reliable relationship between conditioned responses and relapse to opioid use has yet to be experimentally demonstrated (Heather & Greeley, 1990). Higher methadone dose levels have been found to be associated with reduced heroin use among maintenance patients (see section 1.5.). Results from the present study suggest that high methadone doses may also reduce conditioned withdrawal. It may be the case that in conjunction with high methadone

doses, conditioned responses among methadone patients may weaken as a function of time on a maintenance program. These factors may reduce the likelihood of a relapse to heroin use among many patients, and hence prospective studies involving repeated assessment of conditioned responses may be appropriate.

4.4.1. Summary

In the present study, stabilised methadone maintenance patients were exposed to drug-related stimuli and subjective and objective responses were recorded. It was found that the intensity of subjective opioid withdrawal reported by these patients increased significantly after presentation of a drug-related stimulus. The hypothesis that higher methadone dose levels would be associated with a reduced conditioned response to drug-related stimulus was confirmed. The increment in subjective withdrawal was negatively associated with the methadone dose level, such that patients prescribed higher methadone doses exhibited smaller changes in conditioned withdrawal severity. Outside of the methadone clinic patients may come into contact with people and places previously associated with the use of heroin. The findings from the present study suggest that classical conditioning is a potential mechanism for producing subjective reports of opioid withdrawal among methadone patients exposed to drug-related stimuli.

CHAPTER FIVE

STEADY-STATE PHARMACOKINETICS AND PHARMACODYNAMICS AMONG METHADONE PATIENTS WHO EXPERIENCE OPIOID WITHDRAWAL SYMPTOMS

5.1 Introduction

Inadequate dosing with methadone in a maintenance program is characterised by complaints of unpleasant withdrawal symptoms (methadone dose 'not holding'), particularly at the end of each inter-dosing interval. Even in programs with dosing strategies designed to meet the individual needs of patients, there are some patients who experience withdrawal symptoms and reduced methadone efficacy during part of the inter-dosing interval. In Chapter Two it was reported that 34% of a non-selected and representative sample of 114 patients in a large, metropolitan, public maintenance program regularly experienced withdrawal (designated the non-holders) during the once daily inter-dosing interval. This finding was consistent with recent published studies (Schall et al., 1996; Torrens et al., 1998) and highlighted that withdrawal symptoms, sufficient to cause discomfort (and potentially lead to other drug use or program dropout), occur in a significant proportion of methadone users with potential for adverse public health outcomes.

When compared with those patients who did not report significant withdrawal symptoms (designated the holders), it was found that the average daily methadone dose across both groups exceeded 60 mg. There were no differences with respect to demographics, the concurrent use of other drugs or the length of stay in the program. As factors affecting the pharmacological effectiveness of methadone (e.g. physiological and pathological status, concurrent drug use) did not appear to be reliably related to

withdrawal severity, other factors, possibly of a pharmacokinetic or pharmacodynamic nature, may be important. The studies presented in this Chapter were designed to determine the pharmacokinetic and pharmacodynamic factors associated with withdrawal severity, and to determine the relationship between plasma methadone concentration and subjective and objective methadone effects.

5.1.2. The relationship between plasma methadone concentrations and withdrawal severity.

It has been argued that there is a minimum effective methadone plasma concentration, whereby trough concentrations above this level will prevent withdrawal symptoms. For example, Dole (1980; 1988; 1994) has commented that the critical minimum plasma methadone concentration is between 100 ng/mL and 150 ng/mL, with levels below 50 ng/mL clearly insufficient. In an early study, steady state plasma methadone concentrations of below 200 ng/mL were associated with increased patient complaints (dose not holding), a higher frequency of urines containing illicit drugs and poorer psychosocial rehabilitation (Holmstrand et al., 1978). These authors have argued that optimising the methadone dosage regimen to achieve target trough plasma methadone concentrations of 100-200 ng/mL would improve the effectiveness of methadone maintenance treatment.

Other workers, however, have shown that there was no correlation between trough plasma methadone concentrations (ranging from 100-300 ng/mL) and either withdrawal symptoms (e.g. Bell et al., 1988; 1990; DeVos et al., 1996; Horns et al., 1975; Schall et al., 1996) or rehabilitation (e.g. Byrne, 1996; Torrens et al., 1998).

Horns and colleagues (1975) measured trough racemic plasma concentrations in 17 patients once per week during a 26 week period of stable dosage (dose range

approximately 20-85 mg). In the fortnight before the study, methadone dosage was unknown to the patients. During the study period patients were aware of their dose level and could negotiate dose increases (maximum 5mg/week). The authors hypothesised that when given control of their dose level, patients would adjust their dose in such a manner that trough plasma methadone concentrations would converge in a more narrow range than existed at the outset of the study. This hypothesis was consistent with the view that there is a minimum effective methadone concentration. However, this hypothesis was not supported. The range of patients' methadone plasma concentrations (100-300ng/mL) was not significantly different to pre-study levels. Further, there were no correlations between plasma concentrations above 100ng/mL and either symptom complaints or reports of not-holding.

Subjective reports of withdrawal severity tend to be higher than objective ratings (see Section 1.13). Thus, while patient ratings may have validity and value in the clinic setting, within the research setting they may have potential for bias and random error. Nevertheless, studies incorporating objective ratings of withdrawal severity have also been unable to demonstrate a linear relationship between trough plasma methadone concentration and withdrawal. For instance, Loimer & Schmid (1992) examined the relationship between trough plasma concentrations and opioid withdrawal in 104 methadone patients, who were stabilised on a mean dose of 83.3 mg/day (s.d. 32.4) and had participated in treatment for between 2 and 45 months (mean 13.3 months). They found no significant differences in trough plasma methadone concentrations between patients experiencing subjective (self-report) and objective (investigator rated) withdrawal and those who did not. Although there was a linear relationship between oral dose levels and plasma concentrations, there was not a linear relationship between plasma methadone concentrations and opioid withdrawal. Specifically, there was no significant difference between the subjective withdrawal complaints of patients with trough plasma concentrations of less than 150 ng/mL and those with trough

concentrations above 600ng/mL. While patients with lower trough plasma concentrations (<150 ng/mL) displayed significantly more objectively measured withdrawal signs (mean of 7.4 from a possible 29) than those on 150-600ng/mL (mean of 2.3) and greater than 600 ng/mL (mean of 3.7), there was no significant difference between the higher plasma concentration groups.

Recent studies have also found that there is not a linear relationship between trough plasma methadone concentrations and rehabilitation. For example, Byrne (1996) reported that high trough plasma concentrations (mean 526 mg/L) in eight patients did not prevent these patients from continuing illicit drug use. Torrens and colleagues (1998) assessed trough plasma racemic methadone concentrations in 93 patients (73% males, enrolled in treatment for between 6 and 42 months, mean daily dose 87mg, 10-235mg) enrolled in a low threshold methadone program. Patients had a mean trough plasma methadone concentration of 365ng/mL (s.d. 216, 47-1041 ng/mL). There was no correlation between trough plasma concentration and withdrawal severity, and no significant difference in trough concentrations between those experiencing withdrawal or not, or continuing illicit drug use or not.

In summary, previous studies suggest that the relationship between trough plasma methadone concentrations and either withdrawal severity or other drug use is not linear. An alternative hypothesis is that the decline in opioid effects and onset of withdrawal symptoms that occurs in some patients towards the end of the 24-hour dosing interval is determined as much by the rate of decline of plasma methadone concentration as by trough concentration. There is support for this hypothesis from several lines of evidence.

Firstly, the study presented in Chapter Three examined the temporal pattern of symptom presentation during a single inter-dosing interval. It was found that direct opioid effect symptoms peaked within two-hours of oral administration of methadone, and then

declined in the remainder of the 24-hour period, while withdrawal symptoms showed an inverse relationship, peaking in the period immediately prior to the methadone dose. Despite a higher oral methadone dose, patients reporting that their dose did not 'hold' reported a lesser degree of opioid effect and a greater intensity of opioid withdrawal during the 24-hour period. Importantly, these patients also reported a greater degree of change in withdrawal intensity and opioid effect during the inter-dosing interval. These differences could not be accounted for by patient characteristics (e.g. age, gender), other drug use, methadone dose level or the amount of time enrolled on the methadone program. While there was a change in pharmacodynamic response over the inter-dosing interval in all patients, the degree of change was greater in the sub-group of non-holders. This suggests that the difference between trough and peak methadone effects and thus between trough and peak methadone concentrations may be critical.

Secondly, the results of the study presented in Chapter Three were consistent with a more recent published study. Hiltunen and colleagues (1995) compared plasma methadone concentrations with subjective (self-report) and objective (investigator rated) withdrawal in 16 stabilised methadone patients before daily dosing and, 2.5, 5, 9, and 24-hours after intake. Withdrawal severity was measured with validated questionnaires (Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS); Handelsman et al., 1978). The methadone patients were stabilised on a mean daily methadone dose of 98mg, and had been enrolled on the program for between 6 and 12 months. Mean plasma methadone concentration for the sample was approximately 200ng/mL at trough, and approximately 400ng/mL at peak, approximately 2.5 hours after methadone dosing. It appeared that no patient had a trough plasma concentration below 200 ng/mL[1].

[1] Results were presented graphically without publication of the actual values of plasma concentrations or withdrawal scores.

It was found that the majority of subjective withdrawal ratings correlated with changes in the methadone plasma concentration. The symptoms most closely related were alertness, running nose, yawning and anxiety. The total SOWS score (maximum of 64) ranged from approximately 20 at trough plasma concentration, dropping to approximately 5 at 2.5 hours after dosing before climbing again. The total OOWS score (maximum of 13) showed a similar pattern, peaking at approximately 3 at trough and approximately 0.5 at peak plasma concentration (2.5-5 hours after dosing). However, only a few objectively rated withdrawal signs were closely related to changes in methadone plasma concentrations. These were rhinorrhea, piloerection and anxiety. This finding was consistent with reports that patients may experience subjective symptoms in the absence of observable objective signs. In summary, the results of this study suggest that daily variations in plasma methadone concentration reflect changes in withdrawal severity. However, the study did not quantify the relationship between plasma methadone changes and withdrawal, did not make comparisons with a non-drug using control group to clearly demonstrate that the reported changes were a result of methadone administration, and did not determine concentration-effect relationships, and as such further work is required.

Thirdly, there have been reports of rapid metabolism in patients maintained on high methadone dose levels. In one study, two patients with marked withdrawal symptoms exhibited extremely rapid declines of plasma methadone concentrations during the latter part of the inter-dosing interval, even though the trough concentrations exceeded 200 ng/mL. Both patients were subsequently prescribed a dose divided over three times per day. The divided dosage regimen resulted in more stable plasma concentrations of between 150ng/mL and 200 ng/mL throughout the entire inter-dosing interval, and no clinical evidence of withdrawal (Walton et al., 1978). Tennant (1987) studied 18 patients who complained of withdrawal. In a subgroup (4 of the 18) of patients, who were subjected to pharmacokinetic analysis, evidence of extremely rapid metabolism

was identified. Thus, some maintenance patients with enhanced metabolism experience dramatic changes in methadone plasma concentration during the inter-dosing interval and experience opioid withdrawal. Dividing the daily dose reduces the degree of change in plasma concentration as well as the associated withdrawal.

The pharmacokinetics, and in particular, the terminal elimination half-life of methadone are variable after single doses in healthy volunteers (e.g. Wolff et al., 1997), people with chronic pain (Plummer et al., 1988; Sawe, 1986; Inturisi et al., 1987) and methadone patients (e.g. Meresaar et al., 1981; Verebely et al., 1975). Anggard and colleagues (1974) assessed 6 patients who received methadone in increasing doses of 10, 20, 40 and 80mg/day during a 1-month period. Results suggested that there was considerable inter-patient variation in plasma half-lives and steady state levels (disposition) of the drug. Nilsson and colleagues (1982) reported that one-third of patients beginning a Swedish methadone program complained of withdrawal symptoms during the latter part of the inter-dosing interval. These patients demonstrated significantly smaller volumes of distribution and thus shorter elimination half-lives. They postulated that these pharmacokinetic characteristics would reduce the therapeutic effectiveness of methadone.

In a subsequent study, Nilsson and colleagues (1983) assessed 8 patients who complained of withdrawal and showed poor treatment progress. These patients were stabilised on a methadone dose between 50mg and 100mg, and had been enrolled on the program for between 10 and 31 months. Comparisons were made with 12 new patients who were administered doses between 30mg and 60mg, and had been on methadone for 25 days. The patients considered to be therapeutic failures had a significantly lower methadone plasma half-life (24.5(s.d. 2.6) hours compared with 34.0 (s.d. 7.0)) and a significantly smaller volume of distribution (3.09 l/kg (s.d. 0.06) compared with 4.56 l/kg (s.d. 1.0)). These studies suggest that as the half-life and volume of distribution is

variable it could therefore be expected that the rates of decline in plasma concentrations and likelihood of withdrawal symptoms toward the end of each 24-hour dosing period would also vary considerably. Thus, some patients would experience withdrawal symptoms daily while others may never experience them.

5.1.3. The present study

Evidence to support a link between plasma methadone concentrations and responses would require concurrent measurement of plasma methadone concentration and a range of opioid effects (including withdrawal) amongst a group of stable methadone maintenance patients over a 24-hour inter-dosing interval. These data were collected in the present study with the aims of determining both plasma methadone concentration-effect relationships and whether pharmacokinetic and/or pharmacodynamic factors influenced withdrawal severity. Previously published studies have limited data collection periods and have utilised observer rated withdrawal severity as an objective measure. This study was designed to build on previous research by incorporating repeated sampling over a 24-hour inter-dosing interval and measuring the physiological effects of methadone. The first phase of this study was to pilot the instruments for measuring the physiological effects of methadone. The main experiment was designed to determine the relationship between the rate of change in methadone plasma concentration and response. Data were also collected using the Profile of Mood States (McNair et al, 1971) to determine the relationship between methadone plasma concentration and the magnitude and temporal pattern of mood states. With the exception of pilot work, the literature relating to the effect of methadone on mood state and the associated results will be presented in Chapter Six. The third phase involved a single case study of a non-holder from the main experiment who was subsequently prescribed by the clinic a split-methadone dose. The results and discussion of this case-study will be presented in Chapter Seven.

Aims

In the present study plasma methadone concentration and a variety of pharmacodynamic responses were assessed over a complete inter-dosing interval. The aims were:

1. To evaluate subjective and physiological changes in methadone patients by comparing responses with those of non-opioid using controls.

2. To characterise the relationship between plasma racemic methadone concentration and pharmacodynamic responses.

3. To compare methadone patients who reported significant withdrawal symptoms (non-holders) with a group who did not (holders), in order to determine whether the magnitude and temporal pattern of their subjective and physiological response to methadone also differed.

4. To determine whether pharmacokinetic and/or pharmacodynamic factors influence withdrawal severity.

Hypotheses

1. The temporal pattern of methadone responses, including physiological responses, will be associated with changes in methadone plasma concentration.

2. The rate of decline of methadone plasma concentration will determine the presence or absence of withdrawal symptoms during the 24 hour inter-dosing interval, and in those who experience withdrawal symptoms, the rate of decline of methadone plasma concentrations will determine the severity of these symptoms.

5.2. PILOT STUDY OF PHYSIOLOGICAL MEASUREMENT TOOLS

5.2.1. Introduction

As described in Chapter One (see Sections 1.9 and 1.10) there are a number of direct opioid effects that might be amenable to physiological measurement. The aim of this pilot study was to determine the utility of a variety of physiological measures of methadone effect, namely blood pressure, heart rate, skin temperature and sweating, pupil size and pain threshold (a measure of analgesic effect). This section will review published studies that have used such physiological measurements.

A number of studies have demonstrated physiological changes during methadone maintenance. Martin and colleagues (1973) examined six patients before, during and after stabilisation on 100mg of methadone. After six months of methadone treatment patients had an increased body temperature and lower blood pressure, heart rate, and respiratory rate than before treatment.

Gritz and colleagues (1975) investigated the effects of methadone on ten maintenance patients (median dose 65mg/day, enrolled for a median of 5 months) compared with 10 abstinent patients (enrolled in a therapeutic community for a median of 2.0 months) and 5 non-drug using controls (see Table 5.1). Physiological measures included sublingual temperature via a standard mercury thermometer, blood pressure, heart rate, and respiration via a thermistor placed inside the patient's nostril. Two measures were significantly different among the groups. The mean heart rate of the abstinent patients was significantly higher than the normal controls and the methadone patients. The respiration rate of the methadone patients was significantly lower than the abstinent patients and the controls. There was a trend for abstinent patients to have higher mean blood pressure than both the controls and methadone patients. The authors did not find a

correlation between the physiological measures and the methadone dose level, suggesting that there was not a dose-response relation for these effects.

Table 5.1. Summary of physiological effects of methadone published by Gritz and colleagues. (1975). Values represent mean(s.d.).

Sample	Abstinent [1]	Control	Methadone
Length of Enrolment	-	-	5 months
Mean Dose	-	-	65 mg
n	n=10	n=10	n=10
Sublingual Temp. (F)	98.3 (0.6)	98.5 (0.4)	98.2 (0.5)
Systolic BP (mmHg)	132.6 (22.2)	117.4 (9.2)	127.4 (16.4)
Diastolic BP (mmHg)	82.5 (17.1)	70.8 (7.6)	79.6 (9.8)
Heart rate (bpm)	76.6 (9.5)	66.2 (6.1)	66.0 (10.9)
Respiration (bpm)	17.4 (3.2)	16.4 (2.3)	13.6 (2.8)

The studies reviewed above have focussed upon qualitative differences between methadone patients and either abstinent ex-users or non-opioid using controls. Two published studies have reported repeated physiological measures from methadone patients during an inter-dosing interval (see Table 5.2). Aylett (1982) observed withdrawal signs during a dose adjustment procedure in patients starting a methadone maintenance program. Patients, who had been opioid abstinent for 24 hours, were given methadone in a schedule of 10mg every 10 minutes during a 1 hour period. It was found that the mean systolic blood pressure and pulse rates were higher in patients exhibiting opioid withdrawal. In general, systolic blood pressure and heart rate declined as the methadone dose levels, and possibly methadone plasma concentrations, increased.

McCaul and colleagues (1982) studied the effects of methadone during a four hour post-dose period in four male methadone patients. It was found that skin temperature, measured by a probe attached to the middle finger, increased to a peak of 94.3°F ninety minutes after dose administration and then remained stable for the next two hours. Systolic blood pressure and respiration decreased slightly. It was also reported that heart rate fell during the inter-dosing interval (exact values not reported). Pupil diameter was measured via Polaroid photographs in a luminance of 100 foot candles (or approximately 10 lux). It was found that the pupil diameter constricted by 1.25mm ninety minutes after dosing and remained constricted for the remainder of the study period.

Table 5.2. Previously published physiological changes in methadone patients during an inter-dosing interval. Values represent Mean(s.d.).

	Methadone Induction			Methadone Maintenance		
Minutes Post-Dose	**0** [1]	**30** [1]	**60** [1]	**0** [2]	**90** [2]	**120-240**[2]
Enrolment Length	1 day	1 day	1 day	4-12 yr.	4-12 yr.	4-12 yr.
Mean Dose (mg)	0	55	87	40-80	40-80	40-80
n	n=20	n=22	n=6	n=4	n=4	n=4
Heart rate (bpm)	97.7(16.9)	91.8(15.0)	90.0 (8.3)	-	-	-
Pupil Constriction (mm)	-	-	-	-	1.25	-
Skin Temperature (°F)	-	-	-	89.5	94.3	
Systolic BP (mmHg)	135 (14.7)	127 (11.4)	119 (16.6)	114.6	-	110.6
Respiration (bpm)	-	-	-	12-15	10.8-13.8	

1: Aylett, 1982. Methadone levels represent cumulative dose.
2: McCaul et al., 1982. Standard deviations were not reported.

These studies suggest that methadone administration induces short-term physiological changes among new and stabilised patients, which might parallel changes in methadone

plasma concentrations. However, it is not clear whether these changes represent a direct effect of methadone, the relief of opioid withdrawal, or a mixture of these. Nevertheless, these studies suggest that blood pressure, heart rate and respiration rate will decrease, and skin temperature will increase, as plasma methadone concentrations increase after dosing. Accordingly, the temporal pattern of these responses may be different between those patients who experience a more rapid rate of decline in plasma concentrations and withdrawal, and those who do not.

The present pilot study also involved measures of pupil size. Opioid miosis is an objective index of opioid effect, and may provide a more reliable measure of opioid effect than cardio-vascular changes. Inturrisi & Verebely (1972) measured pupil size and plasma racemic methadone concentrations after a single oral dose of 15mg in 5 opioid naïve males. The onset, peak, and 24-hr duration of methadone induced pupil constriction coincided with the time course of plasma concentration. Specifically, pupil size constricted by approximately 1.5mm at peak (4-6 hours after dosing) and 0.8mm at the 24-hour trough plasma concentration.

Loimer and colleagues (1991) compared the pupil size of patients with trough plasma concentrations less than 400ng/mL (n=9, mean(SE) dose 73.4(11.4)mg) with a group with concentrations greater than 400ng/mL (n=12; 85(5.4)mg). Pupil diameter was measured by a computer assisted monitor in a laboratory with luminance of 160 lux. There was a non-significant trend for patients with lower trough plasma concentrations to have larger pupil size (mean(SE) of 3.1(0.7)mm compared with 2.0(0.1)mm), consistent with a reduced opioid effect.

These published studies have measured pupil size by either a Polaroid camera (i.e. Inturrisi & Verebely, 1972; McCaul et al., 1982) or a computer assisted technique (Loimer et al., 1991) and have demonstrated similar patterns of opioid induced miosis.

While the instrument used to photograph the eye appears to have little impact on the reliability of measurement, it has been found that lighting intensity and binocular or monocular exposures affect pupil size. Weinhold & Bigelow (1993) conducted a quantitative examination of lighting intensity on opioid induced miosis. Seven patients received their usual dose (50-60mg; enrolled for 10-56 months). Polaroid photographs of the pupil were then taken -15, 5, 15, 30, 45, 60, 90, 120 and 180 minutes after dose administration. Peak miosis was recorded in moderately dim lighting 90 minutes after dosing. Pupil diameters were on average 0.35mm larger when the photograph was taken with one eye closed. Although the authors presented their results graphically, it appeared that at 4 footlamberts (approximately 43 lux) pupil size changed from approximately 5.7mm at trough to 4.8mm after 90 minutes. In comparison, when recordings were taken when the light intensity was 16 footlamberts (approximately 170 lux) the values changed from 4.8mm at trough to 3.9mm at plasma peak. This suggested that pupil diameter decreased 1.0mm with each log unit increase in light intensity. As such, reliable measurements of pupil size require that the light intensity of the testing environment remains constant.

The final objective measure to be assessed in this study is pain threshold, an indicator of the analgesic effect of methadone. The duration of the analgesic effect of methadone is approximately 4 to 8 hours (e.g. Gourlay et al., 1986: A review of methadone analgesia is presented in Section 1.9.1.). In steady state conditions, methadone patients self-report lower pain sensitivity than non-opioid users (e.g. Lehofer et al., 1997). It is unclear whether pain sensitivity will vary in parallel with changes in methadone plasma concentration. However, as analgesia is an opioid effect (see section 1.9.1.), it may be expected that pain sensitivity will be greater during opioid withdrawal, and therefore tolerance to painful stimuli will be greatest during periods of maximal opioid effect. The technique that will be assessed in this study involves measuring pain threshold via electrical stimulation. Brennum and colleagues (1992) used a similar technique to assess

the analgesic effects of lidocaine in non-drug users. In their study, pain detection was operationalised as the lowest stimulation intensity perceived by the subject, while pain threshold was recorded as the highest stimulation tolerated. Electrical thresholds were determined with an instrument producing a 50hz train of 1msec constant-current square -wave. This technique was able to demonstrate that subjects' pain threshold score 90 minutes after 5mL of lidocaine increased to 10mA, from a baseline of 1mA. Thus, electrical stimulation appears to be a valid quantitative measure of pain threshold, and as such, a similar instrument and methodology will be assessed in this study.

5.2.2. The present pilot study

Previous studies have demonstrated physiological changes among patients in methadone treatment that are associated with changes in plasma methadone concentrations. This pilot study was designed to assess the utility of a number of physiological tools in examining the nature and extent of physiological responses to methadone, namely blood pressure, heart rate, skin temperature and sweating, pupil size and pain threshold (a measure of analgesic effect). Based upon previous findings, the following hypotheses were made:

Hypotheses:

1. That the physiological measures used in this study will differentiate methadone patients from non-drug using controls consistent with subjective measures of opioid withdrawal and direct opioid effect.

2. That for methadone patients, administration of methadone will be associated with decreased blood pressure, heart rate, pupil size and decreased opioid withdrawal, including decreased sweating.

3. That for methadone patients, administration of methadone will be associated with increased skin temperature, pain threshold and subjective reports of direct opioid effect.

5.2.3. Method

5.2.3.1. Participants

Ethical approval for this study was obtained from the Social Science Ethics Committee at the University of Adelaide. The Research Review Committee of the Drug & Alcohol Services Council (DASC) approved access to the methadone patients.

Data were collected from 5 patients enrolled in the South Australian Public Methadone Maintenance Program. Participants were recruited by advertisements placed in the waiting room of the methadone dispensing area. They were assured that all information provided was anonymous and confidential, that the Methadone Program did not employ the researcher, and that the decision to participate would not affect their treatment program. Data were collected in a private room attached to the waiting area immediately prior to the usual daily methadone dose, and generally took 120 minutes to complete.

Comparisons were also made with a control group of 5 postgraduate students from the Psychology Department at the University of Adelaide. Controls gender ratio, age and weight ranges were within the range of the methadone patients. None of the controls had taken any other psychoactive drug (other than alcohol, nicotine or caffeine) within one month of the study. Control data were collected in a research room within the Department of Psychology. All study participants were volunteers and received $10.00 for participation.

5.2.3.2. Procedure and Measures

Methadone patients arrived at the testing area 30 minutes before their daily methadone dose was due. In addition to general demographic and treatment program details, measures were then made using the following tests:

The Opiate Withdrawal Scale (OWS) included 16 opioid withdrawal symptoms that were extracted from the Short Opiate Withdrawal Scale (Gossop, 1990) and the Subjective Opiate Withdrawal Scale (Handelsman et al., 1987) (see Appendix 6). The Morphine Benzedrine Group Scale (MBG)(Haertzen and Hickey, 1987) included 16 items, and has been found to be a valid and reliable measure of positive opioid effect (see Appendix 5).

The Profile of Mood States (POMS) (McNair et al., 1971) contains a list of 65 adjectives describing mood states. Participants were instructed to rate each item on a scale of 0 (not at all) to 4(extremely) based on how they were feeling at that moment (i.e. "Right now"). The POMS is divided into six empirically derived sub-scales that reflect distinct types and qualities of identifiable affective state. Sub-scales include:

Vigour - a mood of ebullience and high energy;

Depression - depressed affect and a sense of inadequacy;

Tension - heightened musculo-skeletal tension;

Anger - irate mood and antipathy toward others;

Fatigue - weariness and low energy level;

Confusion - bewilderment and disorganised cognitive efficiency.

In addition to these sub-scales, the Total Mood Disturbance (TMD) score is a single global estimate of affective state, which is derived by summing the scores across all six factors, weighting Vigour negatively.

Heart rate and blood pressure were measured via an automatic Digital Blood Pressure and Heart Rate Monitor (OMRON model HEM-703c). Skin temperature and sweating were measured via an ambulatory device incorporating solid state temperature (°C) and humidity (%) sensors, designed by the Department of Clinical & Experimental Pharmacology at the University of Adelaide.

Pupil diameter was measured using a Polaroid Spectra Two Camera (Model 636) with a Polaroid Close-up Lens (Model F112), permitting a picture to be taken 25.4cms from the pupil, and producing an image 50% of actual size. Photographs were taken in standard ambient room lighting. A small measuring scale was attached above the eyebrow for reference.

Pain Threshold was measured by an electrical stimulator (Grass model S6) generating a 10hz train of 1msec constant current. Electrode Gel (Spectre 360, Parker Laboratories) was used to provide conductance between the ear lobe clip and skin. Voltage was increased at the rate of 1 volt per second. The patients were instructed to apply the same interpretation of 'painful' throughout the study and indicate when they first perceived the stimulus (Pain Detection) and when they perceived the stimulus as intolerable (Pain Threshold).

Patients then took their normal methadone dose. Each measure was then repeated 60 minutes after dose ingestion. The control subjects did not receive methadone, but were treated in the same manner as the patients in all other respects.

5.2.4. Results

Five methadone patients and five non-opioid using controls, matched for age and gender, participated in this trial. Methadone patients had a mean age of 27.6 years (s.d. 4.5, 23-32) and 3 (60%) were male. Patients had been enrolled in the methadone program for a mean of 832 days (s.d. 733.7 days, 1 - 6 years). The mean daily methadone dose was 68.0 mg/day (s.d. 25.6, 45 - 110). Measurement of current body weight was recorded for all patients (mean 66.0 kg, s.d. 17.5, 48-90) allowing computation of the ratio of oral methadone dose to weight (mean 1.08 mg/kg, s.d. 0.34, 0.56-1.4). Controls had a mean age of 27.8 years (s.d. 3.8, 24-32) and 3 (60%) were male. Mean weight for controls was 71.6 kg (s.d. 13.2, 54-90). There were no significant differences between the groups for age, gender ratio or body weight.

5.2.4.1. Pre- and post- methadone dose comparisons of measures for methadone patients.

The results of related samples t-tests for pre- and post-methadone dose differences in scores for each measure are presented in Table 5.1. All measures, except skin temperature, showed temporal trends consistent with hypotheses. However, relatively few of these comparisons reached statistical significance. Those measures that did reach statistical significance were: Self-reported opioid withdrawal symptoms (mean of 9.2 compared with 3.6; $t=2.71$, $p<0.05$); Self-reported direct opioid effect symptoms (mean of 4.8 compared with 9.2; $t=-2.16$, $p<0.05$); Sweating (mean of 52.2% compared with 43.2%; $t=2.87$, $p<0.05$); and Pain Threshold (mean of 26.8 volts compared with 34.4 volts; $t=-4.15$, $p<0.01$).

As measures exhibited hypothesised temporal trends, a series of analyses were conducted to determine the sample size required for these trends to reach significance.

Table 5.2 presents the minimum required sample size for each measure, for alpha (α) levels of 0.05 and 0.01, based upon the effect size for each each measure reported in this pilot study, and with statistical power of 90%. Effect size (r_m) was calculated using the following formula: $r_m = \sqrt{t^2 / t^2 + df}$. Sample size (S) was calculated using the formula: $S = t^2.(1 - r_m^2) / r_m^2$ (Friedman, 1982).

Table 5.2.1: Results from related samples t-tests of pre- and post - methadone dose differences in subjective and physiological measures among methadone patients (n=5).

Measure	n	Pre-dose mean (s.d.)	Pre dose range	Post-dose mean (s.d.)	Post-dose range	t value	p
Opioid Measures							
Withdrawal	5	9.2 (4.3)	4-13	3.6 (4.0)	0-10	2.71	<0.05
Effect	5	4.8 (4.8)	0-10	9.2 (4.4)	4-14	-2.16	<0.05
Systolic BP (mmHg)	5	116.4 (9.2)	108-128	114.0 (12.7)	96-125	0.53	ns
Diastolic BP(mmHg)	5	76.4 (11.4)	61-93	68.4 (10.8)	57-84	1.13	ns
Heart Rate (BPM)	5	71.4 (11.2)	60-88	69.0 (5.2)	63-76	0.86	ns
Skin Temp. (°C)	5	31.4 (3.0)	28-35	29.4 (3.6)	25-34	2.11	ns
Sweating (%)	5	52.2 (17.1)	28-75	43.2 (15.6)	24-67	2.87	<0.05
Pain Threshold (V)	5	26.8 (3.6)	22-30	34.4 (7.3)	26-42	-4.15	<0.01
Pupil Size (mm)	3[a]	3.5 (1.2)	2.4-4.7	3.2 (1.0)	2.1-4.1	1.72	ns
POMS							
Tension	5	6.8 (4.1)	2-13	3.2 (2.4)	0-6	1.44	ns
Depression	5	4.0 (4.8)	0-12	5.2 (4.4)	0-11	-0.45	ns
Anger	5	0.2 (0.5)	0-1	0.0 (0.0)	0-0	1.0	ns
Vigour	5	9.0 (5.8)	3-16	14.2 (8.0)	8-26	-1.16	ns
Fatigue	5	8.0 (7.2)	0-17	5.0 (4.2)	0-11	1.22	ns
Confusion	5	6.4 (4.0)	0-11	5.0 (1.9)	2-7	0.69	ns
Total Mood Disturbance	5	16.8 (16.4)	1-42	4.2 (16.3)	-22-18	1.36	ns

a: Pupil measurement could not be recorded for two brown eyed patients as the photograph did not provide a clear distinction between pupil and iris.

Table 5.2.2. Required sample sizes for subjective and physiological measures based upon a statistical power of 90%.

Measure	Effect Size (r_m)	Sample Size Required for Alpha (α) = 0.05	Sample Size Required for Alpha (α) = 0.01
Opioid Measures			
Withdrawal	.80	8	12
Effect	.73	13	19
Systolic BP	.25	160	227
Diastolic BP	.49	34	48
Heart Rate	.40	58	82
Skin Temperature	.72	13	19
Sweating	.82	8	12
Pain Threshold	.9	8	12
Pupil Size	.65	17	24
POMS			
Tension	.58	21	30
Depression	.22	255	361
Anger	.45	44	62
Vigour	.50	34	48
Fatigue	.52	34	48
Confusion	.33	78	110
Total Mood Disturbance	.56	27	38

5.2.4.2. Comparisons between methadone patients and non-opioid using controls.

Comparisons on each measure were made between the methadone patients and non-opioid using controls. A series of repeated measures multivariate analyses of variance were performed, with group (methadone, control) as the between-subject independent variable, the individual measure as the within subjects dependent variable, and time between recordings as the within subjects independent variable.

Figure 5.2.1. presents the self-reported withdrawal symptoms of both groups. The methadone patients reported a consistently greater number of withdrawal symptoms throughout the study period (mean (s.d.) 9.20(4.32) compared with 0.20(0.45) at the first time period, and 3.60(4.04) compared 0.40(0.55) at the second time period). The number of withdrawal symptoms reported by the methadone patients decreased sixty minutes after the ingestion of the dose, whereas the reported symptoms were relatively stable for the control subjects. These findings were found to be significant with a significant main effect for group ($F(1,8)=15.03$; $p<0.001$), a significant main effect for time ($F(1,8)=6.68$; $p<0.05$), and a significant interaction effect between group and time ($F(1,8)=7.82$;$p<0.05$).

Figure 5.2.1: Mean self-reported withdrawal symptoms of methadone patients (n=5) and non-opioid using controls (n=5).

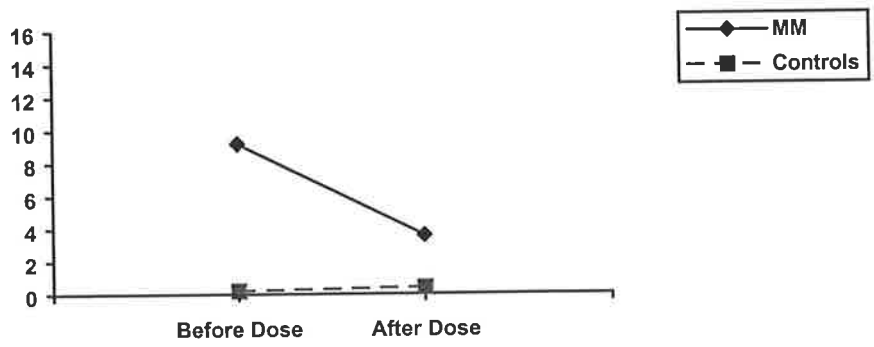
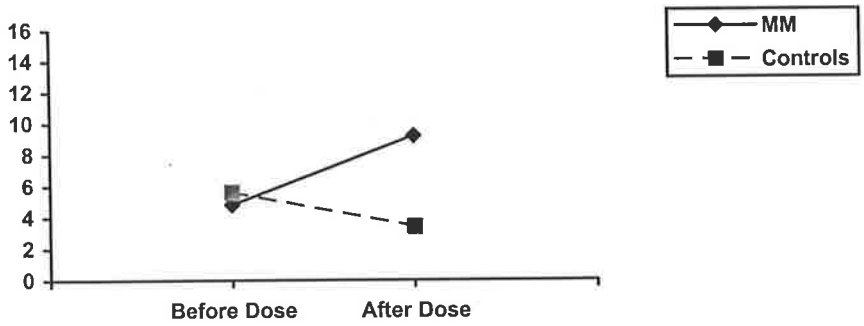


Figure 5.2.2. presents the self-reported degree of positive opioid effect, as measured by the MBG, of both groups. The methadone patients reported a greater degree opioid effect after dosing (4.80(4.76) compared with 5.60(2.07) at the first time period, and 9.20(4.43) compared 3.40(1.67) at the second time period: (F(1,8)=1.66:ns). The degree of positive opioid effect reported by the methadone patients increased sixty minutes after the ingestion of the dose, whereas the reported symptoms were relatively stable for the control subjects. While there was not a significant main effect for time (F(1,8)=1.03; ns), there was a significant interaction effect between group and time (F(1,8)=9.27; $p<0.01$).

Figure 5.2.2. Mean self-reported direct opioid effect reported by methadone patients (n=5) and non-opioid using controls (n=5).



There were no significant differences in either systolic (Figure 5.2.3.) or diastolic (Figure 5.2.4.) blood pressure between the groups (systolic F(1,8)=1.24, n.s.; diastolic F(1,8)=0.79, n.s.) or in the pattern of changes over time (systolic F(1,8)=3.17, n.s.; diastolic F(1,8)=1.77, n.s.), and there were no interaction effects (systolic F(1,8)=0.66, n.s.; diastolic F(1,8)=2.36, n.s.). Nor were there were significant differences for heart rate between the groups (F(1,8)=2.17, n.s.), main effects for time (F(1,8)=0.39, n.s.) or interaction effects (F(1,8)=0.78, n.s.) (Figure 5.2.5.).

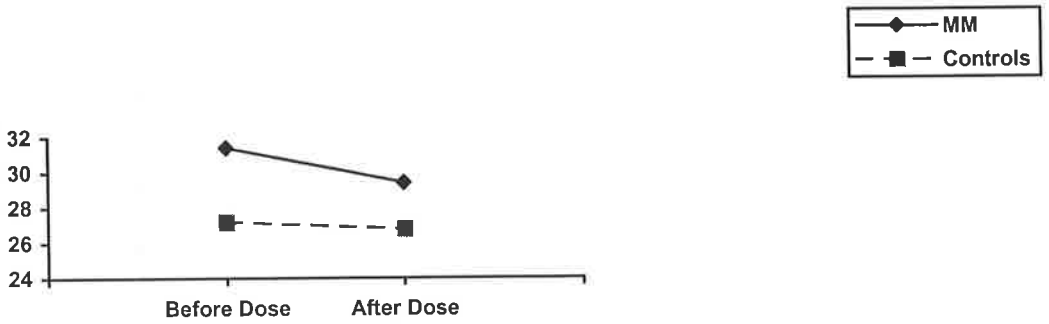
Figure 5.2.3: Mean systolic blood pressure (mmHg) of methadone patients (n=5) and non-opioid using controls (n=5).

Figure 5.2.4. Mean diastolic blood pressure (mmHg) of methadone patients (n=5) and non-opioid using controls (n=5).

Figure 5.2.5. Mean heart rate (breaths per minute) of methadone patients (n=5) and non-opioid using controls (n=5).

Methadone patients had a significantly higher skin temperature at both time periods (mean of 31.4 °C (3.05) compared with 27.2 °C (1.30) at the first time period, and 29.4 °C (3.65) compared with 26.8 °C (2.49) at the second time period: $F(1,8)=5.17$; $p<0.05$) (Figure 5.2.6.). Skin temperature for both groups remained relatively stable throughout the testing period. There was no significant main effect for time ($F(1,8)=1.77$; ns), nor was there a significant interaction effect between group and time ($F(1,8)=0.79$; ns).

Figure 5.2.6. Mean skin temperature (°C) of methadone patients (n=5) and non-opioid using controls (n=5).

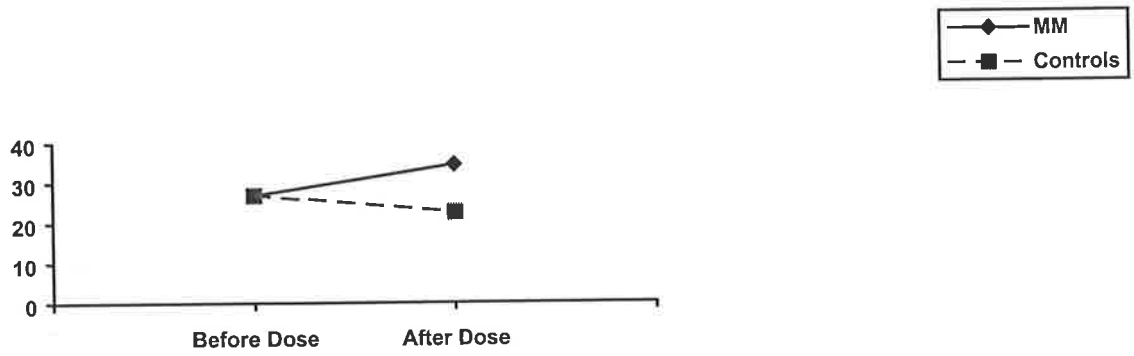


When compared with the controls, the degree of sweating was greater for the methadone patients before methadone administration, and lower after methadone (mean of 52.2 % (17.08) compared with 48.0% (5.29) at the first time period, and 43.2% (15.58) compared with 47.8% (5.45) at the second time period) (Figure 5.2.7.). However, this difference was not significant ($F(1,8)=0.01$; ns). The degree of sweating for the methadone patients decreased after the methadone dose, while that of the controls was relatively stable. This was confirmed with a significant main effect for time ($F(1,8)=8.43$; $p<0.01$), and a significant interaction effect between group and time ($F(1,8)=7.71$; $p<0.01$).

Figure 5.2.7: Mean sweating (%) of methadone patients (n=5) and non-opioid using controls (n=5).

Both groups had the same mean pain threshold at the first time period (26.8 volts s.d.=3.63 for patients and s.d.=6.42 for controls) (Figure 5.2.8.). However, the pain threshold for the methadone patients after the methadone dose increased to 34.4(7.27) volts whereas the pain threshold for the controls decreased slightly to 22.4 (4.34) volts. There were no significant main effects for group ($F(1,8)=3.42$; ns) or time ($F(1,8)=1.23$; ns), while there was a significant interaction effect ($F(1,8)=17.31$; $p<0.001$), confirming a significant difference between the groups in the temporal variation of pain threshold.

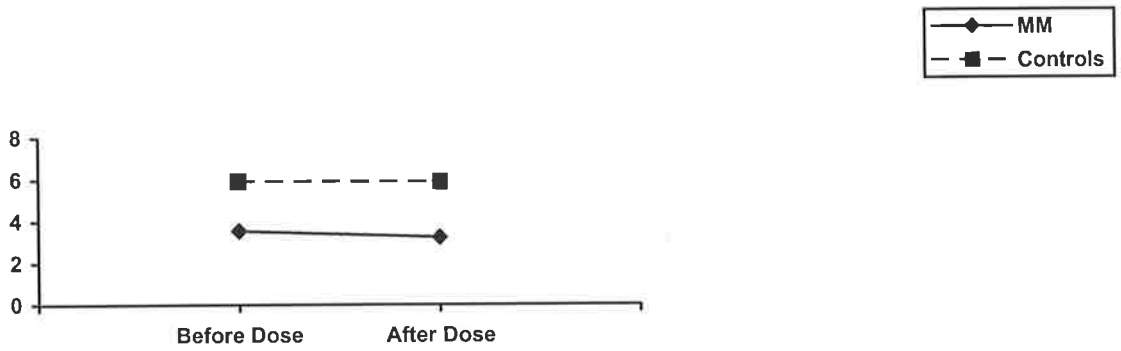
Figure 5.2.8. Mean pain threshold (Volts) of methadone patients (n=5) and non-opioid using controls (n=5).



The mean pupil size of the methadone patients was consistently smaller than the controls at both time periods ($F(1,6)=21.78$; $p<0.001$) (Figure 5.2.9.). The mean pupil size decreased after the methadone dose (3.53(1.15)mm before dosing compared with

3.23mm(1.01) after dosing), and remained stable for the controls (5.90(1.49)mm at time one and 5.90(0.53) at time two), however this temporal pattern was not significant (Time: F(1,6)=2.63; ns: Interaction: F(1,6)=2.63; ns) .

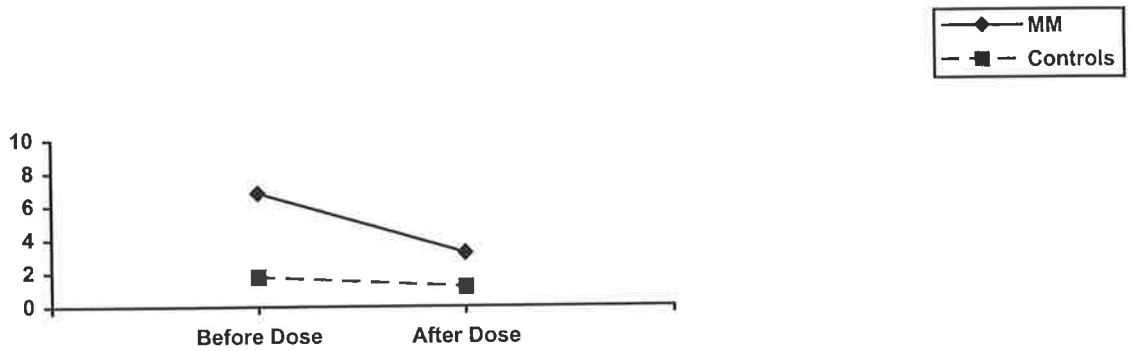
Figure 5.2.9. Mean pupil size (mm) of methadone patients (n=3) and non-opioid using controls (n=5).



5.2.4.3. Profile of Mood State comparisons between methadone patients and non-opioid using controls.

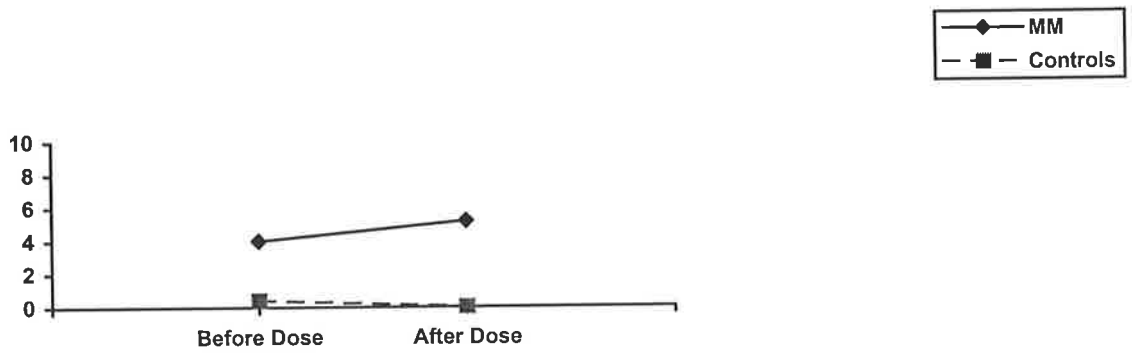
Methadone patients reported significantly greater Tension than controls at both time periods (mean of 6.80(4.09) compared with 1.80(1.30) at the first time period, and 3.20(2.39) compared with 1.20(1.09) at the second time period: $F(1,8)=14.41$; $p<0.001$) (Figure 5.2.10.). Methadone patients' scores on the scale decreased after the methadone dose, whereas those of the controls remained relatively stable. However, there was no significant main effect for Time ($F(1,8)=2.63$; ns) nor an interaction between group and time ($F(1,8)=1.34$; ns).

Figure 5.2.10. Mean scores on the Tension subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).



A similar pattern was found for Depression (Figure 5.2.11) (mean of 4.00(4.85) compared with 0.40 (0.56) at the first time period, and 5.20(4.40) compared with 0.00(0.00) at the second time period) with a significant main effect for group ($F(1,8)=7.59$; $p<0.05$), while there was no main effect for time ($F(1,8)=0.09$; ns), nor an interaction between group and time ($F(1,8)=0.36$; ns).

Figure 5.2.11. Mean scores on the Depression subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).



Scores on the Anger subscale were very low at the first time period for both the methadone patients (mean 0.20(0.45)) and the controls (mean 0.60(0.89)) (Figure 5.2.12.). No subject in either group recorded a score for Anger at the second time period. As there was no variance at this period statistical analyses were not warranted.

Figure 5.2.12: Mean scores on the Anger subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).

The control group reported significantly greater Vigour (Figure 5.2.13.) than the methadone patients at both time periods (mean of 19.20(7.89) compared with 9.00(5.83) at the first time period, and 18.60(4.51) compared with 14.20(8.01) at the second time period: $F(1,8)=4.61$; $p<0.05$). The Vigour scores remained relatively stable for the controls, and increased after the methadone dose for the patients. However, there was not a significant main effect for time ($F(1,8)=.81$; ns), nor was there a significant interaction effect ($F(1,8)=1.29$; ns).

Figure 5.2.13. Mean scores on the Vigour subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).

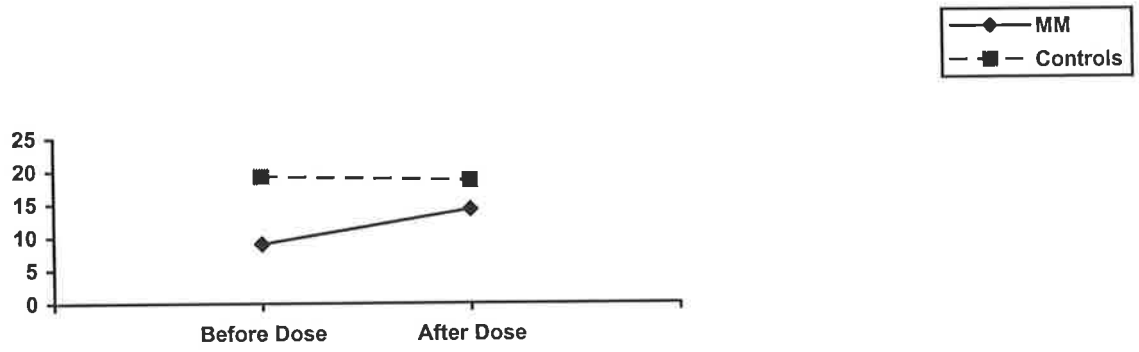


Figure 5.2.14. presents the Fatigue scores of both groups. The methadone patients reported consistently greater fatigue throughout the study period (8.00(7.18) compared

with 4.00(2.92) and the first time period, and 5.00(4.18) compared 1.00(1.41) at the second time period), although this difference was not statistically significant (F(1,8)=2.62:ns). The Fatigue scores decreased for both groups at the second time period, although there was a significant main effect for time (F(1,8)=4.87; p<0.05), there was not a significant interaction effect between group and time (F(1,8)=0.02; ns).

Figure 5.2.14. Mean scores on the Fatigue subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).

Methadone patients reported significantly greater Confusion (Figure 5.2.15.) than the controls (mean of 6.40(4.04) compared with 2.60(1.52) at the first time period, and 5.00(1.87) compared with 1.40(0.89) at the second time period: F(1,8)=12.28; p<0.001). There was no main effect for time (F(1,8)=1.44; ns), nor an interaction effect between group and time (F(1,8)=.01; ns).

Methadone patients reported significantly greater Total Mood Disturbance (Figure 5.2.16.) than the controls (mean of 16.80(16.41) compared with -9.80(11.64) at the first time period, and 4.20(16.13) compared -15.00(4.58) at the second time period: F(1,8)=12.33; p<0.001). There was no main effect for time (F(1,8)=3.04; ns), nor an interaction effect between group and time (F(1,8)=.53; ns).

Figure 5.2.15. Mean scores on the Confusion subscale of the POMS for methadone patients (n=5) and non-opioid using controls (n=5).

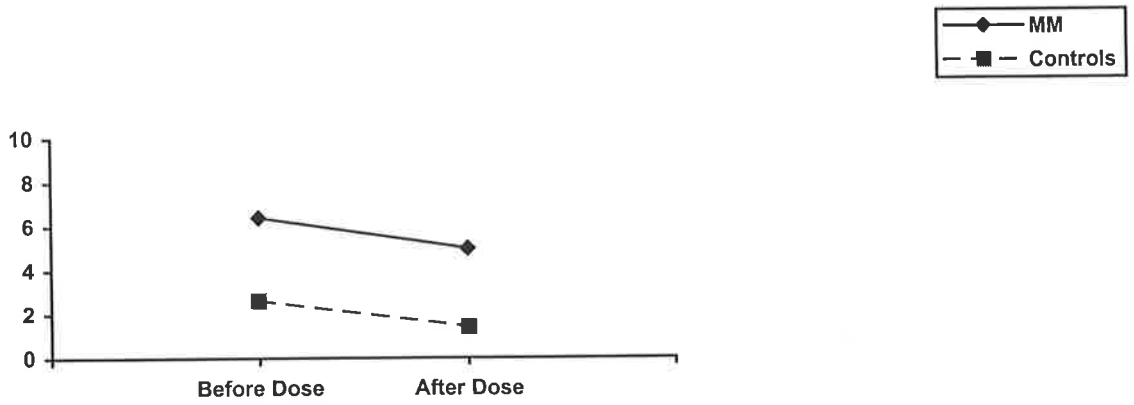
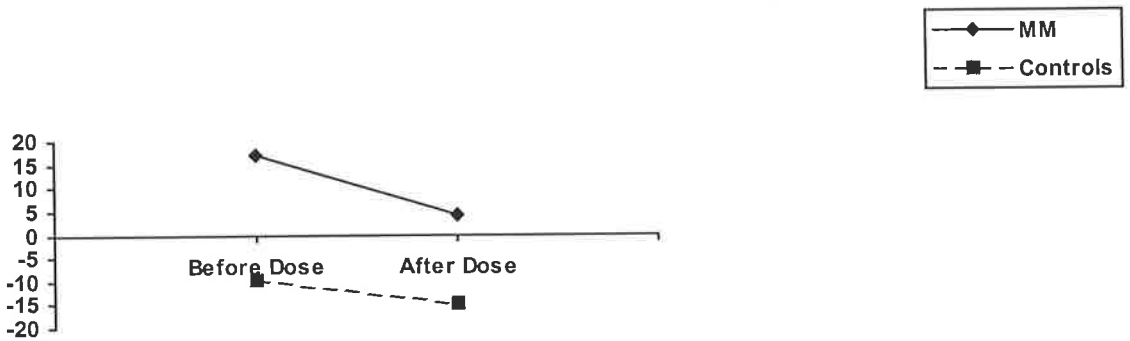


Figure 5.2.16. Mean scores on the Total Mood Disturbance composite scale for methadone patients (n=5) and non-opioid using controls (n=5).



5.2.5. Summary of pilot study

The primary aim of this pilot study was to determine the utility of various measures of the physiological effect of methadone administration. When compared with non-opioid using controls, it was found that methadone patients exhibited significantly higher skin temperature and significantly lower pupil size. Although not significant between the groups, methadone patients exhibited lower blood pressure and heart rate than controls. In contrast to the relatively stable degree of sweating and pain threshold of the controls, the methadone patients displayed a significant decrease in the degree of sweating and a

significant increase in pain threshold after dosing. These physiological differences were consistent with greater degree of subjective opioid withdrawal and the greater change in subjective opioid effect reported by the methadone patients. The degree of these physiological effects, and the direction of change in these effects, measured in methadone patients were in accord with the work of Aylett (1982), Gritz and colleagues (1975) and McCaul and colleagues (1982). Thus, the findings of this pilot study have confirmed the hypothesis that the physiological responses measured in this study are able to differentiate methadone patients from non-opioid using controls.

When assessing the effect of methadone administration within the methadone patients, it was found that blood pressure, heart rate, sweating and pupil size decreased after methadone administration, consistent with the reduction of withdrawal symptoms and negative mood states. In contrast to the work of McCaul and colleagues (1982), who reported that skin temperature increased by 5°F within 90 minutes of methadone dosing, it was found in this study that skin temperature decreased by 2°C 60 minutes after dosing, although this change was not significant. Although caution is warranted in drawing conclusions from a small sample size and time-frame, there are a number of possible reasons for this discrepancy. It may be the case that there is a potential for measurement error when measuring skin temperature due to factors such as ambient room temperature, the degree of sweating associated with opioid withdrawal or individual differences. Nevertheless, the methadone induced effect upon sweating in this pilot study was not statistically significant, and it was calculated that a sample size of between 8 and 12 patients would be required for statistical significance.

Pain threshold was shown to increase after methadone administration, consistent with an increased subjective opioid effect. As such it appears that this physiological measure has utility as a physiological measure of methadone effect. All of the remaining

physiological changes were in hypothesised directions, and were largely in accord with the work of Aylett (1982), Gritz and colleagues (1975) and McCaul and colleagues (1982). However, only reduced sweating and increased pain threshold reached statistical significance. Calculations indicated that a sample size of between 8 and 30 participants will be required to provide sufficient statistical power for determining group differences among these methadone responses.

One problem identified in this pilot study was the use of a Polaroid camera to measure pupil size. In this study, the pupil size of patients remained relatively stable after methadone administration. This was in contrast to the findings of McCaul and colleagues (1982) who reported a reduction in pupil size of 1.25mm 90 minutes after dosing, and Inturrisi & Verebely (1972) who reported a reduction of 1.5mm from 4 to 6 hours after dosing. It is likely that this discrepancy was a result of the use of the Polaroid camera. The photographs produced from this camera were not of sufficient clarity to allow reliable measurement of the pupil size of patients with dark brown eyes. As such, it was decided that for the main experiment videotaped images of the eye would be used for pupil size measurement. Although this technique was not used in the reviewed literature, it was decided that as videotape equipment permits changes in the brightness and contrast of images, this technique would be more suitable for patients with brown eyes.

5.3. MAIN EXPERIMENT

5.3.1. Method

5.3.1.1. Participants

Ethical approval was obtained from the Royal Adelaide Hospital Research Ethics Committee to conduct this study. The Research Review Committee of the Drug & Alcohol Services Council approved access to the methadone patients.

Participants in this study were recruited via advertisements placed in the methadone dispensing area of the South Australian Public Methadone Maintenance Program. Inclusion criteria were enrolment for a minimum of six months, and achievement of a stabilised daily oral methadone dose. Participants excluded from the study were those who were: 1) pregnant; 2) carrying significant illness such as HIV; 2) using benzodiazepines beyond the therapeutic range; or 4) using any other medication that may have interfered with methadone pharmacokinetics or that may have altered the responses being measured. Participants were assured that all information provided was anonymous and confidential, that they could withdraw from the project at any time, that the methadone program did not employ the researcher, and that the decision to participate would not affect their treatment regimen.

Participants in the control group were postgraduate students from the Department of Psychology at the University of Adelaide, and were age- and gender-matched with the methadone patients. They had no history of methadone treatment and had not taken any other psychoactive drug (other than alcohol, nicotine or caffeine) within one month of the study. All participants were volunteers and were reimbursed AUS$50.00 for their participation.

5.3.1.2. Procedure and measures.

Each participant was treated in exactly the same manner. Patients who met the inclusion criteria were admitted to an inpatient unit 60 minutes before their daily methadone dose was due, and remained in the unit for the subsequent 24-hour period. Upon arrival (0900), a urine sample was collected for subsequent analysis, and information was collected on current treatment regime (methadone dose level and time enrolled on the program) and general demographic factors. An 18 gauge indwelling venous catheter (Jelco™ Critikon Corp, Tampa, Fla) was inserted into a forearm vein and kept patent with a Teflon stylet (Jelco™). A 5mL blood sample was collected to ascertain pre-dose methadone plasma concentration. The blood sample was centrifuged and the plasma was stored at -20° C until assay for racemic methadone concentrations. Measures were then made using the following tests:

Subjective measures:

1. Self-report Opioid Withdrawal

The Opioid Withdrawal Scale (OWS) included 16 opioid withdrawal symptoms that were extracted from the Short Opiate Withdrawal Scale (Gossop, 1990) and the Subjective Opiate Withdrawal Scale (Handelsman et al., 1987)(see Appendix 6). Symptoms in the OWS were: nausea, stomach cramps, muscle spasms, cold flushes, heart pounding, tense muscles, bone/joint aches and pains, yawning, teary eyes, runny nose, gooseflesh, sweating, hot flushes, restlessness, feelings of weakness and salivation. A four category Likert type scale was used from none (0) to severe (3). The maximum score for withdrawal symptoms was 16, and withdrawal severity was 48.

2. *Self-report Positive Opioid Effect*

The Morphine Benzedrine Group Scale of the Addiction Research Center Inventory (MBG) (Haertzen &Hickey, 1987) includes 16 items, each of which require a yes (1) or no (0) response, producing a maximum score of 16. It has been found to be a valid and reliable self-report measure of positive opioid effect. (Haertzen & Hickey, 1987).

3. *Pain Detection and Threshold*

Pain detection and threshold were measured by a stimulus applied to one ear lobe, which was delivered by an electrical stimulator (Grass model S6) generating a 10hz train of 1msec constant current. Electrode gel (Spectre 360, Parker Laboratories) was used to provide conductance between the ear lobe clip and skin. Voltage was increased at the rate of 1 volt per 1.42 seconds. Participants were instructed to apply the same interpretation of 'painful' throughout the study. A recording of voltage was taken when the participant was first aware of the stimulus (Pain Detection) and also when they perceived stimulus as intolerable (Pain Threshold).

4. *Mood State*

Data were also collected using the Profile of Mood States (POMS) (McNair et al., 1971). A description of the POMS and associated results are presented in Chapter Six.

Physiological Measures

1. Respiration, heart rate and blood pressure

Respiratory and pulse rates were measured by direct observation of the subject. Blood pressure was measured via an automatic Digital Blood Pressure and Heart Rate Monitor (OMRON model HEM-703c).

2. Skin Temperature and Sweating

Skin Temperature and sweating were measured via an ambulatory device incorporating solid state temperature (°C) and humidity (%) sensors, designed by the Department of Clinical & Experimental Pharmacology, and produced by the Department of Medicine at the University of Adelaide.

3. Pupil Diameter

Pupil diameter was recorded via a videotaped image of the eye using a Super-VHS camera (Panasonic Model NV-MS4A). Images were taken under constant illumination of 150 lux, measured via a Luxmeter (RS Components Ltd., Model 610-815). A small measuring scale was attached above the eyebrow for reference. Three images of the pupil were printed via a standard video printer in a 30-second period, and the mean pupil size was recorded.

4. Salivation

After rinsing with tepid water, participants were asked to chew on a $2cm^2$ piece of parafilm for two minutes and to expectorate the saliva into a pre-weighed plastic tube. The weight of the saliva was taken as a measure of salivation.

The normal daily dose of methadone was then administered as a syrup under supervision of the researcher. A five mL blood sample was collected at the following times after dosing: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 12 and 23 hours, resulting in a total of 13 blood samples (70mL in total) over the 24-hour inter-dosing interval. Participants were monitored at all times for discomfort arising from the venous catheter and for phlebothrombosis or thrombophlebitis. The withdrawal scores, physiological and subjective opioid effects were measured at the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 9, 12 and 23 hours, resulting in a total of 11 measurement times. These times coincided with the corresponding blood sampling times. The control subjects were also tested over a single 24-hour period. The control group did not undergo the pharmacokinetic studies or receive methadone, but were treated in the same manner as the patients in all other respects.

5.3.1.3. Plasma methadone concentration analysis

Plasma methadone concentration analyses were conducted by a researcher at the Department of Clinical & Experimental Pharmacology at the University of Adelaide. The following procedure was used. Racemic methadone was quantified in plasma using a reversed phase HPLC system which comprised an LC-6A pump (Shimadzu, Kyoto, Japan) delivering a flow rate of 1.0 mL/min, an LC-10A auto injector (Shimadzu), an 8 x 10 Radial Compression Module (Waters, Milford, MA, USA) containing a 100 mm x 5 mm Nova-Pak C18 4 μm cartridge (Waters) with an Alltima C18 5 μ pre-column (7.5

x 4.6 mm, Alltech, Deerfield, IL, USA), a UVIDEC-100-V spectrophotometer (Jasco, Tokyo, Japan) set at 210 nm and a DP800 data station (ICI Instruments, Melbourne, Australia). Optimal separation of the compounds was achieved with a mobile phase comprising 35% acetonitrile and 0.2% triethylamine in 50 mM NaH2PO4 with the final pH adjusted to 5.0 with orthophosphoric acid. Plasma samples (0.5 mL) and internal standard (50 μL 10 μg/mL nordextropropoxyphene in 50mM NaH2PO4) were aliquoted into 10 mL tapered bottom plastic tubes, alkalinized (0.2 mL 0.1M NaHCO3 pH 10) and extracted with 5 mL of 30:70 (v/v) diethyl ether:hexane for 15 minutes on a rotary mixer. Samples were then centrifuged (2000 x g) for 10 minutes and the organic phase transferred to a clean 10 mL tapered bottom tube containing 0.25mL phosphate buffer (50 mM NaH2PO4 pH 2.0) and vortexed for 15 seconds. Samples were then centrifuged (2000 x g) for 10 minutes and the organic phase aspirated to waste and 100 μL of the phosphate buffer was injected onto the chromatography column.

Retention times for racemic methadone and nordextropropoxyphene were 7 and 9 minutes, respectively. Quantification of racemic methadone was performed with calibration curves over the concentration range of 30-1200 ng/mL prepared in methadone-free human plasma. Inter-assay variability during the assay validation study was monitored with quality control (QC) samples prepared in duplicate at three concentrations: low (LQC, 100 ng/mL), medium (MQC, 400 ng/mL) and high (HQC, 700 ng/mL). Inter-assay inaccuracy and precision (%bias±SD, n=6) was 7.6±5.3% (LQC), 5.6±6.3% (MQC) and 3.0±2.8% (HQC). Similarly, intra-assay inaccuracy and precision (n=10) was 4.9±4.5% (LQC), 2.4±1.8% (MQC) and 4.2±3.4% (HQC). The assay was both precise and accurate at the limit of quantification (30 ng/mL) with inter-assay inaccuracy and precision (n=6) being 6.8±4.8%.

5.3.1.4. Pharmacokinetic, pharmacodynamic and statistical analyses

The area under the plasma concentration versus time curve (AUC) from 0 to 23 hours was calculated by the linear trapezoidal method. The peak and trough plasma concentrations were determined from visual inspection of the data. Peak to trough plasma concentration ratios were calculated by dividing the peak by the trough plasma concentration. The terminal half-life of methadone was not calculated in this chronic dosing study because the sampling time was substantially shorter than the necessary three half-lives to allow accurate estimation of this parameter. The rate of hourly change in plasma methadone concentration from the peak concentration until the trough concentration was calculated for each patient.

Self-identification as either a 'holder' or 'non-holder' was consistent with a median split of peak withdrawal severity for all participants and was therefore used as the independent variable. Two-way repeated measures analyses of variance were used to determine differences in the pharmacodynamic responses among methadone patients and the control subjects, and holders and non-holders. Tukey's HSD post-hoc tests were used to determine significant differences at each measurement point. It was reasoned that the initiating stimulus for withdrawal may be a period of rapid decline in plasma methadone concentration. Because of this, and because the decline in plasma concentration was not monotonic in many participants, the maximum rate of decline in plasma methadone concentration was used for each participant. The relationship between the maximum rate of decline and the number of opioid withdrawal symptoms occurring in the period after peak concentration had been reached was determined by a Pearson product-moment correlation coefficient. Student's t-test was used to detect differences in various pharmacokinetic parameters between holders and non-holders. All data were analysed using SPSS for Windows (version 6.o; Norussis, 1993).

The sigmoid Emax model was used to relate the intensity of effect, E, to the plasma methadone concentration by employing the Hill equation if the effect was greater than the baseline effect (equation 1) or an adaptation of the equation if the effect was smaller than the baseline effect (equation 2).

$$E = \frac{E_{max} x\ C^N}{EC_{50}^N + C^N} \qquad (1)$$

$$E = E_{max} - \frac{E_{max} x\ C^N}{EC_{50}^N + C^N} \qquad (2)$$

where Emax is the maximum attainable effect, C is the plasma methadone concentration, EC50 is the plasma methadone concentration which produces 50% of the maximum effect and N is the sigmoidicity or slope factor, which determines the steepness of the curve. The appropriateness of using this model for data such as ours has been discussed by Holford and Sheiner (1981). The assumptions in using this approach were that concentrations of methadone in plasma and brain were in equilibrium (since these patients were at steady state with respect to methadone dosing), that there was no discernible delay between changes in plasma methadone concentrations and the measured effects (Inturrisi et al., 1990), that tolerance to the effects had long since occurred and was stable, and that the effects were exclusively mediated by methadone, and not by an active metabolite. The equations were fitted to unweighted data, using non-linear least-squares regression analysis (Regression, Blackwell Scientific Publications, Oxford, UK) to yield estimates of EC50 and N. Where values of R^2 were statistically non-significant (i.e. $p>0.05$), data from the participant were not included. This occurred because, in some patients, the plasma concentration versus time profile was too flat and/or the pharmacodynamic responses changed relatively little over the inter-dosing interval.

5.3.2. Results.

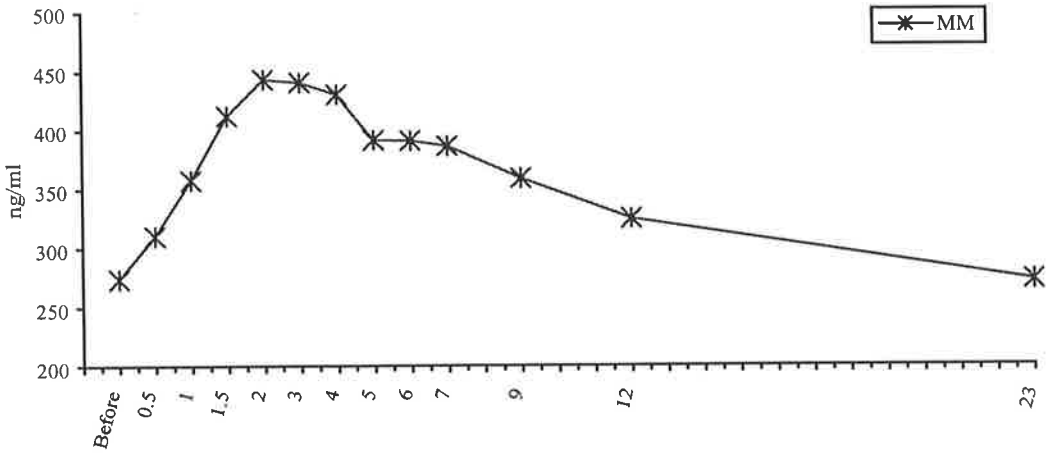
A total of 28 methadone patients agreed to participate in this study and met the inclusion criteria. Of these 29% (n=8) did not attend the scheduled testing period and either could not be contacted to arrange another time or subsequently withdrew from the study. A further 7% (n=2) were unable to participate as the general condition of their veins precluded either insertion of the indwelling venous catheter or repeated blood sampling by standard methods. Thus, data were collected from a total of 18 (64%) methadone patients, comprising nine self-reported holders and nine self-reported non-holders.

Patients had a mean age of 35.33 years (s.d. 6.82; 21-45), a mean body weight of 74.17 kilograms (s.d. 10.48, 60-94) and 61% (n=11) were male. Participants had been enrolled in the methadone program for a mean of 3.15 years (s.d. 2.85; 6mth.-10years). The mean oral daily methadone dose was 64.78 mg (s.d. 34.34; range 20-130), the mean methadone dose to body weight ratio was 0.88 mg/kg (s.d. 0.50, 0.12-1.91), and patients had not had a methadone dose change for at least two months. All patients smoked cigarettes. Although the inclusion criteria were stated clearly to the patients, subsequent urinalyses detected other drug use in 67% (n=12) of participants, with the majority of these showing a positive urinalysis result for cannabinoids (n=10), while one patient had used barbiturates and two patients had used opioids other than methadone. Seven patients were prescribed therapeutic dose levels of benzodiazepines. Four patients self-reported the regular consumption of alcohol in quantities of less than 40 grams daily.

Ten control participants (6 males and 4 females), whose ages (mean (s.d.) of 27.88 (3.55), 24-32 years) and body weight (71.60 (12.56), 54-90 kgs.) were within the range of those of the patients, also volunteered for the study. None had taken any other psychoactive drug (other than nicotine or caffeine) within two months of the study.

Changes in plasma methadone concentration over the 24-hour interdosing interval for the methadone patients are presented in Figure 5.3.1. Mean peak concentration (mean (s.d.) of 443.32 (236.11) 61.68-899.82 ng/mL) was achieved approximately 3 hours after oral administration and declined to trough concentration (271.85 (152.67), 43.57-613.75 ng/mL) slowly over the remaining hours. The mean area under the curve (AUC) was 7.80 mg.h/L (s.d. 4.35, 1.20-18.06). The mean peak-to-trough plasma concentration ratio was approximately 1.7 (mean (s.d.) 1.73 (0.29), 1.24-2.50).

Figure 5.3.1. Mean plasma methadone concentrations of methadone patients during one 24-hour inter-dosing interval (n=18).



5.3.2.1. Pharmacodynamic responses

Results from repeated measures analyses of variance, comparing the pharmacodynamic responses between methadone patients (n=18) and the controls (n=10), are presented in Table 5.3.1.

Table 5.3.1: Repeated measures analyses of variance for pharmacodynamic response during one 24-hour inter-dosing interval comparing methadone patients (n=18) with non-drug using controls (n=10).

Measure	Effect	df	F
Withdrawal Symptoms	Group	1,26	20.25 (597.37) ***
	Hours since dose	10,260	9.47 (30.10) ***
	Group X Hours since dose	10,260	9.94 (31.61) ***
Withdrawal Severity	Group	1,26	13.63 (1352.73) ***
	Hours since dose	10,260	7.15 (91.49) ***
	Group X Hours since dose	10,260	7.42 (94.85) ***
MBG	Group	1,26	4.60 (173.79) *
	Hours since dose	10,260	13.54 (53.88) ***
	Group X Hours since dose	10,260	12.05 (47.92) ***
Systolic BP	Group	1,26	0.12 (100.29)
	Hours since dose	10,260	2.49 (144.51) **
	Group X Hours since dose	10,260	0.61 (35.17)
Diastolic BP	Group	1,26	0.20 (107.39)
	Hours since dose	10,260	1.63 (86.96)
	Group X Hours since dose	10,260	1.07 (86.96)
Heart Rate	Group	1,26	17.29 (9974.79) ***
	Hours since dose	10,260	2.12 (150.49) **
	Group X Hours since dose	10,260	2.63 (186.73) ***
Respiration Rate	Group	1,26	1.75 (17.54)
	Hours since dose	10,260	4.76 (5.98) ***
	Group X Hours since dose	10,260	5.38 (6.78) ***
Saliva	Group	1,26	2.58 (22.28)
	Hours since dose	10,260	1.23 (0.45)
	Group X Hours since dose	10,260	1.37 (0.50)
Skin Temperature	Group	1,26	3.84 (91.15) *
	Hours since dose	10,260	4.08 (5.87) ***
	Group X Hours since dose	10,260	5.53 (7.95) ***
Sweating	Group	1,26	3.62 (1406.37) *
	Hours since dose	10,260	0.87 (33.28)
	Group X Hours since dose	10,260	1.94 (74.01) *
Pain Detection	Group	1,26	13.00 (3113.40) **
	Hours since dose	10,260	7.15 (62.04) ***
	Group X Hours since dose	10,260	7.80 (67.70) ***
Pain Threshold	Group	1,26	23.44 (6774.61) ***
	Hours since dose	10,260	6.70 (114.55) ***
	Group X Hours since dose	10,260	11.28 (192.92) ***
Pupil Size	Group	1,26	28.22 (188.05) ***
	Hours since dose	10,260	8.01 (1.77) ***
	Group X Hours since dose	10,260	7.04 (1.56) ***

Note: Values enclosed in parentheses represent mean square errors.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Subjective responses

The measure of opioid subjective effect, the MBG scale, was positively correlated with methadone concentration, reaching a peak 2 to 3 hours after administration (Table and Figure 5.3.2.). However, the effect was relatively short-lived, with values returning to control levels after 7 hours. There was a significant main effect between the groups ($F(1,26)=4.60$; $p<0.05$), and for time ($F(10,260)=13.54$; $p<0.0001$) as well as an interaction effect between group and time ($F(10,260)=12.05$; $p<0.0001$).

The sum of self-reported opioid withdrawal symptoms (see Table and Figure 5.3.3.), and the mean intensity of these symptoms (see Table and Figure 5.3.4.), were inversely related to plasma concentration, with peak scores on both variables achieved immediately prior to dosing. The number of withdrawal symptoms was significantly greater in the patients than in the control group at all times with the exception of 2 hours post-dosing (mean (s.d.) of 1.39 (1.46) for the patients compared with 0.60 (0.84) for the controls). There was a significant main effect between the groups ($F(1,26)=20.25$; $p<0.0001$), and for time ($F(10,260)=9.47$; $p<0.0001$), as well as a significant interaction effect between group and time ($F(10,260)=9.94$; $p<0.0001$) indicating that there was a significant difference between methadone patients and controls in the manner that withdrawal symptoms were exhibited throughout the 24-hour period.

The severity of opioid withdrawal was significantly greater at all times in the patients than in the controls and was least severe from 2 to approximately 8 hours after dosing. There was a significant main effect between the groups ($F(1,26)=13.63$; $p<0.0001$), and for time ($F(10,260)=7.15$; $p<0.0001$), as well as a significant interaction effect between group and time ($F(10,260)=7.42$; $p<0.0001$).

Table 5.3.2: Comparison of mean direct opioid effect scores, as measured by the Morphine Benzedrine Group (MBG) Scale, of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 16.

Hours since dose	Controls	Methadone
Before dose	5.60 (1.96)	3.17 (2.62) **
1	3.40 (1.58)	7.83 (4.19) ***
2	5.20 (1.03)	9.28 (3.32) ***
3	4.00 (1.49)	9.06 (4.08) ***
4	3.60 (1.27)	7.61 (3.52) ***
5	3.60 (1.27)	6.22 (3.02) **
6	3.20 (1.55)	5.33 (2.74) **
7	4.40 (1.43)	4.22 (2.94)
9	2.80 (2.15)	3.33 (2.28)
12	3.60 (2.37)	2.94 (2.31)
23	3.80 (1.30)	1.44 (1.72) *

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.2. Mean direct opioid effect scores as measured by the Morphine Benzedrine Group Scale (MBG) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval.

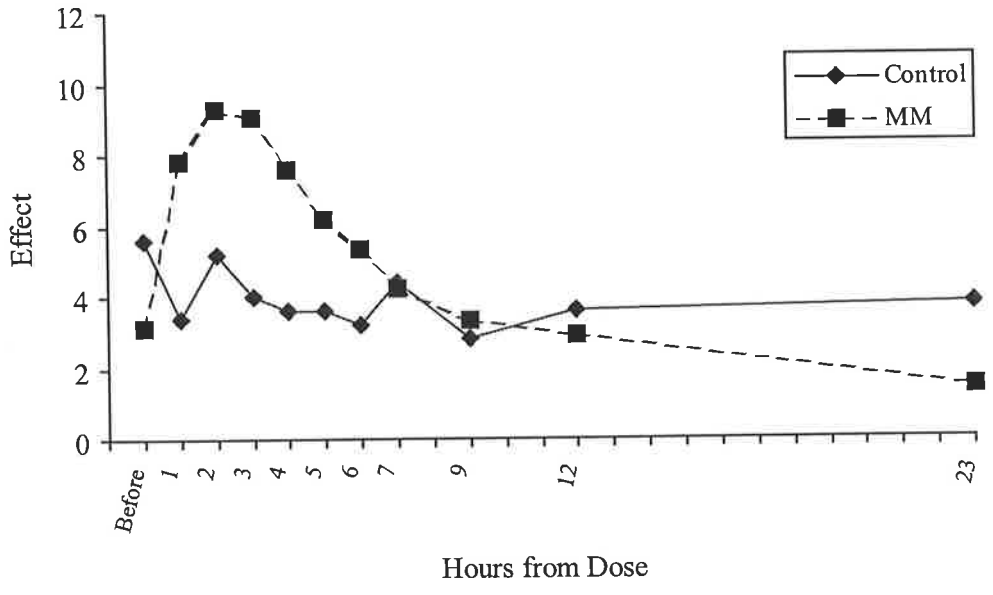


Table 5.3.3. Comparison of mean withdrawal of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 16.

Hours since dose	Controls	Methadone
Before dose	0.20 (0.42)	4.11 (3.22) ***
1	0.40 (0.52)	1.56 (1.25) **
2	0.60 (0.84)	1.39 (1.46)
3	0.00 (0.00)	1.39 (1.46) ***
4	0.00 (0.00)	1.56 (1.76) **
5	0.00 (0.00)	1.72 (1.97) **
6	0.80 (1.69)	2.39 (2.59) *
7	0.40 (0.52)	2.94 (2.96) **
9	0.20 (0.42)	4.39 (3.66) ***
12	0.20 (0.42)	5.17 (4.52) ***
23	0.20 (0.42)	8.33 (4.33) ***

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.3. Mean withdrawal symptoms of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval.

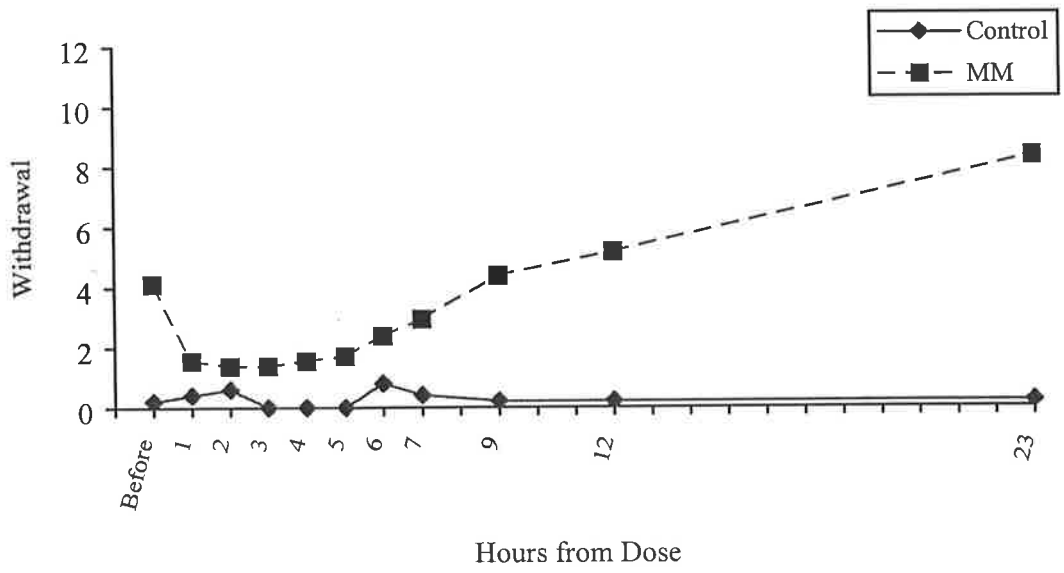
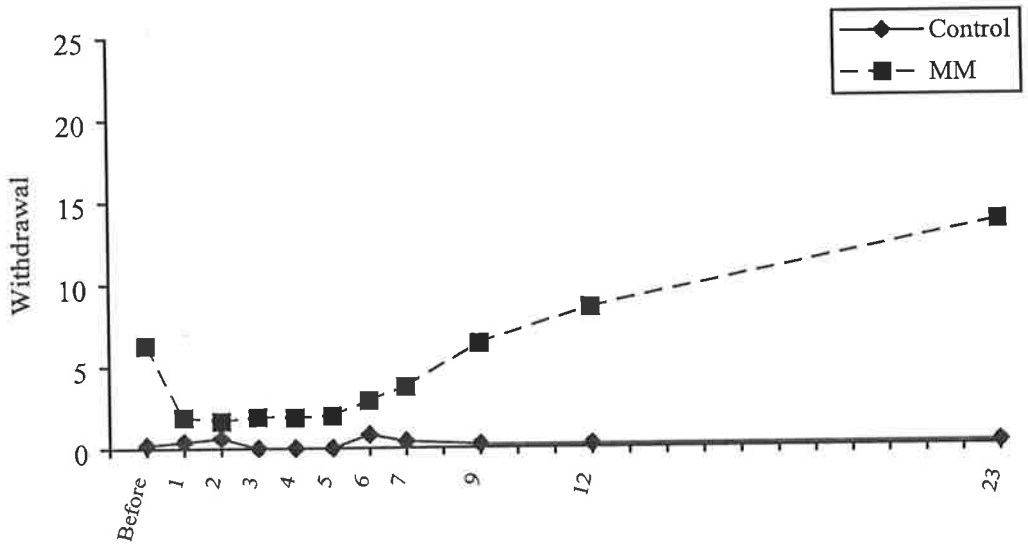


Table 5.3.4. Comparison of mean withdrawal severity of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 48.

Hours since dose	Controls	Methadone
Before dose	0.20 (0.42)	6.33 (5.47) ***
1	0.40 (0.52)	1.94 (1.70) **
2	0.60 (0.84)	1.67 (1.68) *
3	0.00 (0.00)	1.94 (2.29) **
4	0.00 (0.00)	1.89 (2.27) **
5	0.00 (0.00)	2.00 (2.50) **
6	0.80 (1.69)	2.94 (3.51) *
7	0.40 (0.52)	3.78 (4.51) *
9	0.20 (0.42)	6.39 (6.81) ***
12	0.20 (0.42)	8.56 (9.98) **
23	0.20 (0.42)	13.67 (10.68) ***

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.4. Mean withdrawal severity of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval.



The two measures derived from the electrical stimulus, threshold of detection (see Table and Figure 5.3.5.) and threshold of pain (see Table and Figure 5.3.6.), both increased following methadone administration. Although both measures were significantly different between methadone patients and controls, the greatest differences from control values were for pain threshold ($F(1,26)=23.44$; $p<0.0001$). Pain threshold was significantly increased in all patients compared with controls at all times (except just before dosing), reached a peak between 2 and 3 hours after dosing, and lasted approximately 6 hours after dosing.

Table 5.3.5. Comparison of mean pain detection of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (Volts).

Hours since dose	Controls	Methadone
Before dose	16.40 (7.23)	18.33 (5.54)
1	14.40 (4.70)	25.50 (5.98) ***
2	14.00 (4.42)	24.33 (4.72) ***
3	14.01 (4.41)	24.56 (4.64) ***
4	14.00 (4.42)	23.00 (5.62) ***
5	14.00 (4.42)	21.61 (6.15) ***
6	13.98 (4.40)	20.11 (6.15) **
7	14.40 (4.30)	18.89 (5.95) *
9	14.00 (4.41)	18.28 (7.27)
12	13.60 (4.09)	18.11 (6.74) *
23	13.60 (3.86)	16.67 (4.45)

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Figure 5.3.5. Mean pain detection of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (Volts).

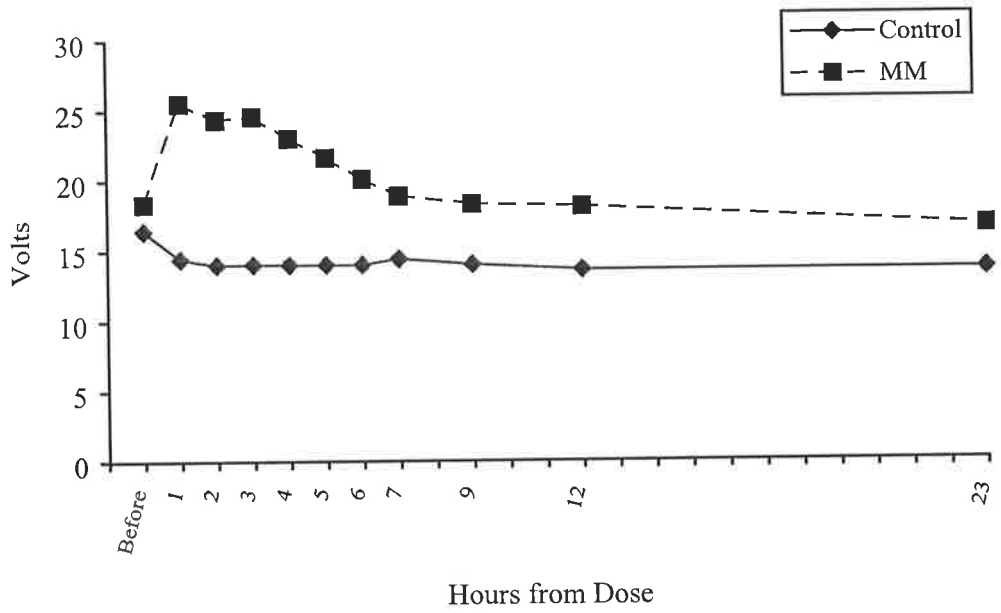
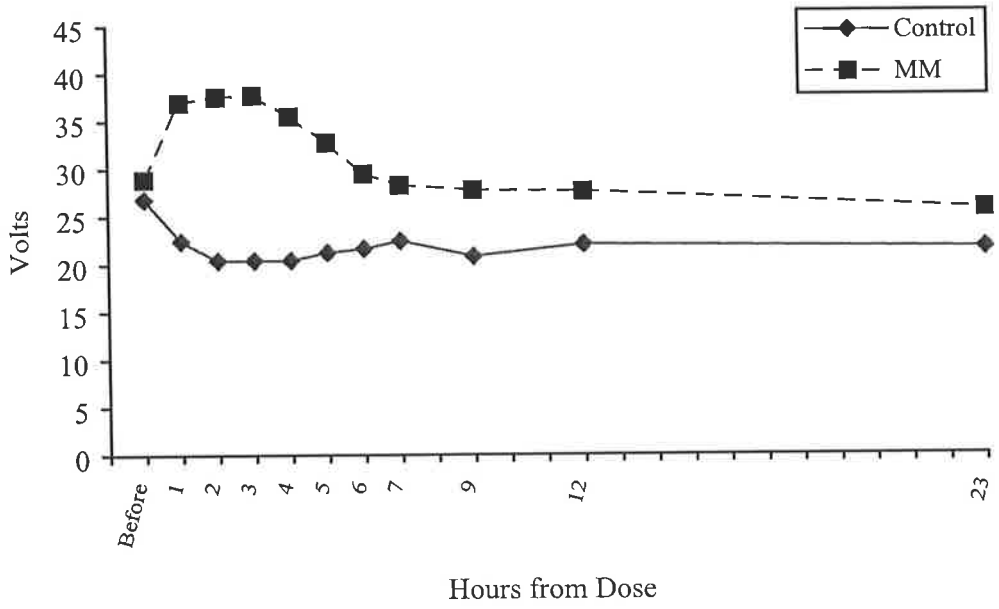


Table 5.3.6. Comparison of mean pain threshold of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (Volts).

Hours since dose	Controls	Methadone
Before dose	26.80 (6.05)	28.89 (7.39)
1	22.40 (4.09)	36.89 (6.37) ***
2	20.40 (4.08)	37.50 (7.21) ***
3	20.40 (3.37)	37.67 (7.59) ***
4	20.40 (3.38)	35.44 (10.78) ***
5	21.20 (2.53)	32.72 (8.66) ***
6	21.60 (3.09)	29.44 (7.09) ***
7	22.40 (3.37)	28.22 (7.09) **
9	20.80 (2.86)	27.67 (7.49) **
12	22.00 (1.89)	27.56 (7.15) **
23	21.60 (3.10)	25.67 (4.99) **

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Figure 5.3.6. Mean pain threshold of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (Volts)



Objective responses

There were no significant differences between the methadone patients and controls for either systolic blood pressure (see Table and Figure 5.3.7.) or diastolic blood pressure (see Table and Figure 5.3.8.) at any time point. However, there was a main effect for time for systolic blood pressure ($F(10,260)=2.49$; $p<0.01$) with the highest values for both patients and controls occurring approximately 1 hour after dosing (mean (s.d.) of 121.17(13.06) mmHg for patients and 125.00(9.04) mmHg for controls). Lowest systolic blood pressure for patients (115.89 (11.41) mmHg) and controls (115.40 (12.80) mmHg) occurred approximately 4 hours after dosing.

Table 5.3.7.. Comparison of mean systolic blood pressure of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (mmHg)

Hours since dose	Controls	Methadone
Before dose	118.60 (8.04)	116.83 (12.51)
1	125.00 (9.04)	121.17 (13.06)
2	120.80 (7.53)	116.83 (8.47)
3	122.20 (13.83)	120.67 (13.16)
4	115.40 (12.80)	115.89 (11.41)
5	116.00 (12.20)	116.00 (13.03)
6	119.60 (11.52)	115.61 (10.94)
7	117.20 (7.58)	120.11 (12.07)
9	120.60 (4.84)	117.67 (12.61)
12	119.60 (12.94)	120.44 (14.30)
23	121.60 (10.68)	122.28 (8.48)

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.7. Mean systolic blood pressure of methadone patients (n=18) and non-opioid controls (n=10) during 24-hour inter-dosing interval. (mmHg).

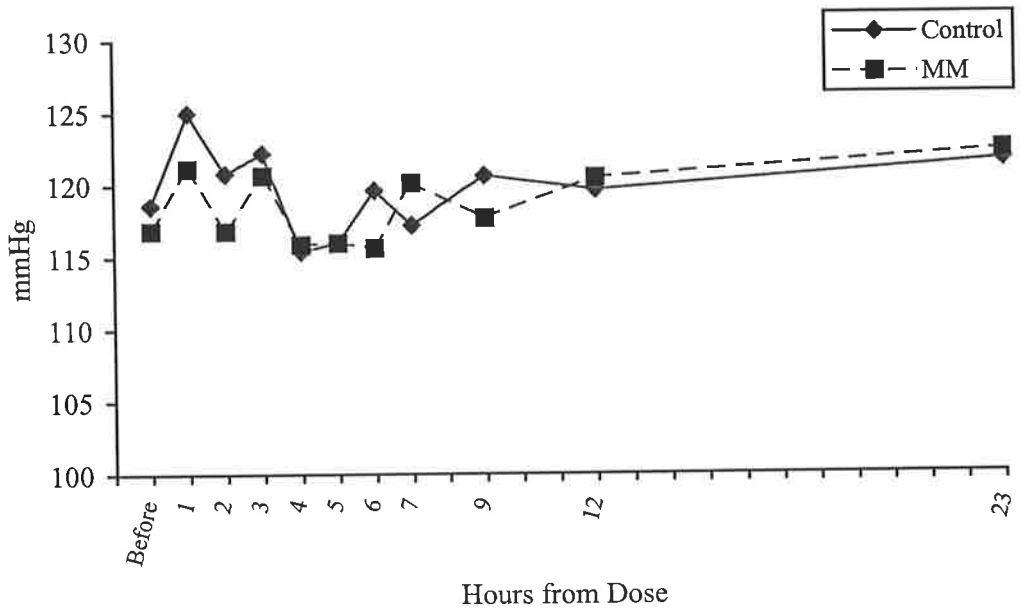
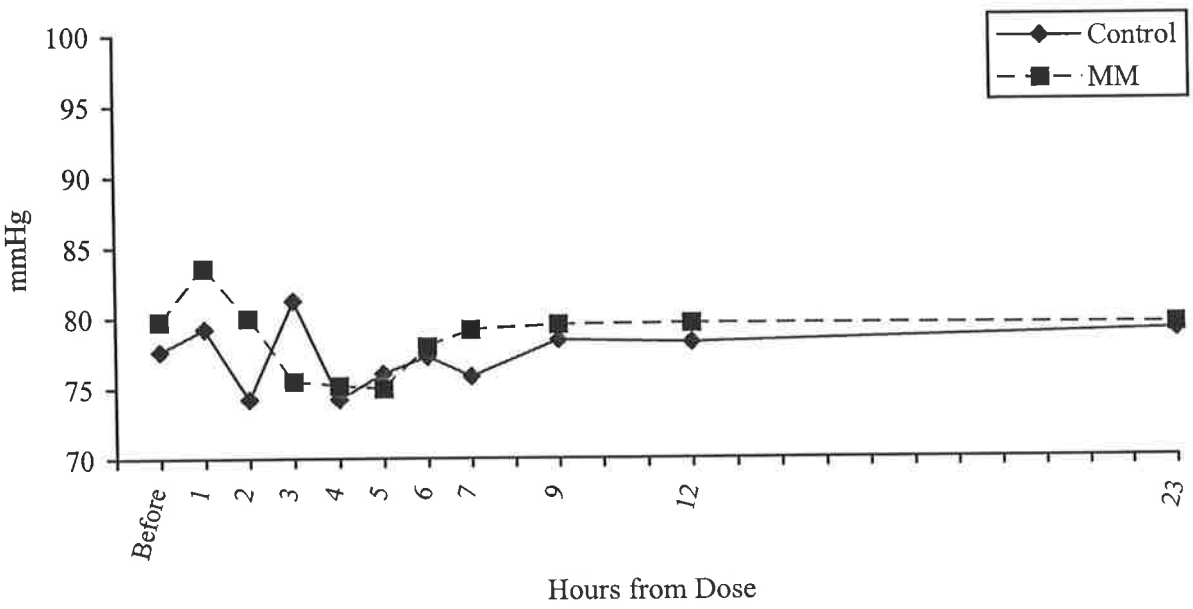


Table 5.3.8.. Comparison of mean diastolic blood pressure of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.). (mmHg)

Hours since dose	Controls	Methadone
Before dose	77.60 (3.69)	79.78 (12.25)
1	79.20 (4.34)	83.56 (14.41)
2	74.20 (6.30)	80.00 (13.07)
3	81.20 (9.56)	75.50 (9.98)
4	74.20 (4.39)	75.17 (9.43)
5	76.00 (4.62)	74.94 (6.66)
6	77.20 (8.20)	77.94 (10.96)
7	75.80 (5.47)	79.17 (12.99)
9	78.40 (6.82)	79.50 (11.06)
12	78.20 (2.94)	79.56 (9.41)
23	79.00 (5.25)	79.44 (12.89)

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.8.. Mean diastolic blood pressure of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (mmHg).



Heart rate and respiration rate both decreased after methadone administration. Heart rate was significantly slower in methadone patients at every time point except 4 and 23 hours after dosing (see Table and Figure 5.3.9.). There were significant main effects for group ($F(1,26)=17.29$; $p<0.0001$) and for time ($F(10,260)=2.12$; $p<0.01$), and a significant interaction effect between group and time ($F(10,260)=2.63$; $p<0.0001$). There was a significant reduction in the respiratory rates of the methadone patients 3 hours after dosing, while the respiratory rates of controls remained relatively stable during the 24-hour period ($F(10,260)=5.38$; $p<0.0001$). The respiratory rates of the patients were significantly faster than those in the controls before the dose and from approximately 9 hours after the dose (see Table and Figure 5.3.10.).

Table 5.3.9.. Comparison of mean heart rate of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.). (beats per minute)

Hours since dose	Controls	Methadone
Before dose	81.60 (12.52)	71.28 (14.43) *
1	82.00 (11.83)	71.06 (11.04) **
2	78.60 (16.74)	68.44 (11.77) *
3	80.20 (9.53)	67.28 (9.74) **
4	74.40 (7.91)	68.28 (9.07)
5	76.80 (10.03)	64.17 (7.35) ***
6	79.40 (8.40)	65.78 (8.27) ***
7	88.40 (13.61)	67.00 (11.15) ***
9	75.40 (7.53)	67.61 (11.04) *
12	85.80 (9.81)	65.11 (8.78) ***
23	77.60 (6.98)	73.56 (13.95)

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Figure 5.3.9.. Mean heart rate of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (beats per minute)

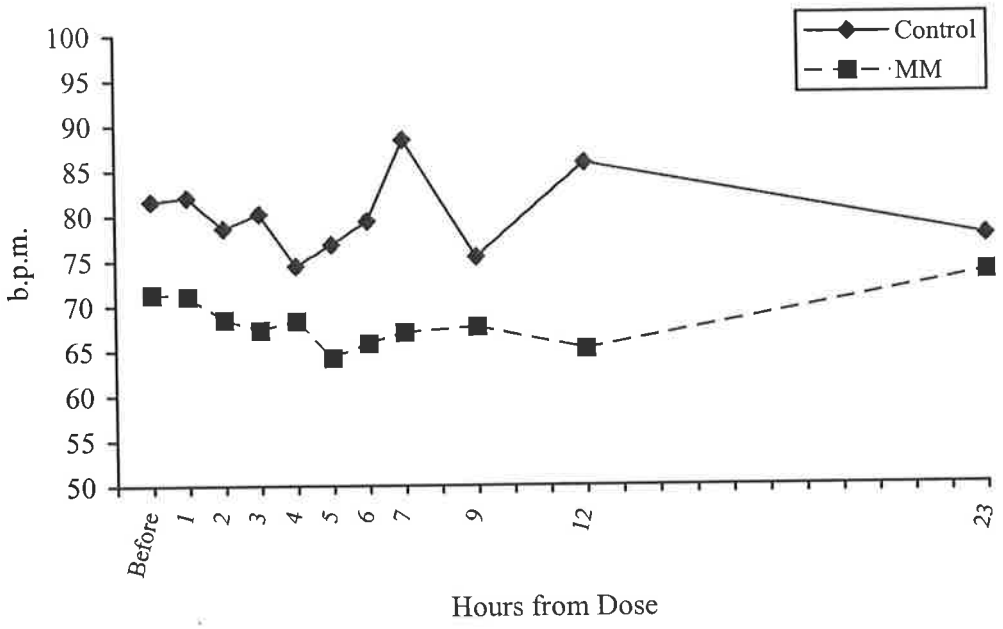


Figure 5.3.10. Mean respiration rate of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (breathes per minute)

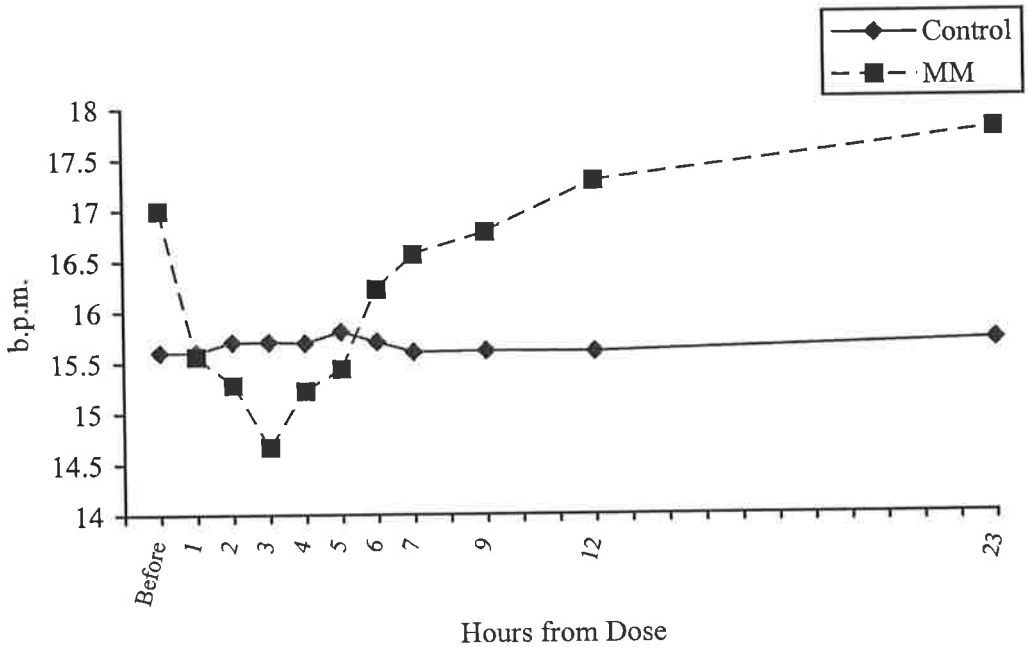


Table 5.3.10. Comparison of mean respiration rate of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.). (breathes per minute)

Hours since dose	Controls	Methadone
Before dose	15.60 (0.52)	17.00 (2.06) **
1	15.60 (0.52)	15.56 (1.34)
2	15.70 (0.48)	15.28 (0.83)
3	15.70 (0.48)	14.67 (1.09) ***
4	15.69 (0.47)	15.22 (1.48)
5	15.80 (0.42)	15.44 (1.50)
6	15.70 (0.48)	16.22 (2.07)
7	15.60 (0.52)	16.56 (2.38)
9	15.61 (0.51)	16.78 (1.93) *
12	15.60 (0.52)	17.28 (2.19) **
23	15.70 (0.48)	17.78 (1.52) ***

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

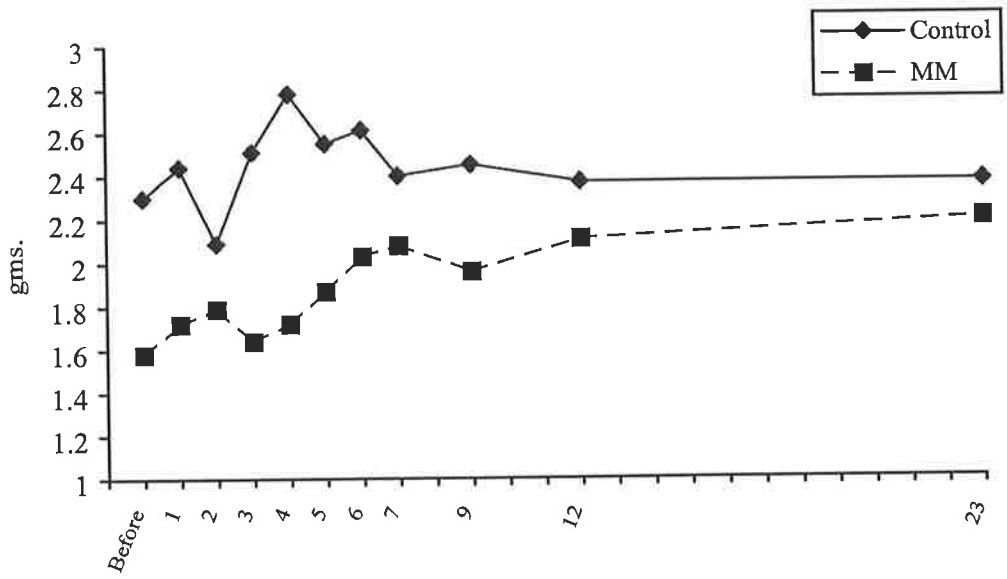
Although reduced salivation is a direct opioid effect, this measure did not show significant change over the inter-dosing interval ($F(10,260)=1.23$; $p>0.05$). However, methadone patients produced less saliva than controls during the inter-dosing interval, and these levels reached significance immediately prior to dosing, and 1, 3, 4 and 5 hours after dosing (see Table and Figure 5.3.11.).

Table 5.3.11.. Comparison of mean saliva production of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.). (grams)

Hours since dose	Controls	Methadone
Before dose	2.30 (0.50)	1.58 (1.19) *
1	2.44 (0.82)	1.72 (1.09) *
2	2.09 (0.47)	1.79 (1.07)
3	2.51 (0.87)	1.64 (0.77) **
4	2.78 (0.72)	1.72 (0.92) ***
5	2.55 (0.41)	1.87 (1.28) *
6	2.61 (0.35)	2.03 (1.58)
7	2.40 (0.72)	2.08 (1.31)
9	2.45 (0.48)	1.96 (1.12)
12	2.37 (0.85)	2.11 (1.27)
23	2.37 (0.43)	2.20 (1.60)

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.11. Mean saliva production of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. (grams)



Skin temperature and sweating remained relatively stable in the patients after methadone administration. In particular, the mean skin temperature of the controls increased throughout the 24-hour period, while remaining relatively stable in the patients ($F(1,26)=3.84$; $p<0.05$). The mean skin temperature of the patients was greater than controls until 9 hours after dosing (see Table and Figure 5.3.12). The mean degree of sweating by the patients was significantly greater than controls between 1 and 4 hours after dosing, as well as 23 hours after dosing (see Table and Figure 5.3.13). There was a significant main effect for group ($F(1,26)=3.62$); $p<0.05$) and a significant interaction effect ($F(10,260)=1.94$); $p<0.05$).

The pupil size was significantly smaller in the patients than in the control group over the entire interdosing interval ($F(1,26)=28.22$, $p<0.0001$). There was a main effect for time ($F(10,260)=8.01$, $P<0.0001$) as well as a significant interaction effect ($F(10,260)=7.04$, $p<0.0001$). The period of greatest miosis lasted no more than approximately 10 hours (see Table and Figure 5.3.14).

Table 5.3.12.. Comparison of mean skin temperature (°C) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.).

Hours since dose	Controls	Methadone
Before dose	27.20 (1.23)	29.72 (1.67) ***
1	26.80 (2.35)	29.50 (2.46) **
2	28.40 (2.27)	29.56 (2.18)
3	28.20 (1.55)	29.83 (2.04) *
4	28.40 (1.43)	29.44 (2.23)
5	28.20 (1.23)	29.44 (2.20) *
6	28.20 (2.04)	29.61 (1.82)
7	27.40 (2.07)	29.06 (2.04) *
9	29.40 (1.43)	29.33 (1.61)
12	30.40 (1.08)	29.22 (1.17) **
23	28.80 (1.55)	29.17 (1.51)

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.12. Mean skin temperature (°C) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.).

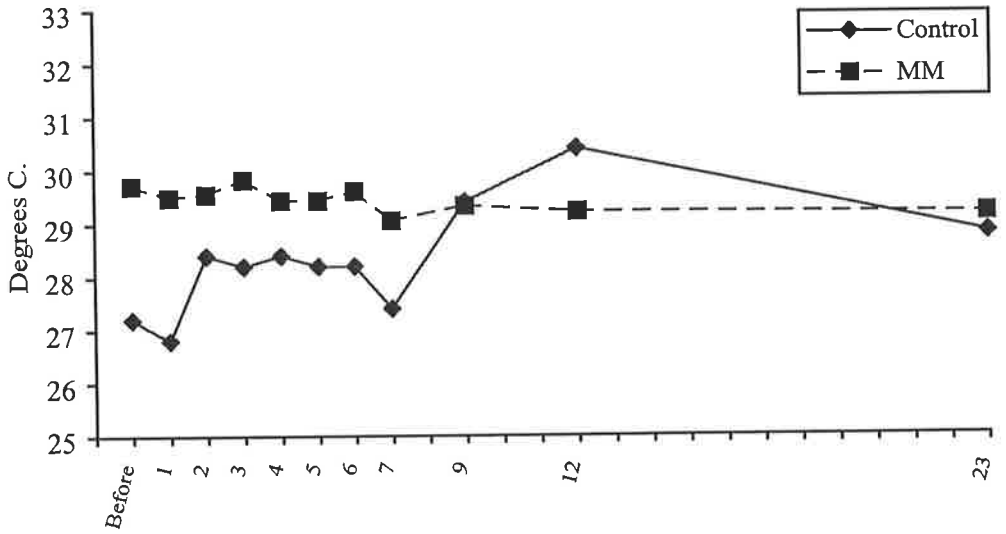


Table 5.3.13. Comparison of mean sweating (%) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.).

Hours since dose	Controls	Methadone
Before dose	46.80 (5.83)	51.39 (8.39)
1	47.80 (5.14)	54.89 (10.96) **
2	47.60 (5.36)	54.39 (10.74) *
3	48.00 (4.57)	55.94 (11.16) **
4	47.00 (4.90)	52.89 (9.95) *
5	48.00 (5.33)	51.28 (7.32)
6	52.20 (9.20)	51.83 (9.04)
7	48.20 (2.49)	52.72 (9.01) *
9	49.40 (6.10)	52.28 (8.84)
12	51.40 (4.14)	49.22 (8.89)
23	48.60 (4.55)	57.22 (9.96) **

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.13. Mean sweating (%) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval.

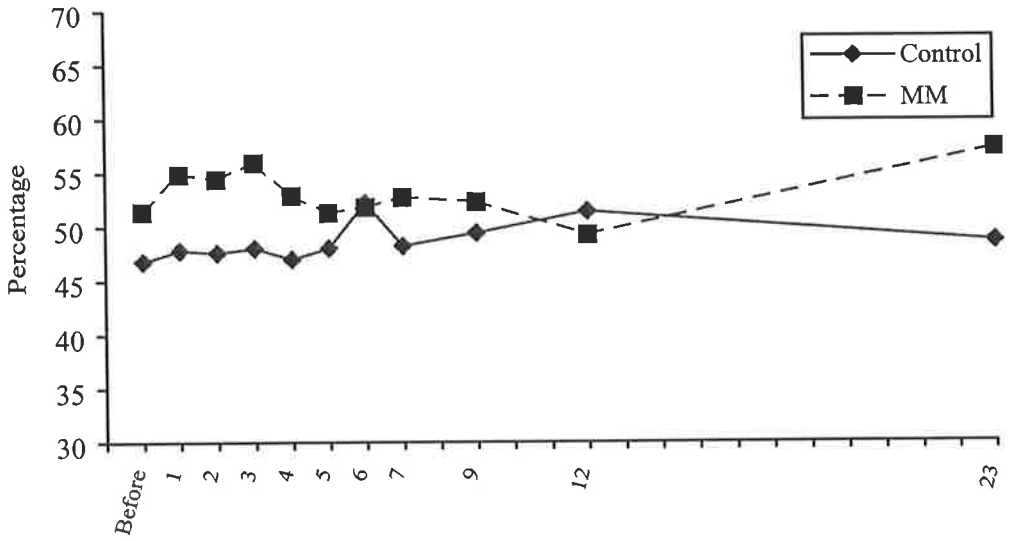
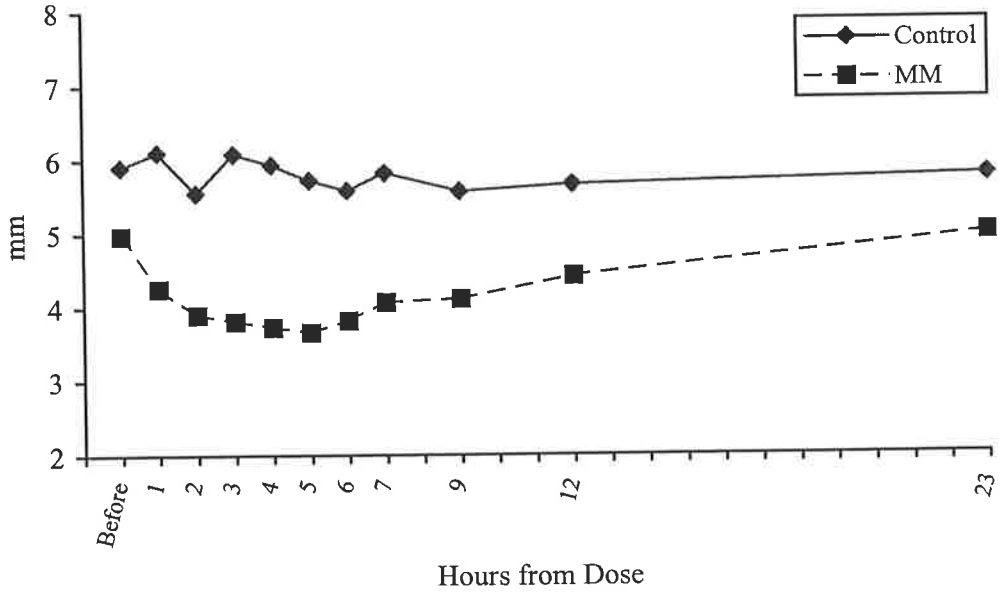


Table 5.3.14. Comparison of mean pupil size (mm) of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.).

Hours since dose	Controls	Methadone
Before dose	5.90 (0.46)	4.98 (1.15) **
1	6.10 (0.56)	4.26 (0.93) ***
2	5.55 (0.84)	3.90 (0.99) ***
3	6.08 (0.34)	3.81 (0.81) ***
4	5.93 (0.55)	3.73 (1.08) ***
5	5.72 (0.46)	3.66 (1.03) ***
6	5.58 (0.48)	3.82 (1.13) ***
7	5.82 (0.46)	4.07 (1.11) ***
9	5.57 (0.66)	4.11 (0.99) ***
12	5.66 (0.35)	4.42 (1.01) ***
23	5.77 (0.60)	4.99 (1.14) *

* p<0.05; ** p<0.01; *** p<0.001

Figure 5.3.14 Mean pupil size (mm) of methadone patients (n=18) and non-opioid controls (n=10) during 24-hour inter-dosing interval. Values are mean (s.d.).



5.3.2.2. Pharmacokinetics and comparison of holders and non-holders.

The methadone patients were subdivided into those who self-identified as regularly experiencing significant withdrawal ('non-holders') and those who did not ('holders'). Table 5.3.15 presents the demographic details of these groups. There were no significant differences between holders and non-holders with respect to age (t=0.61, n.s.), time on the program (t=-1.26, n.s.), body weight (t=-1.01, n.s.), methadone dose (t=-1.39, n.s.) or the methadone dose to weight ratio (t=-1.29, n.s.). Fisher's Exact tests did not reach statistical significance for the male to female ratio, or other drug use between the groups.

Table 5.3.15: Demographic, treatment and pharmacokinetic characteristics for Holder (n=9) and Non-Holder (n=9) groups.

	Hold (n=9)	Not Hold (n=9)
Gender (M/F; Male%)	6/3; 67%	5/4; 56%
Age (years)	36.33 ± 6.93	34.33 ± 6.96
Body Weight (kg)	71.66 ± 9.14	76.66 ± 11.66
Time on Methadone Program (years)	2.32 ± 1.76	3.99 ± 3.55
Oral Methadone Dose (mg/day)	53.77 ± 30.05	75.77 ± 36.49
Methadone dose/body weight ratio (mg/kg/day)	0.73 ± 0.36	1.03 ± 0.58
Pre-dose Plasma Concentration (ng/mL)	255.51 ± 169.53	288.18 ± 144.36
Trough Concentrations above 200 ng/mL (n; %)	6; 67%	6; 67%
Peak Concentration for each patient (ng/mL)	440.62 ± 265.78	490.91 ± 241.67
Area Under Curve (mg.h/L)	7.40 ± 4.97	8.19 ± 3.89
Peak-to-Trough Concentration Ratio (ng/mL)	1.77 ± 0.30	1.68 ± 0.29
Positive urinalyses (n; %)		
Benzodiazepines	2; 22%	5, 56%
Cannabinoids	4; 44%	6; 67%
Other opiates	2; 22%	0; 0%

Unless indicated values are mean ± SD.

Comparisons between the two groups were made on several different pharmacokinetic parameters. The mean plasma concentration versus time profiles for the holders and non-holders are plotted in Figure 5.3.15 and described in Table 5.3.16. (overall statistics for all patients are also provided for information). There were no significant differences between the groups in methadone plasma concentration at any time point. There was a significant main effect for the temporal pattern ($F(12,156)=19.42$; $p<0.0001$) of plasma concentration change. However, there was not a significant main effect for group ($F(1,13) = 0.12$; n.s.) nor was there a significant interaction effect ($F(12,156)=0.15$; n.s.).

Figure 5.3.15 Mean plasma racemic methadone concentration for methadone patients (n=18) during one 24-hour inter-dosing interval (ng/mL).

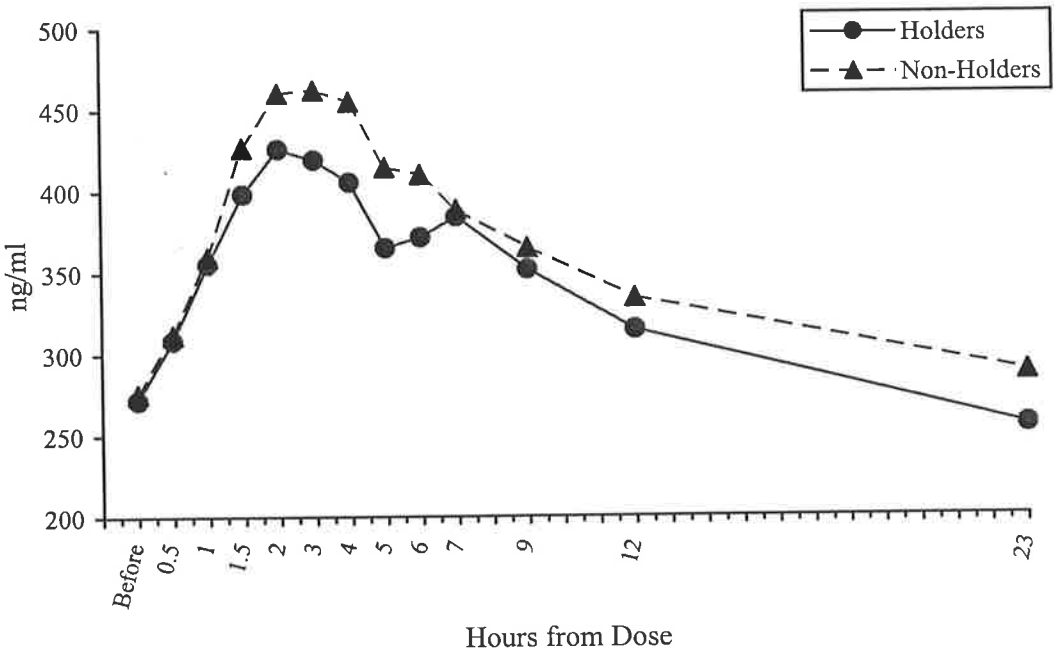


Table 5.3.16. Comparison of mean plasma racemic methadone concentration of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. (ng/mL).

Hours since dose	All Patients		Holders		Non-Holders	
	n	Mean (s.d., s.e.)	n	Mean (s.d., s.e.)	n	Mean (s.d., s.e.)
Before dose	18	273.55 (160.61, 37.86)	9	271.52 (193.02, 64.34)	9	275.58 (132.48, 44.16)
0.5	18	310.08 (172.03, 40.55)	9	308.44 (198.85, 66.28)	9	311.72 (152.79, 50.93)
1	18	357.44 (190.87, 44.99)	9	355.14 (213.76, 71.25)	9	359.74 (178.07, 59.36)
1.5	18	412.38 (215.37, 50.76)	9	398.24 (237.04, 79.01)	9	426.51 (204.77, 68.26)
2	18	443.32 (236.11, 55.65)	9	425.97 (246.21, 82.07)	9	460.68 (239.11, 79.70)
3	18	440.86 (244.69, 57.67)	9	419.35 (256.61, 88.54)	9	462.36 (235.88, 78.63)
4	18	430.51 (245.05, 57.76)	9	405.58 (272.04, 90.68)	9	455.44 (228.48, 76.16)
5 [a]	17	391.44 (235.87, 57.20)	8	365.05 (281.82, 99.64)	9	414.90 (201.11, 67.04)
6	18	390.97 (215.97, 50.90)	9	371.60 (247.91, 82.64)	9	410.33 (191.87, 63.96)
7 [a]	17	386.42 (215.69, 52.31)	8	384.15 (248.05, 87.70)	9	388.44 (197.99, 65.99)
9 [a]	17	358.77 (191.33, 46.40)	8	351.70 (220.49, 77.96)	9	365.05 (174.86, 58.29)
12	18	324.41 (189.46, 44.66)	9	314.53 (220.70, 73.57)	9	334.29 (165.36, 55.12)
23	18	271.85 (153.67, 36.22)	9	255.52 (169.54, 56.51)	9	288.18 (144.36, 48.12)

a: Blood sample not collected due to failure of indwelling venous catheter
For comparisons between Holders and Non-Holders: ✠ $p<0.05$; ✠✠ $p<0.01$; ✠✠✠ $p<0.001$

Pharmacokinetic parameters for the groups are also presented in Table 5.3.15.. The pre-dose plasma methadone concentrations ranged from 43.57 ng/mL to 613.75 ng/mL in the holders and from 99.91 ng/mL to 546.39 ng/mL in the non-holders (t=-0.44, n.s.). Peak concentrations were achieved after approximately 3 hours and were not significantly different (t=-0.42, n.s.) between the groups. The highest plasma concentration for holders ranged from 68.60 ng/mL to 980.26 ng/mL, and for the non-holders it ranged from 146.23 ng/mL to 885.49 ng/mL. There were no significant differences between the groups for the area under the curve (t=-0.37; n.s.) or the mean peak to trough plasma concentration ratio (t=0.61; n.s.). There was a significant positive correlation ($r=0.74, p<0.001$) between AUC and the weight-adjusted daily methadone dose.

5.3.2.2.1. Pharmacodynamic responses

Table 5.3.17. presents the results from the repeated measures analyses of variance comparing the various pharmacodynamic responses between the holders (n=9) and the controls (n=10). Table 5.3.18 presents the comparisons between the non-holders (n=9) and the controls (n=10), and Table 5.3.19. presents the comparisons between the holders (n=9) and the non-holders (n=9).

Table 5.3.17: Repeated measures analyses of variance for pharmacodynamic response comparing holders (n=9) with non-drug using controls (n=10).

Measure	Effect	df	F
Withdrawal Symptoms	Group	1,26	16.66 (91.23) ***
	Hours since dose	10,260	9.94 (10.90) ***
	Group X Hours since dose	10,260	10.53 (11.55) ***
Withdrawal Severity	Group	1,26	16.39 (139.50) **
	Hours since dose	10,260	9.21 (16.80) ***
	Group X Hours since dose	10,260	9.73 (17.76) ***
MBG	Group	1,26	3.58 (118.34)
	Hours since dose	10,260	8.49 (24.69) ***
	Group X Hours since dose	10,260	8.06 (23.44) ***
Systolic BP	Group	1,26	0.02 (13.50)
	Hours since dose	10,260	2.83 (161.16) **
	Group X Hours since dose	10,260	0.60 (33.84)
Diastolic BP	Group	1,26	0.16 (39.32)
	Hours since dose	10,260	2.80 (138.00) **
	Group X Hours since dose	10,260	1.88 (92.69) *
Heart Rate	Group	1,26	16.56 (9543.14) ***
	Hours since dose	10,260	1.22 (94.07)
	Group X Hours since dose	10,260	1.92 (147.39) *
Respiration Rate	Group	1,26	0.99 (4.88)
	Hours since dose	10,260	6.18 (4.01) ***
	Group X Hours since dose	10,260	6.96 (4.52) ***
Saliva	Group	1,26	0.06 (0.59)
	Hours since dose	10,260	2.20 (0.81) **
	Group X Hours since dose	10,260	1.79 (0.66) *
Skin Temperature	Group	1,26	0.72 (19.39)
	Hours since dose	10,260	2.72 (4.66) **
	Group X Hours since dose	10,260	3.37 (5.79) ***
Sweating	Group	1,26	0.73 (271.54)
	Hours since dose	10,260	1.28 (40.73)
	Group X Hours since dose	10,260	1.84 (58.61) *
Pain Detection	Group	1,26	8.15 (1828.10) **
	Hours since dose	10,260	4.60 (37.91) ***
	Group X Hours since dose	10,260	4.90 (40.41) ***
Pain Threshold	Group	1,26	18.59 (4499.73) ***
	Hours since dose	10,260	4.60 (59.34) ***
	Group X Hours since dose	10,260	7.89 (101.78) ***
Pupil Size	Group	1,26	25.39 (143.24) ***
	Hours since dose	10,260	6.78 (1.21) ***
	Group X Hours since dose	10,260	4.36 (0.78) ***

Note: Values enclosed in parentheses represent mean square errors.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 5.3.18: Repeated measures analyses of variance for pharmacodynamic response comparing non-holders (n=9) with non-drug using controls (n=10).

Measure	Effect	df	F
Withdrawal Symptoms	Group	1,26	96.35 (1048.04) ***
	Hours since dose	10,260	11.69 (39.09) ***
	Group X Hours since dose	10,260	12.15 (40.66) ***
Withdrawal Severity	Group	1,26	46.66 (26.34.85) ***
	Hours since dose	10,260	11.28 (155.36) ***
	Group X Hours since dose	10,260	11.57 (159.35) ***
MBG	Group	1,26	3.90 (138.15) *
	Hours since dose	10,260	19.42 (59.77) ***
	Group X Hours since dose	10,260	16.97 (52.23) ***
Systolic BP	Group	1,26	0.16 (182.74)
	Hours since dose	10,260	2.25 (92.12) **
	Group X Hours since dose	10,260	1.43 (58.30)
Diastolic BP	Group	1,26	0.19 (132.72)
	Hours since dose	10,260	1.70 (56.29)
	Group X Hours since dose	10,260	1.78 (59.02) *
Heart Rate	Group	1,26	10.84 (5442.53) **
	Hours since dose	10,260	2.00 (149.01) *
	Group X Hours since dose	10,260	2.00 (149.10) *
Respiration Rate	Group	1,26	2.40 (24.80)
	Hours since dose	10,260	4.43 (5.67) ***
	Group X Hours since dose	10,260	4.94 (6.33) ***
Saliva	Group	1,26	20.04 (53.79) ***
	Hours since dose	10,260	0.69 (0.17)
	Group X Hours since dose	10,260	1.60 (0.39)
Skin Temperature	Group	1,26	11.82 (143.69) ***
	Hours since dose	10,260	2.89 (4.41) ***
	Group X Hours since dose	10,260	4.17 (6.36) ***
Sweating	Group	1,26	7.97 (2294.78) **
	Hours since dose	10,260	0.90 (26.66)
	Group X Hours since dose	10,260	2.31 (68.80) **
Pain Detection	Group	1,26	11.44 (2812.92) **
	Hours since dose	10,260	8.69 (56.62) ***
	Group X Hours since dose	10,260	9.59 (62.48) ***
Pain Threshold	Group	1,26	22.37 (5509.43) ***
	Hours since dose	10,260	8.51 (122.45) ***
	Group X Hours since dose	10,260	13.58 (195.50) ***
Pupil Size	Group	1,26	24.91 (133.97) ***
	Hours since dose	10,260	8.12 (1.71) ***
	Group X Hours since dose	10,260	8.67 (1.83) ***

Note: Values enclosed in parentheses represent mean square errors.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 5.3.19: Repeated measures analyses of variance for pharmacodynamic response comparing holders (n=9) with non-holders (n=9).

Measure	Effect	df	F
Withdrawal Symptoms	Group	1,26	30.05 (494.79) ***
	Hours since dose	10,260	19.95 (85.20) ***
	Group X Hours since dose	10,260	2.51 (10.72) **
Withdrawal Severity	Group	1,26	21.78 (1483.66) ***
	Hours since dose	10,260	16.11 (259.68) ***
	Group X Hours since dose	10,260	4.40 (70.95) ***
MBG	Group	1,26	0.01 (0.73)
	Hours since dose	10,260	24.18 (129.81) ***
	Group X Hours since dose	10,260	1.79 (9.61) *
Systolic BP	Group	1,26	0.11 (92.05)
	Hours since dose	10,260	1.44 (108.21)
	Group X Hours since dose	10,260	1.02 (76.60)
Diastolic BP	Group	1,26	0.04 (26.18)
	Hours since dose	10,260	1.69 (118.53)
	Group X Hours since dose	10,260	1.79 (125.66) *
Heart Rate	Group	1,26	0.82 (543.35)
	Hours since dose	10,260	2.25 (145.17) **
	Group X Hours since dose	10,260	0.63 (40.48)
Respiration Rate	Group	1,26	0.47 (7.29)
	Hours since dose	10,260	9.69 (17.78) ***
	Group X Hours since dose	10,260	0.89 (1.64)
Saliva	Group	1,26	4.11 (40.94) *
	Hours since dose	10,260	1.67 (0.77)
	Group X Hours since dose	10,260	1.29 (0.60)
Skin Temperature	Group	1,26	1.91 (54.63)
	Hours since dose	10,260	0.90 (1.01)
	Group X Hours since dose	10,260	0.73 (0.82)
Sweating	Group	1,26	2.11 (938.19)
	Hours since dose	10,260	1.79 (96.66) *
	Group X Hours since dose	10,260	0.65 (34.86)
Pain Detection	Group	1,26	0.38 (100.41)
	Hours since dose	10,260	14.52 (171.06) ***
	Group X Hours since dose	10,260	0.50 (5.91)
Pain Threshold	Group	1,26	0.12 (48.51)
	Hours since dose	10,260	15.78 (370.92) ***
	Group X Hours since dose	10,260	1.05 (24.65)
Pupil Size	Group	1,26	0.01 (0.15)
	Hours since dose	10,260	17.32 (3.97) ***
	Group X Hours since dose	10,260	2.62 (0.60) ***

Note: Values enclosed in parentheses represent mean square errors.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Subjective responses

The different patterns of withdrawal symptomatology are presented in Table 5.3.20 and Figure 5.3.16. When compared with controls, the mean number of withdrawal symptoms were significantly greater in the holders only in the periods immediately prior to each methadone dose. In contrast, the non-holders reported significantly more withdrawal symptoms than controls at every time period. The number of reported withdrawal symptoms were consistently greater for the non-holders than the holders throughout the inter-dosing interval ($F(1,16)= 30.05$; $p<0.0001$). A similar pattern was observed for the reported intensity of withdrawal (see Table 5.3.21 and Figure 5.3.17). The non-holders consistently reported a greater intensity of withdrawal throughout the inter-dosing interval than the holders ($F(1,26)=21.78$, $p<0.0001$).

Table 5.3.22 and Figure 5.3.18. present the different patterns of positive opioid effect as measured by the MBG. There was little difference in the degree of opioid effect reported by the holders and the controls ($F\ (1,26) = 3.58$, n.s.), with the holders reporting significantly more opioid effect only during the first four hours after dosing, and significantly less effect only immediately prior to dosing. In contrast the non-holders reported significantly more direct opioid effect than the controls ($F(1,26) = 3.90$, $p<0.05$), and this was most apparent during the six hours post-dose. The non-holders reported a greater temporal variation of opioid effect than the holders during the inter-dosing interval. While there was not a main effect for group ($F(1,26) = 0.01$, n.s.), there was a significant time by group interaction effect ($F(10,260) = 1.79$, $p<0.05$), suggesting that there was a significant difference between these groups in the temporal variation of MBG score. This was most apparent 3 hours after dosing, where the non-holders reported a significantly greater MBG score.

Table 5.3.20. Comparison of mean withdrawal symptoms of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 16.

Hours since dose	Controls	Holders	Non-Holders
Before dose	0.20 (0.42)	3.00 (3.00) *	5.22 (3.19) ***
1	0.40 (0.52)	0.89 (0.78)	2.22 (1.30) *** ✠✠
2	0.60 (0.84)	0.44 (0.73)	2.33 (1.41) *** ✠✠✠
3	0.00 (0.00)	0.33 (0.71)	2.44 (1.24) *** ✠✠✠
4	0.00 (0.00)	0.22 (0.44)	2.89 (1.54) *** ✠✠✠
5	0.00 (0.00)	0.44 (0.53)	3.00 (2.06) *** ✠✠✠
6	0.80 (1.69)	0.78 (0.97)	4.00 (2.74) *** ✠✠✠
7	0.40 (0.52)	1.56 (2.19)	4.33 (3.08) *** ✠✠
9	0.20 (0.42)	2.11 (1.69)	6.67 (3.74) *** ✠✠✠
12	0.20 (0.42)	2.67 (2.40)	7.67 (4.85) *** ✠✠✠
23	0.20 (0.42)	5.11 (2.03) ***	11.56 (3.50) *** ✠✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders & Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.16. Mean withdrawal symptoms of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum possible score is 16.

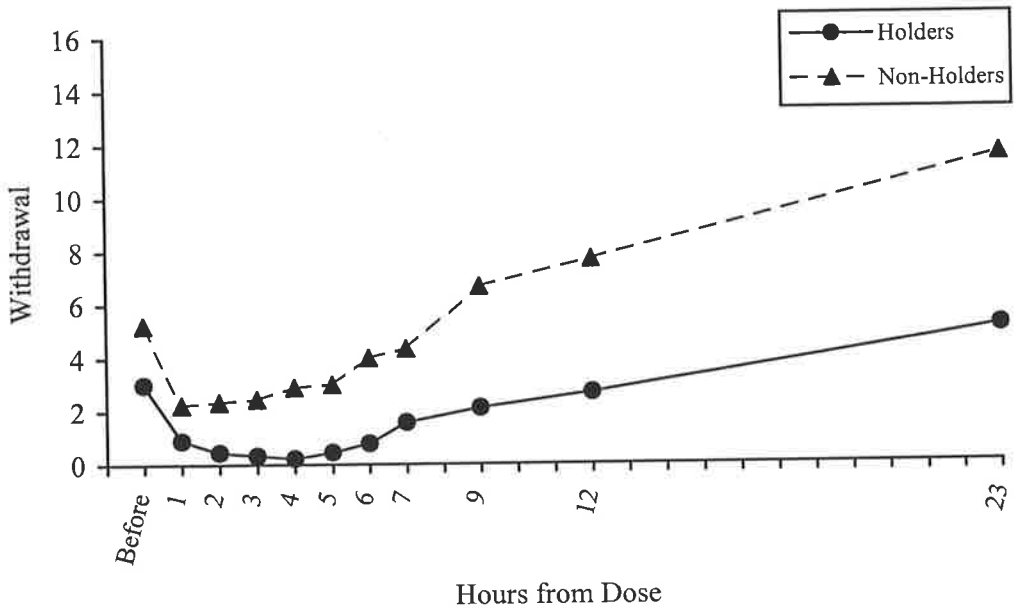


Table 5.3.21. Comparison of mean withdrawal severity of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 48.

Hours since dose	Controls	Holders	Non-Holders
Before dose	0.20 (0.42)	3.56 (3.64)	9.11 (5.73) *** ✠✠
1	0.40 (0.52)	1.11 (1.05)	2.78 (1.86) *** ✠✠
2	0.60 (0.84)	0.56 (0.88)	2.78 (1.56) *** ✠✠✠
3	0.00 (0.00)	0.33 (0.71)	3.56 (2.19) *** ✠✠✠
4	0.00 (0.00)	0.33 (0.71)	3.44 (2.24) *** ✠✠✠
5	0.00 (0.00)	0.44 (0.53)	3.56 (2.74) *** ✠✠✠
6	0.80 (1.69)	0.78 (0.97)	5.11 (3.82) *** ✠✠✠
7	0.40 (0.52)	1.67 (2.50)	5.89 (5.18) *** ✠✠
9	0.20 (0.42)	2.22 (1.72)	10.56 (7.52) *** ✠✠✠
12	0.20 (0.42)	3.78 (4.18)	13.33 (11.96) *** ✠✠
23	0.20 (0.42)	6.22 (2.73)	21.11(10.49) *** ✠✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.17: Mean withdrawal severity of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum possible score is 48.

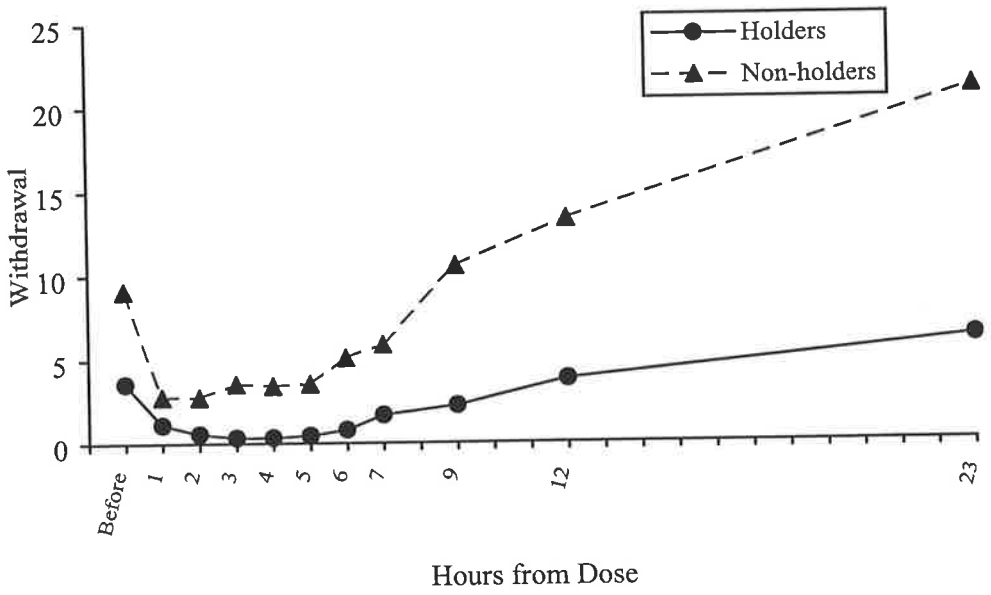
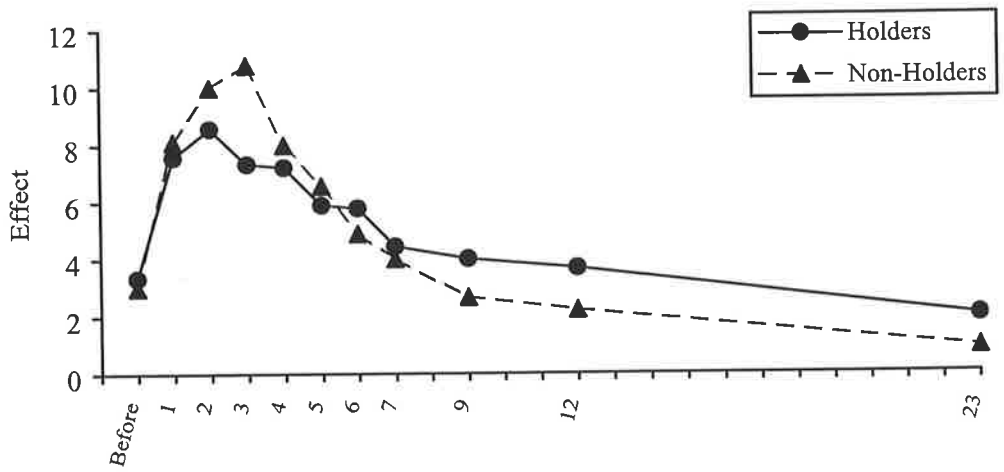


Table 5.3.22. Comparison of mean direct opioid effect scores, as measured by the MBG Scale, of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum possible score is 16.

Hours since dose	Controls	Holders	Non-Holders
Before dose	5.60 (1.96)	3.33 (2.87)	3.00 (2.50) *
1	3.40 (1.58)	7.56 (4.00) *	8.11 (4.60) *
2	5.20 (1.03)	8.56 (3.68) *	10.00 (2.96) ***
3	4.00 (1.49)	7.33 (4.12) *	10.78 (3.42) *** ✠
4	3.60 (1.27)	7.22 (3.11) *	8.00 (4.03) **
5	3.60 (1.27)	5.89 (2.37)	6.56 (3.68) *
6	3.20 (1.55)	5.78 (2.68)	4.89 (2.89)
7	4.40 (1.43)	4.44 (2.70)	4.00 (3.32)
9	2.80 (2.15)	4.00 (2.24)	2.67 (2.24)
12	3.60 (2.37)	3.67 (2.45)	2.22 (2.05)
23	3.80 (1.30)	2.00 (1.94) *	0.89 (1.36) ***

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.18. Mean direct opioid effect scores as measured by the MBG Scale of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum possible score is 16.



The measures of pain detection (Table 5.3.23 and Figure 5.3.19) and pain threshold (Table 5.3.24 and Figure 5.3.20) were significantly higher for both holders and non-holders when compared with the controls. This was most apparent for both measures between 1 and 6 hours post-methadone dose. There were, however, no significant differences between holders and non-holders for either pain detection ($F(1,26) = 0.38$, n.s.) or pain threshold ($F(1,26) = 0.12$, n.s.).

Objective Responses

There were no significant differences between the controls and either the holders or non-holders for systolic blood pressure during the 24-hour period (see Table 5.3.25 and Figure 5.3.21). Similarly the was not a significant main effect for diastolic blood pressure for the comparisons between the controls and holders ($F(1,26) = 0.16$, n.s.), controls and non-holders ($F(1,26) = 0.19$, n.s.), or between the holders and non-holders ($F(1,26) = 0.11$, n.s.)(Table 5.3.26 and Figure 5.3.22.). However, there was a significant interaction effect between time and group (holders and non-holders)($F(10,260) = 1.79$, $p<0.05$), whereby the non-holders had a significantly lower diastolic blood pressure 1 hour after dosing (77.33(10.62) mmHg compared with 89.78(15.54) mmHg) than the holders.

Table 5.3.23. Comparison of mean pain detection scores of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (Volts).

Hours since dose	Controls	Holders	Non-Holders
Before dose	16.40 (7.23)	18.22 (5.14)	18.44 (6.23)
1	14.40 (4.70)	25.11 (5.01) ***	25.89 (7.11) ***
2	14.00 (4.42)	22.89 (4.70) ***	25.78 (4.52) ***
3	14.01 (4.41)	23.33 (3.87) ***	25.78 (5.24) ***
4	14.00 (4.42)	21.44 (3.58) **	24.56 (6.98) ***
5	14.00 (4.42)	20.78 (5.38) *	22.44 (7.06) ***
6	13.98 (4.40)	19.56 (6.31)	20.67 (6.33) *
7	14.40 (4.30)	18.00 (6.08)	19.78 (6.04)
9	14.00 (4.41)	17.33 (8.94)	19.22 (5.52)
12	13.60 (4.09)	18.22 (8.03)	18.00 (5.66)
23	13.60 (3.86)	16.67 (5.29)	16.67 (3.74)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.19. Mean pain detection scores of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. (Volts).

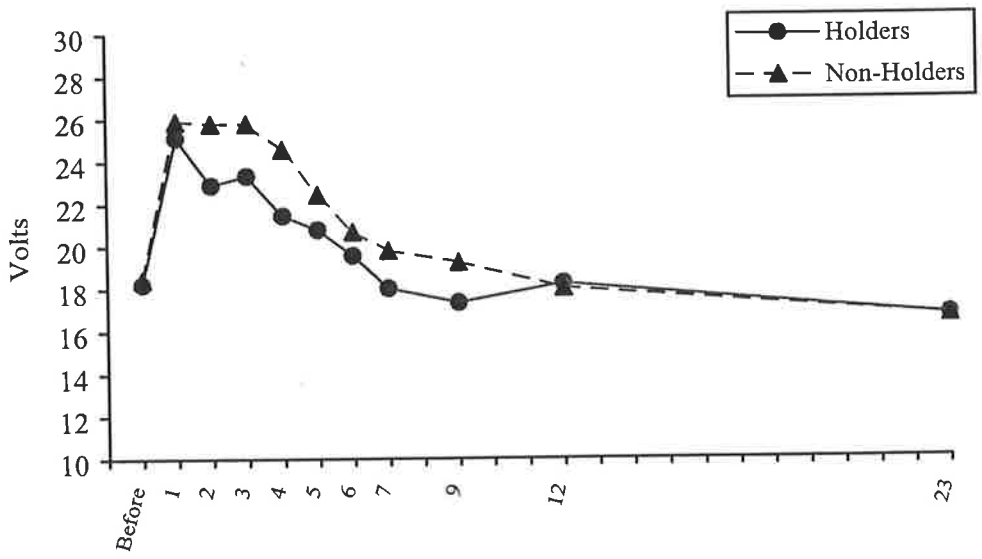


Table 5.3.24. Comparison of mean pain threshold scores of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (Volts).

Hours since dose	Controls	Holders	Non-Holders
Before dose	26.80 (6.05)	28.67 (6.48)	29.11 (8.61)
1	22.40 (4.09)	36.89 (6.64) ***	36.89 (6.49) ***
2	20.40 (4.08)	35.33 (7.55) ***	39.67 (6.56) ***
3	20.40 (3.37)	35.78 (3.80) ***	39.56 (9.99) ***
4	20.40 (3.38)	33.11 (8.19) **	37.78 (12.94) ***
5	21.20 (2.53)	32.00 (8.49) **	33.44 (9.29) ***
6	21.60 (3.09)	29.33 (8.37) **	29.56 (6.07) **
7	22.40 (3.37)	28.22 (8.33)	28.22 (6.12)
9	20.80 (2.86)	28.22 (9.62) *	27.11 (5.11)
12	22.00 (1.89)	28.89 (8.67) *	26.22 (5.43)
23	21.60 (3.10)	25.78 (5.04)	25.56 (5.25)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
Ŧ p<0.05; ŦŦ p<0.01; ŦŦŦ p<0.001

Figure 5.3.20. Mean pain threshold scores of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. (Volts).

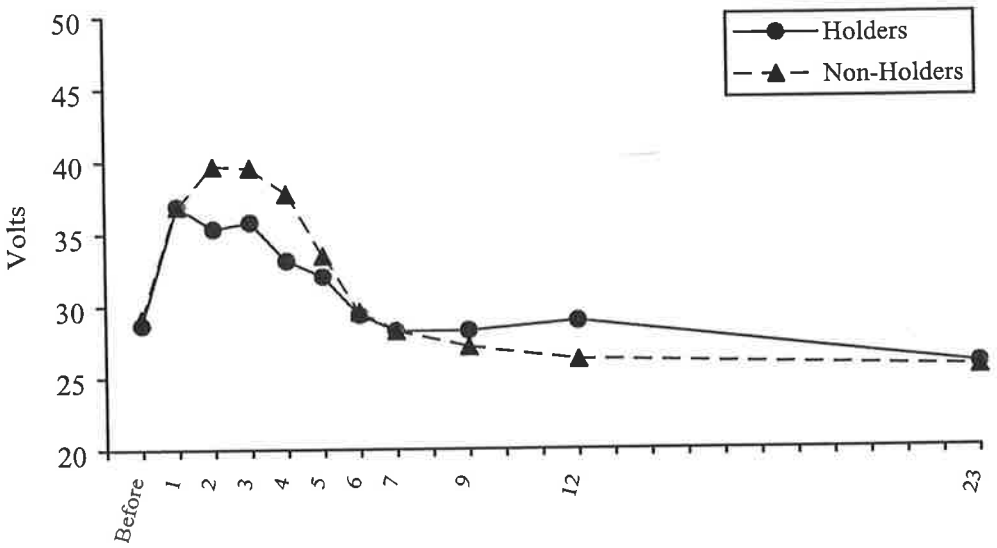


Table 5.3.25. Comparison of mean systolic blood pressure of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.)(mmHg).

Hours since dose	Controls	Holders	Non-Holders
Before dose	118.60 (8.04)	114.67 (12.19)	119.00 (13.16)
1	125.00 (9.04)	126.44 (9.77)	115.89 (14.29)
2	120.80 (7.53)	117.56 (6.27)	116.11 (10.58)
3	122.20 (13.83)	121.78 (14.16)	119.56 (12.84)
4	115.40 (12.80)	117.44 (7.23)	114.33 (14.80)
5	116.00 (12.20)	115.89 (12.35)	116.11 (14.43)
6	119.60 (11.52)	114.67 (10.71)	116.56 (11.74)
7	117.20 (7.58)	120.78 (11.55)	119.44 (13.24)
9	120.60 (4.84)	120.00 (11.45)	115.33 (13.95)
12	119.60 (12.94)	121.33 (12.39)	119.56 (16.72)
23	121.60 (10.68)	120.44 (6.64)	124.11 (10.06)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.21. Mean systolic blood pressure of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. (Volts).

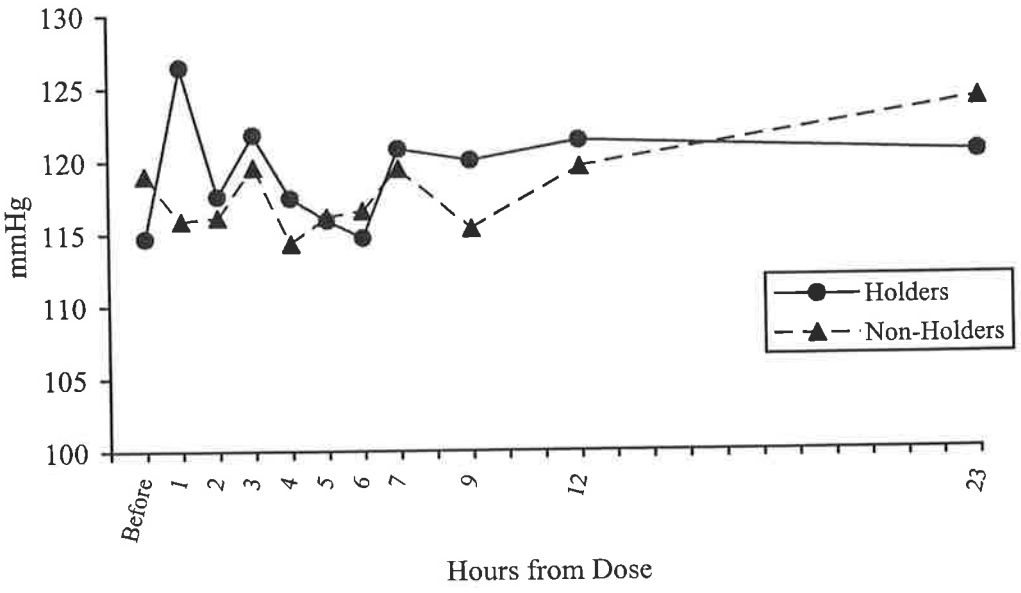
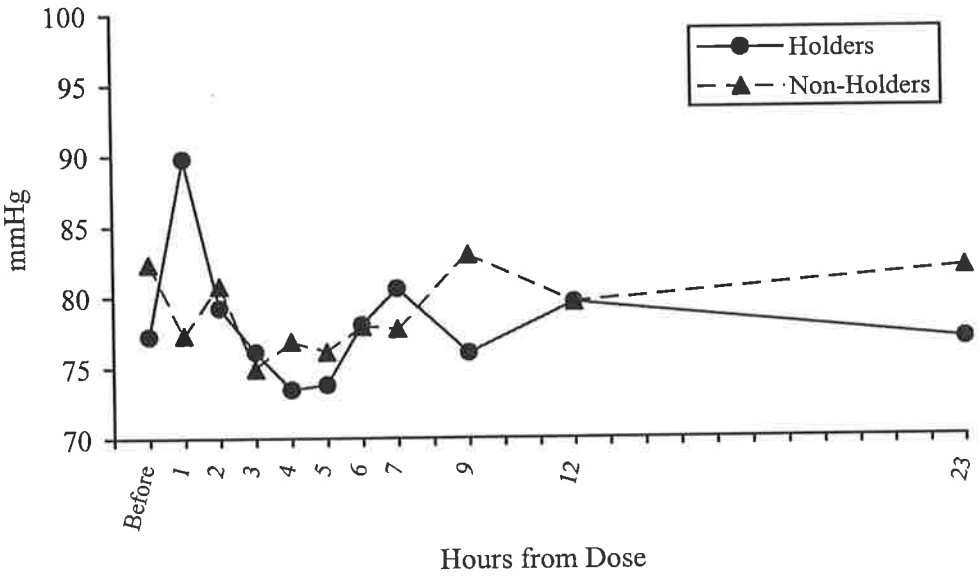


Table 5.3.26. Comparison of mean diastolic blood pressure of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.)(mmHg).

Hours since dose	Controls	Holders	Non-Holders
Before dose	77.60 (3.69)	77.22 (7.12)	82.33 (15.91)
1	79.20 (4.34)	89.78 (15.54)	77.33 (10.62) ✠
2	74.20 (6.30)	79.22 (14.33)	80.78 (12.51)
3	81.20 (9.56)	76.11 (8.85)	74.89 (11.51)
4	74.20 (4.39)	73.44 (8.28)	76.89 (10.67)
5	76.00 (4.62)	73.78 (5.63)	76.11 (7.71)
6	77.20 (8.20)	78.00 (10.70)	77.89 (11.87)
7	75.80 (5.47)	80.56 (12.56)	77.78 (14.01)
9	78.40 (6.82)	76.00 (8.75)	83.00 (12.48)
12	78.20 (2.94)	79.56 (9.00)	79.56 (10.35)
23	79.00 (5.25)	76.88 (4.26)	82.00 (17.89)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.22. Mean diastolic blood pressure of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval.(mmHg).



Heart rate decreased after methadone administration for both the holders and non-holders (Table 5.3.27 and Figure 5.3.23.). There were no significant differences between the holders and non-holders in mean heart rate at any time period. Respiration rate exhibited a similar pattern, decreasing after methadone administration for the holders and non-holders (Table 5.3.28 and Figure 5.3.24.). The respiration rate of the non-holders was significantly faster than those of the holders in the period immediately prior to methadone dosing, but respiration rates were similar for the remainder of the interdosing interval.

The saliva production of the holders and the controls were similar during the 24-hour period (Table 5.3.29 and Figure 5.3.25). However, the non-holders showed a significantly greater reduction in saliva than both the controls ($F(1,26) = 20.04$, $p<0.001$) and the holders ($F(1,26) = 4.11$, $p<0.01$). Specifically, non-holders produced significantly less saliva than the holders during the period of peak opioid effect, 2 to 6 hours after dosing.

Table 5.3.27. Comparison of mean heart rate of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (beats per minute).

Hours since dose	Controls	Holders	Non-Holders
Before dose	81.60 (12.52)	66.67 (13.12) *	75.89 (14.91)
1	82.00 (11.83)	70.56 (12.81)	71.56 (9.71)
2	78.60 (16.74)	68.33 (13.49)	68.56 (10.60)
3	80.20 (9.53)	66.33 (10.74) *	68.22 (9.18) *
4	74.40 (7.91)	68.00 (10.84)	68.56 (7.57)
5	76.80 (10.03)	63.00 (6.96) ***	65.33 (7.95) **
6	79.40 (8.40)	63.11 (8.25) ***	68.44 (7.83) **
7	88.40 (13.61)	63.78 (10.85) ***	70.22 (11.09) ***
9	75.40 (7.53)	65.89 (12.64) *	69.33 (9.60)
12	85.80 (9.81)	65.00 (11.03) ***	65.22 (6.50) ***
23	77.60 (6.98)	70.67 (11.94)	76.44 (15.88)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
Ŧ p<0.05; ŦŦ p<0.01; ŦŦŦ p<0.001

Figure 5.3.23. Mean heart rate of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (beats per minute).

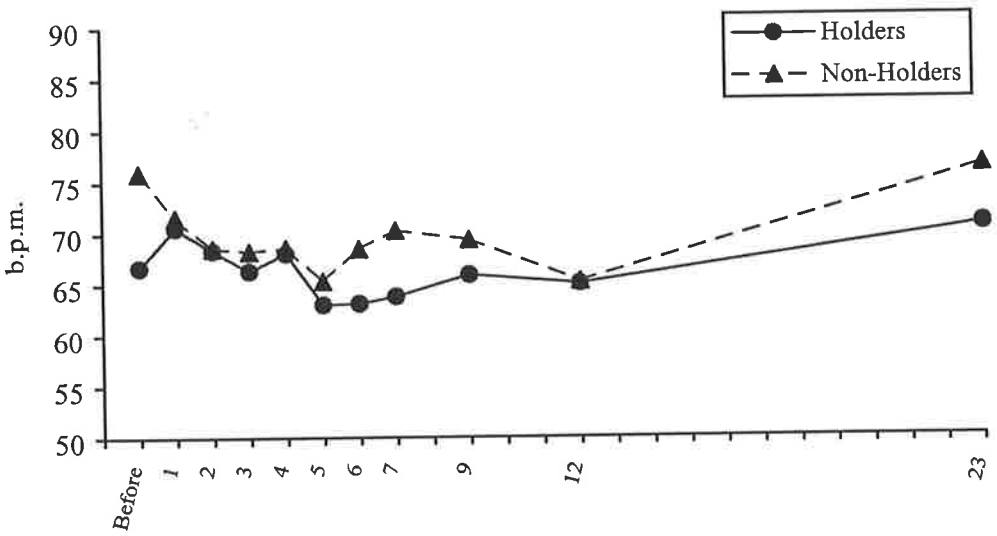


Table 5.3.28. Comparison of mean respiration rate of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (breathes per minute).

Hours since dose	Controls	Holders	Non-Holders
Before dose	15.60 (0.52)	16.11 (2.47)	17.89 (1.05) * ✠
1	15.60 (0.52)	15.11 (1.27)	16.00 (1.33)
2	15.70 (0.48)	15.44 (0.53)	15.11 (1.05)
3	15.70 (0.48)	14.67 (1.23) *	14.67 (1.00) *
4	15.69 (0.47)	15.00 (1.12)	15.44 (1.81)
5	15.80 (0.42)	15.33 (1.12)	15.56 (1.88)
6	15.70 (0.48)	15.89 (1.36)	16.56 (2.65)
7	15.60 (0.52)	16.67 (1.22)	16.44 (3.24)
9	15.61 (0.51)	16.78 (1.64)	16.78 (2.28)
12	15.60 (0.52)	17.22 (1.48) *	17.33 (2.83) *
23	15.70 (0.48)	17.44 (1.01) **	18.11 (1.90) ***

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.24. Mean respiration rate of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (beats per minute).

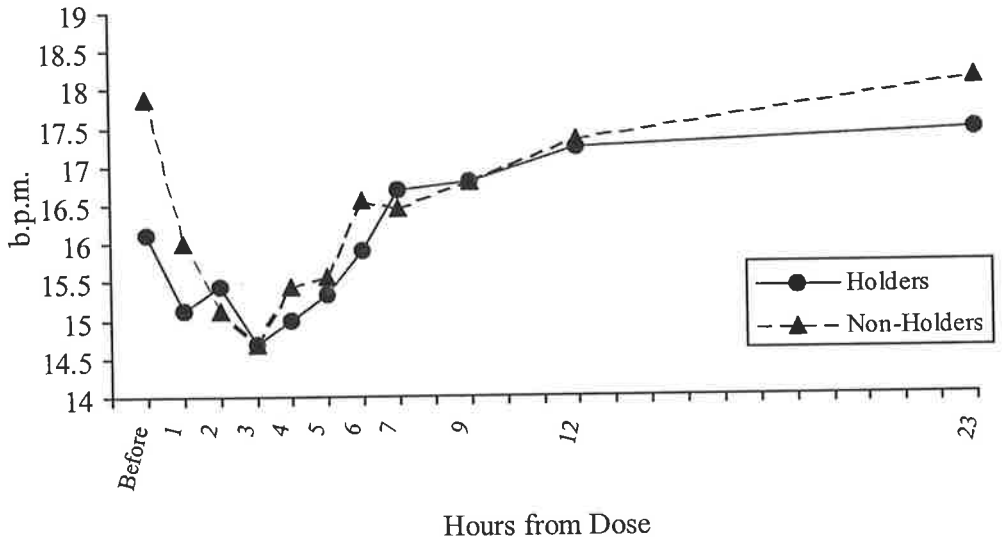
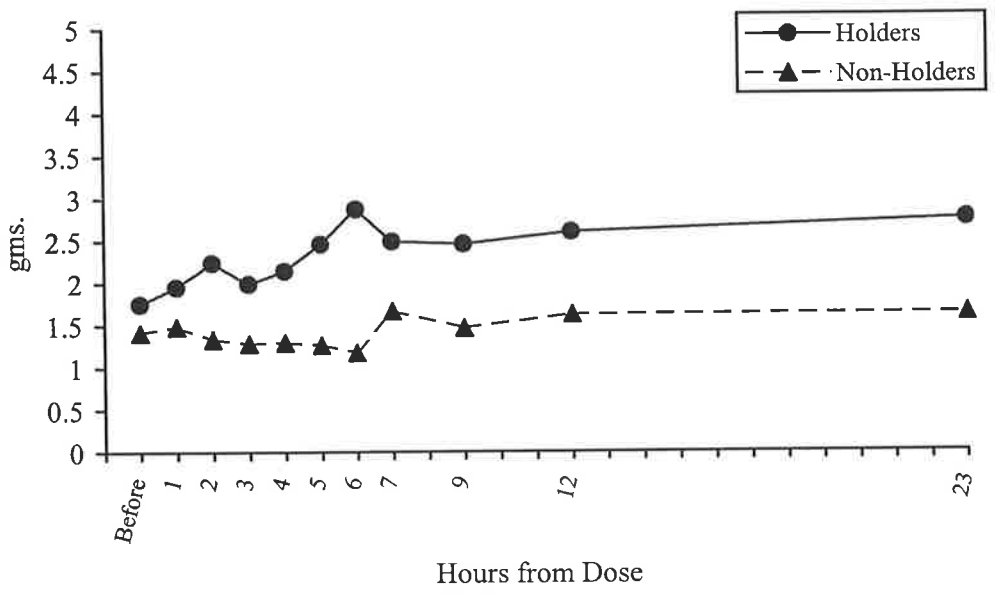


Table 5.3.29. Comparison of mean saliva production of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (grams).

Hours since dose	Controls	Holders	Non-Holders
Before dose	2.30 (0.50)	1.75 (1.42)	1.42 (0.96)
1	2.44 (0.82)	1.95 (1.14)	1.49 (1.06) *
2	2.09 (0.47)	2.24 (1.22)	1.34 (0.71) ✠
3	2.51 (0.87)	1.99 (0.83)	1.29 (0.53) * ✠
4	2.78 (0.72)	2.14 (1.13)	1.30 (0.35) *** ✠
5	2.55 (0.41)	2.46 (1.46)	1.27 (0.74) ** ✠
6	2.61 (0.35)	2.87 (1.79)	1.18 (0.69) ** ✠✠
7	2.40 (0.72)	2.49 (1.65)	1.67 (0.74)
9	2.45 (0.48)	2.46 (1.39)	1.47 (0.46) * ✠
12	2.37 (0.85)	2.60 (1.51)	1.63 (0.77)
23	2.37 (0.43)	2.75 (2.04)	1.64 (0.79)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.25. Mean saliva production of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (grams).



Mean skin temperature (Table 5.3.30 and Figure 5.3.26) and the degree of sweating (Table 5.3.31 and Figure 5.3.27) were not significantly different between the holders and non-holders. While increased sweating and skin temperature are often considered to be withdrawal symptoms, these variables did not produce a consistent pattern of change during the interdosing interval. However, when comparisons were made with the controls, there were differences between the holders and non-holders. The skin temperature of the controls increased steadily during the testing period, but decreased after methadone administration in the holders, producing a significant interaction effect ($F(10, 260) = 3.37$, $p<001$). Similarly, there was a significant time by group interaction effect for sweating between the holders and the controls ($F(10, 260) = 1.84$, $p<0.05$).

However, when comparisons were made between the non-holders and the controls, it was found that the non-holders had a significantly higher skin temperature ($F(1,26) = 11.82$, $p<0.001$). This difference was most apparent during the first 7 hours of testing, producing a significant interaction effect ($F(10,260) = 4.17$, $p<0.001$). A similar pattern was observed for sweating, whereby sweating was significantly greater in the non-holders during the testing period ($F(1,26) = 7.97$, $p<0.01$), particularly during the period from 1 to 4 hours after dosing.

Table 5.3.30. Comparison of mean skin temperature of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.)(°C).

Hours since dose	Controls	Holders	Non-Holders
Before dose	27.20 (1.23)	29.56 (2.01) **	29.89 (1.36) ***
1	26.80 (2.35)	28.89 (2.89)	30.11 (1.90) **
2	28.40 (2.27)	28.89 (2.71)	30.22 (1.30)
3	28.20 (1.55)	29.11 (2.32)	30.56 (1.51) **
4	28.40 (1.43)	28.67 (2.50)	30.22 (1.72) *
5	28.20 (1.23)	28.89 (2.76)	30.00 (1.41)
6	28.20 (2.04)	29.11 (2.21)	30.11 (1.27) *
7	27.40 (2.07)	28.44 (2.19)	29.67 (1.80) *
9	29.40 (1.43)	28.67 (1.66)	30.00 (1.32) ✠
12	30.40 (1.08)	28.89 (1.36) **	29.56 (0.88)
23	28.80 (1.55)	29.00 (2.12)	29.33 (0.50)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.26. Mean skin temperature of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (°C).

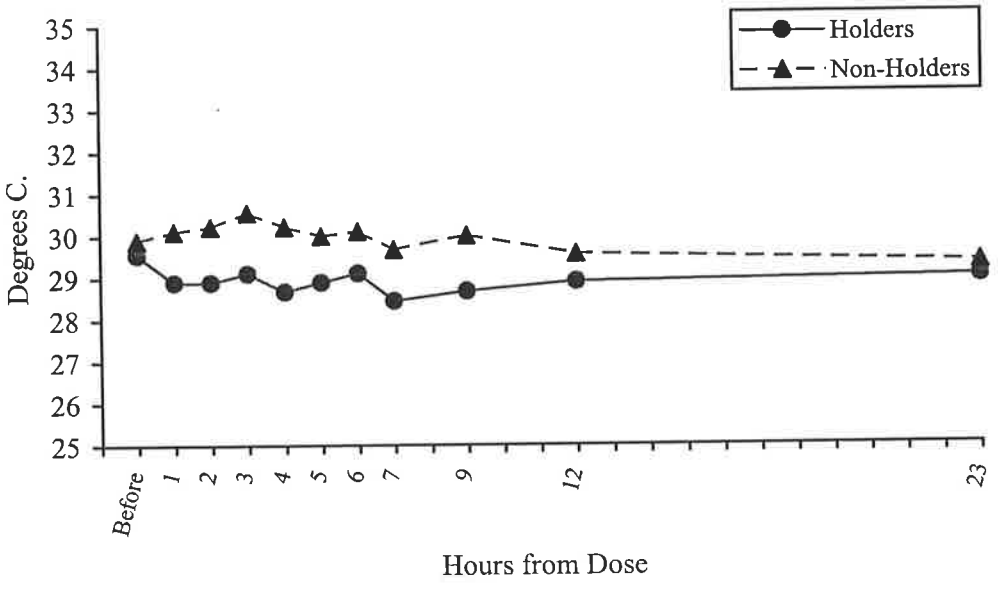
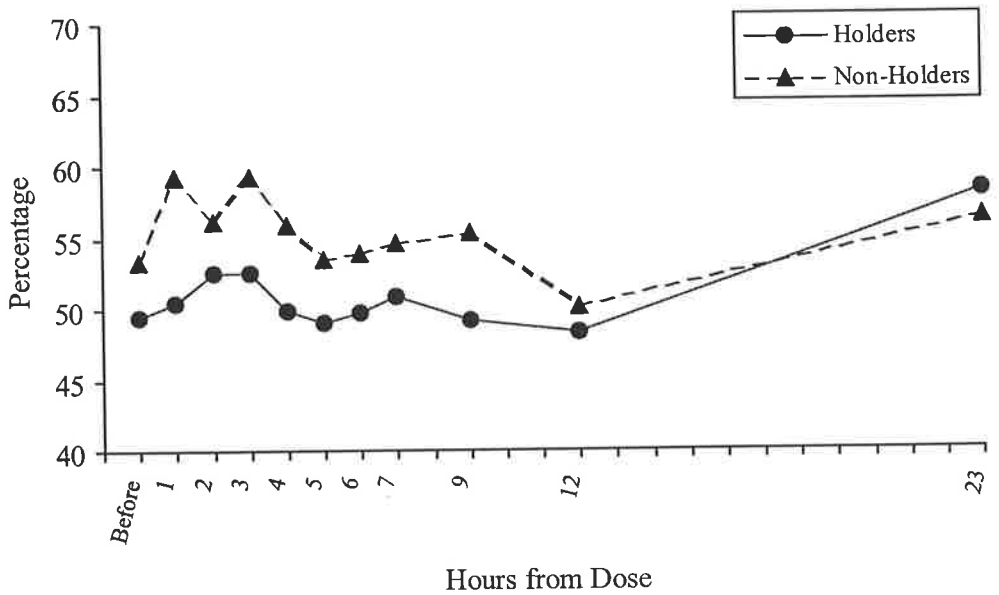


Table 5.3.31. Comparison of mean sweating of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (%).

Hours since dose	Controls	Holders	Non-Holders
Before dose	46.80 (5.83)	49.44 (7.76)	53.33 (8.99)
1	47.80 (5.14)	50.44 (12.49)	59.33 (7.40) * ✠
2	47.60 (5.36)	52.56 (13.83)	56.22 (6.82) *
3	48.00 (4.57)	52.56 (11.35)	59.33 (10.49) *
4	47.00 (4.90)	49.89 (9.08)	55.89 (10.39) *
5	48.00 (5.33)	49.00 (7.55)	53.56 (6.71)
6	52.20 (9.20)	49.78 (7.31)	53.89 (10.53)
7	48.20 (2.49)	50.78 (6.57)	54.67 (10.99)
9	49.40 (6.10)	49.22 (8.47)	55.33 (8.57)
12	51.40 (4.14)	48.33 (9.33)	50.11 (8.89)
23	48.60 (4.55)	58.11 (12.77)	56.33 (6.78)

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 5.3.27. Mean sweating of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (%).



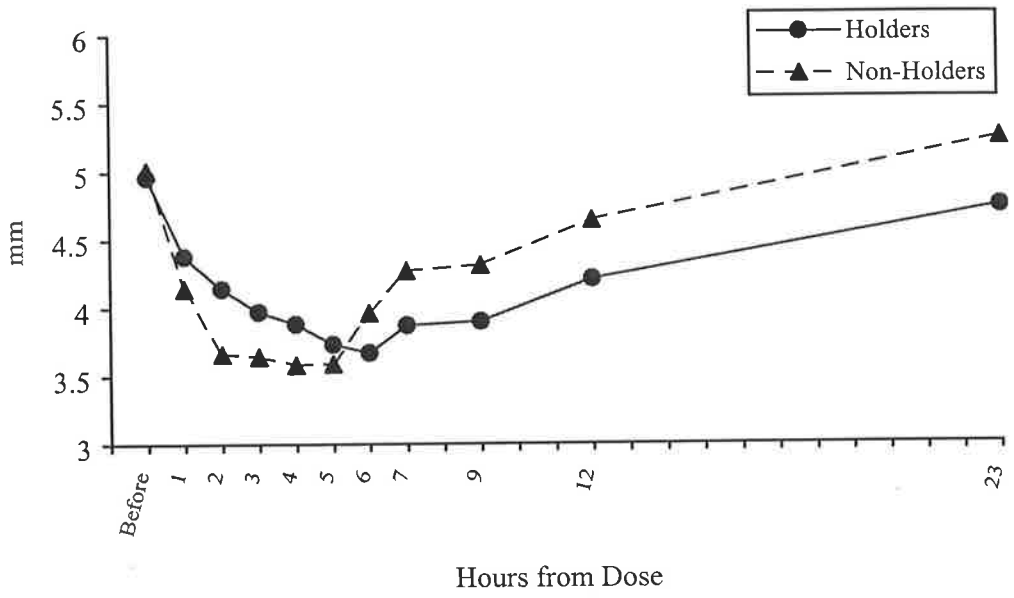
Pupil size decreased for both holders and holders after methadone administration, however, the period of peak miosis was different between these groups (Table 5.3.32 and Figure 5.3.28). When compared with the controls, pupil sizes were significantly smaller for both holders ($F(1,26) = 25.39$, $p<0.001$) and non-holders ($F(1,26) = 24.91$, $p<0.001$). The pupil sizes of holders and non-holders were not significantly different over the interdosing interval ($F1,26) = 0.01$, n.s.). However, there was a significant group by time interaction effect ($F(10,26) = 2.62$, $p<0.001$), suggesting that there was a difference in the temporal pattern of miosis between these groups. For the non-holders peak miosis occurred between approximately 2 and 5 hours after the methadone dose, and then increased steadily during the remainder of the interdosing interval. Miosis occurred more slowly for the holders, with peak miosis approximately 6 hours after the methadone dose.

Table 5.3.32. Comparison of mean pupil size of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.) (mm).

Hours since dose	Controls	Holders	Non-Holders
Before dose	5.90 (0.46)	4.96 (1.43)	5.01 (0.88)
1	6.10 (0.56)	4.38 (1.18) ***	4.14 (0.64) ***
2	5.55 (0.84)	4.14 (1.12) ***	3.66 (0.83) ***
3	6.08 (0.34)	3.97 (0.91) ***	3.64 (0.72) ***
4	5.93 (0.55)	3.88 (0.86) ***	3.58 (1.29) ***
5	5.72 (0.46)	3.73 (0.80) ***	3.59 (1.27) ***
6	5.58 (0.48)	3.67 (1.03) ***	3.96 (1.27) ***
7	5.82 (0.46)	3.87 (0.80) ***	4.27 (1.37) ***
9	5.57 (0.66)	3.90 (0.90) ***	4.31 (1.08) **
12	5.66 (0.35)	4.21 (1.00) ***	4.64 (1.04) *
23	5.77 (0.60)	4.74 (1.33) *	5.24 (0.94)

Tukey's HSD post-hoc comparisons with Control Group: * $p<0.05$; ** $p<0.01$; *** $p<0.001$
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ $p<0.05$; ✠✠ $p<0.01$; ✠✠✠ $p<0.001$

Figure 5.3.28. Mean pupil size of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval (mm).



5.3.2.3. The relationship between plasma methadone concentration and withdrawal severity.

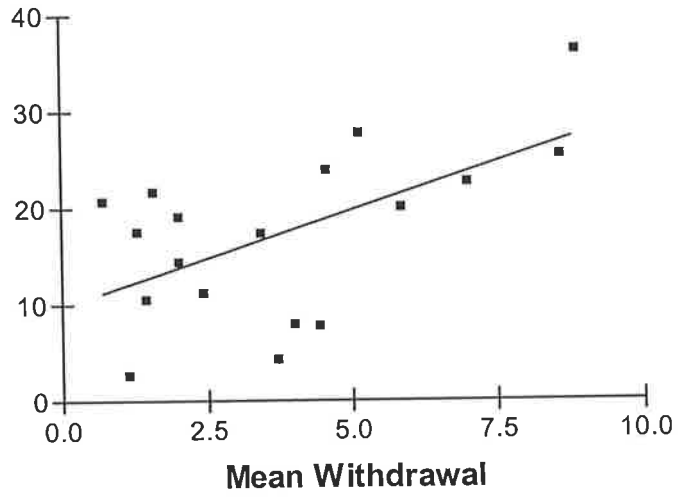
Six of each of the 9 holders and 9 non-holders had trough concentrations above 200 ng/mL. The group of methadone patients was subdivided into those with trough concentrations of 200 ng/ml or less (Low Trough Group; n=6) and those with higher trough concentrations (High Trough Group; n=12). There were no significant differences between the groups for age (Low Trough mean (s.d.) of 34.50 (8.41) years compared with 35.75 (6.25) years; t=-0.36, n.s.), gender ratio (Low Trough 5(83%) males compared with 6(50%) males); Fisher's Exact=0.32), body weight (68.83 (8.52) compared with 76.83 (10.66) kg.; t=-1.72, n.s.) or the amount of time enrolled in the methadone program (2.99 (1.79) compared with 3.23 (0.96) years; t=-0.16, n.s.). There were no significant differences between the groups for the proportion with positive urinalysis results for benzodiazepines (Low Trough 2(33%) compared with 5(42%)),

cannabis (4(67%) compared with 6(50%)), or other opioids (0 Low Trough patients compared with 2(17%) High Trough patients). The Low Trough patients had a significantly lower daily oral methadone dose (35.08 (28.57) mg/day compared with 79.63 (27.03) mg/day; $t=-3.17$, $p<0.05$) and a significantly lower methadone dose to body weight ratio (0.53 (0.45) mg.kg/day compared with 1.06(0.43) mg.kg/day; $t=-2.40$, $p<0.05$).

Repeated measures analyses of variance, with methadone dose entered as a covariate, were conducted to determine group differences in subjective pharmacodynamic response during the interdosing interval. There were no significant main effects for group differences for MBG ($F(1,15)=0.31$, n.s.), withdrawal symptoms ($F(1,16)=0.74$, n.s.) or withdrawal severity $F(1,16)=0.04$, n.s.). There were also no significant time by group interaction effects for MBG ($F(10,150)=0.77$, n.s.), withdrawal symptoms ($F(10,150)=0.59$, n.s.) or withdrawal severity ($F(10,150)=1.03$, n.s.).

Analyses were then conducted to determine the relationship between the rate of decline in methadone plasma concentration and withdrawal severity. When holders were compared with non-holders, there was a higher maximum rate of decline in methadone concentration from the time of peak concentration to trough in the non-holder group (mean (s.d.) of 47.60 (21.30) compared with 74.50 (40.44) ng/mL/h), although this did not reach statistical significance ($t=1.77$, $p=0.09$). However, when the two subjects (holders) whose urinalysis revealed use of other opioids were excluded, the difference was significant (42.14 (20.80) compared with 74.50 (40.44) ng/mL/h, $t=2.10$, $p<0.05$). Figure 5.3.29 presents the significant correlation ($r=0.60$, $p<0.01$) between the maximum rate of decline in plasma concentration and the mean number of withdrawal symptoms during the period from peak plasma concentration to the trough for all 18 patients. This correlation was increased when the two patients who had used additional opioids were excluded ($r=0.67$, $p<0.001$).

Figure 5.3.29.: Correlation between the maximum rate of decline in plasma methadone concentration and the mean number of withdrawal symptoms during the period from peak plasma concentration to trough among methadone patients. (n=18).



5.3.2.4. Plasma Concentration Effect Relationships

The EC50 values showed considerable variability from patient to patient and for each of the responses (Table 5.3.33.). The mean slope factors (N) for withdrawal symptoms and severity, MBG, saliva production, skin temperature and sweating, respiration and heart rates, pain threshold and pupil diameter for the whole group, the holders and non-holders are shown for those patients in whom the model could be satisfactorily fitted to the data. This applied to 9 of the 18 patients for the number of withdrawal symptoms, 8 for withdrawal severity, 10 for MBG, 12 for pupil diameter, 8 for respiration rate, 6 for pain threshold, only 3 for saliva production, 2 for both sweating and heart rate, 1 for skin temperature and none for blood pressure.

Table 5.3.33.: Slope factors (N) and EC_{50} values derived from plasma racemic methadone concentration-effect relationships for all patients and separately from the holder and non-holder patient groups. Mean ± s.d..

	All Patients	Holders	Non Holders
MBG			
N	5.07 ± 1.05	4.11 ± 1.79	5.72 ± 1.33
EC_{50}	430.80 ± 67.33	468.00 ± 59.26	406.00 ± 109.02
	n=10	n=4	n=6
Withdrawal Symptoms			
N	5.47 ± 0.88	4.95 ± 0.85	6.12 ± 1.77
EC_{50}	196.22 ± 27.76	165.40 ± 30.13	234.75 ± 47.14
	n=9	n=5	n=4
Withdrawal Severity			
N	4.32 ± 0.39	4.40 ± 0.62	4.24 ± 0.56
EC_{50}	205.18 ± 43.53	127.31 ± 32.95	283.04 ± 60.96 *
	n=8	n=4	n=4
Saliva			
N	1.94 ± 0.75	0.80	2.51 ± 0.85
EC_{50}	164.86 ± 65.27	35.62	229.48 ± 15.90
	n=3	n=1	n=2
Skin Temperature			
N	0.28	0.28	-
EC_{50}	90.98	90.98	-
	n=1	n=1	-
Sweating			
N	0.91 ± 0.38	0.53	1.29
EC_{50}	295.42 ± 167.03	128.29	462.54
	n=2	n=1	n=1
Respiration Rate			
N	1.04 ± 0.24	0.92 ± 0.67	1.07 ± 0.26
EC_{50}	331.51 ± 77.56	190.56 ± 157.31	378.50 ± 88.39
	n=8	n=2	n=6
Heart Rate			
N	1.06 ± 0.04	-	1.06 ± 0.04
EC_{50}	489.76 ± 104.05	-	489.76 ± 104.05
	n=2	-	n=2
Pain Threshold			
N	2.85 ± 0.76	4.74 ± 1.76	1.90 ± 0.19
EC_{50}	183.83 ± 36.51	101.00 ± 54.14	225.25 ± 33.66
	n=6	n=2	n=4
Pupil Size			
N	1.19 ± 0.10	1.08 ± 0.14	1.27 ± 0.14
EC_{50}	319.00 ± 59.71	324 ± 125.14	316.86 ± 61.20
	n=12	n=5	n=7

The values were not significantly different between the two groups for any of the above responses. There were also no significant differences between the patients for whom the model could or could not be applied with respect to gender, age, drug use or time enrolled on the program. The values were greater than 5 for withdrawal symptoms and MBG, indicating very steep plasma concentration - effect relationships for these subjective responses. In contrast, the values were closer to unity for pupil diameter and respiration rate. The values for N were statistically different between the number of withdrawal symptoms and pupil diameter ($t=5.02$, $p<0.0001$), and between withdrawal severity and pupil diameter ($t=6.44$, $p<0.0001$). Values were also significantly different between MBG and pupil diameter ($t=3.61$, $p<0.006$), MBG and respiration rate ($t=5.09$, $p<0.001$) and withdrawal symptoms and pain threshold ($t=3.11$, $p<0.03$), but did not reach significance between pain threshold and withdrawal severity ($t=2.40$, $p=0.06$). There were no significant differences among the remainder of the subjective responses including between MBG and withdrawal symptoms ($t=0.04$, $p=0.97$), MBG and withdrawal severity ($t=1.47$, $p=0.19$), MBG and pain threshold ($t=2.21$, $p=0.08$) and withdrawal symptoms and withdrawal severity ($t=1.36$, $p=0.22$). Nor were there significant differences among the other responses, including between pain threshold and pupil diameter ($t=2.18$, $p=0.08$), pain threshold and respiration rate ($t=2.16$, $p=0.08$) and pupil diameter and respiration rate ($t=0.70$, $p=0.51$). As the model could be fitted to these data in a relatively small number of patients, caution must be applied to the interpretation of these differences. Statistical differences were not analysed for the remainder of the mean slope factors as the model could be fitted to only a small number of patients.

5.3.3. Discussion

Methadone is well suited as a maintenance pharmacotherapy for opioid users due to its high oral bioavailability and relatively long elimination half-life (see Section 1.6). These attributes have resulted in the usual clinical practice of once daily dosage regimes. However, there remains a substantial proportion of patients who, despite seemingly adequate doses, complain of opioid withdrawal, particularly toward the end of the 24-hour inter-dosing interval. These patients might be accused of manipulating the program for a dose increase (e.g. Bell et al., 1988; Whitehead, 1974), but are nevertheless at risk of poor treatment outcome. In Chapter Three it was shown that maximal direct opioid effects occur approximately 3 hours after dose and that withdrawal displayed a time course that was the opposite of this. It was hypothesised that the time course and severity of these effects would be associated with fluctuations in plasma methadone concentrations during the inter-dosing dosing interval. The study presented in the present Chapter has confirmed this hypothesis in that changes in subjective and physiological responses were correlated with changes in plasma methadone concentration.

5.3.3.1. Comparison of the subjective and physiological changes among methadone patients and non-opioid using controls.

The methadone patients demonstrated significant subjective and physiological changes during the 24-hour inter-dosing interval. The inclusion of a sample of drug-free controls, and the absence of significant changes in subjective and objective response in these participants, indicates that the changes that were recorded among the methadone patients can be reasonably interpreted as resulting from methadone ingestion.

In comparison with the controls, the methadone patients reported significantly more opioid withdrawal at each testing period, with peak withdrawal severity being associated with trough plasma methadone concentrations. Subjective opioid effect showed an inverse relation, with peak direct effect associated with peak plasma methadone concentration. In contrast with the controls, methadone patients reported significantly more subjective opioid effect between one and seven hours post methadone dose, and significantly less opioid effect in the period immediately prior to dosing. The concurrent evaluation of plasma methadone concentration, and the collection of data in a controlled environment, confirms and extends upon the data presented in Chapter Three.

The methadone patients also reported significantly higher pain threshold than the controls at each testing period. Peak pain threshold occurred two to three hours after methadone ingestion and lasted approximately six hours. This was consistent with the reported duration of methadone related analgesia of between four and eight hours (see Section 1.9.1.).

There were also a number of significant differences in physiological responses between the methadone patients and controls. However, there were no significant differences in blood pressure between the groups. The range of blood pressure results was consistent with normal ranges, as hypertension in adults has been defined as persistent resting levels of systolic blood pressure between 140mmHg and 180mmHg, and diastolic pressure between 90mmHg and 105mmHg (Zanchetti et al., 1993). As reviewed in Section 1.10, the literature is unclear regarding the effect of methadone upon blood pressure. In general, the present data may appear to support the assertion within Jaffe & Martin's (1992) review, that Opioid III (mu) agonists have no major effect on blood pressure. However, as determined in the Pilot Study, the effect size of methadone upon blood pressure is relatively small (0.25 for systolic and 0.49 for diastolic blood pressure) and sample sizes of between 34 and 160 participants would be required for statistical

differences to be noted (see Table 5.2.2.). Furthermore, in contrast to the significant methadone induced reduction in systolic blood pressure recorded among patients undertaking methadone induction (Aylett, 1982), stabilised methadone maintenance patients display relatively stable systolic blood pressure (McCaul et al., 1982)(see Table 5.2.). This may imply that stabilisation on a methadone program is associated with a reduction in the acute opioid related changes in blood pressure. Nevertheless, the documented difficulty in determining opioid effects upon blood pressure (Section 1.10) and the relatively small effect-size noted in the present study suggests that changes in blood pressure are not a reliable measure of direct opioid effect among stabilised methadone patients.

There were significant differences between the methadone patients and the controls for the remaining physiological indices. In contrast to the controls, the methadone patients displayed a significantly slower heart rate throughout the 24-hour period. Patients also demonstrated significant time-dependent changes in respiration rate, with a significantly higher respiration rate than controls at trough plasma concentrations, and a significantly slower respiration rate at peak concentrations. These data are consistent with previous research (see Section 1.9.6.), and demonstrate that reduced heart and respiration rates can be recorded among patients who have been stabilised on methadone for several months. Although participation in a methadone maintenance program has a protective effect against opioid overdose fatalities (e.g. Hall et al., 1998), these data suggest that methadone patients, particularly those who continue to inject other opioids, should be alerted to the significant reductions in respiration rate that occur within three hours of methadone dosing.

Despite there being no overall significant difference in saliva production between the patients and controls, methadone patients did produce significantly lesser amounts of saliva at the time of peak plasma methadone concentration. Dental problems are a

common complaint that patients attribute to methadone (see Section 1.9.9. and Chapter Two). The results of the present study suggest that reduced saliva production is a measurable opioid effect among stabilised methadone patients, and as such, may partly contribute to the dental problems of some methadone patients.

Skin temperature and sweating remained relatively stable among the methadone patients during the inter-dosing interval. The mean skin temperature of the patients was greater than the controls until 9 hours after dosing, while the degree of sweating was significantly greater between 1 and 4 hours post-dose as well as immediately prior to dosing. Although excessive sweating is regarded as a common sign of opioid withdrawal (e.g. Gossop, 1990), these data suggest that the excessive sweating of methadone patients can not be attributed completely to either a direct opioid effect or withdrawal. Indeed, it may be characteristic of both direct effect and withdrawal.

The final objective measure was pupil size. Methadone patients displayed a significantly smaller pupil size than the controls at each testing period. The measured methadone induced changes in pupil size were consistent with the work of Inturrisi and Verebely (1972) and McCaul and colleagues (1982), and confirms that although partial tolerance may develop to this miotic effect, methadone patients will continue to have constricted pupils whilst enrolled in a methadone maintenance program (see Section 1.9.3.).

In summary, the present study has now confirmed the hypothesis that both subjective and objective opioid effects are strongly correlated with changes in plasma methadone concentration during the 24-hour inter-dosing interval. In general, these results are largely in accord with those of Hiltunen and colleagues (1995) who showed a significant correlation between plasma methadone concentrations and subjective measures of opioid withdrawal, whereas there was a less strong association with objective measures. Possible reasons for the poorer association with objective measures may be that their

inpatients were not at steady state and they measured the plasma concentration at only four time points over the 24 hour dosing interval. McCaul and co-workers (1982) demonstrated changes in pupil diameter, subjective direct effect, heart rate and skin temperature for the first 4 hours after dosing in long-term methadone users and concluded that these changes were likely to parallel changes in plasma methadone concentrations, which were not measured. The present study has now confirmed such an hypothesis.

5.3.3.2. Comparison of the subjective and physiological changes among holders and non-holders.

The failure of methadone to 'hold' over the entire 24-hour inter-dosing interval was associated with a greater severity of withdrawal symptoms, a shorter duration of subjective opioid effect, and more pronounced time-dependent changes in withdrawal and opioid effects. These findings have confirmed and extended upon the data presented in Chapter Three.

While there were relatively few significant differences in the physiological responses between the groups, post-hoc analyses demonstrated that the non-holders displayed greater time-dependent changes in physiological response that the non-opioid using controls, while the holders displayed physiological changes that were less intense. In the present study, the non-holders demonstrated a significantly greater respiration rate in the period immediately prior to dosing. Skin temperature and the degree of sweating was also greater in the non-holders, while the holders were not significantly different from the controls. Further, non-holders produced significantly less saliva than either the controls or holders from one to nine hours after dosing. In contrast, there were no significant differences between the holders and controls at any testing period. Finally, both groups had significantly smaller pupil sizes than the controls throughout the inter-

dosing interval. However, there were significant time-dependent differences in the miotic effect between the holders and non-holders. For the non-holders, peak miosis occurred between two and five hours after dosing, whereas the miotic effect in holders was more gradual, peaking at six hours after dosing. The finding that the differences between the groups were greater for the subjective responses than for the physiological responses is consistent with the assertion that opioid withdrawal is subjectively severe but objectively mild (see Section 1.13). Further, the time dependent differences in physiological response between the holders and non-holders were consistent with the greater intensity and longer duration of opioid withdrawal, as well as the shorter duration of subjective opioid effect reported by the non-holders.

5.3.3.3. The relationship between methadone pharmacokinetics and opioid withdrawal severity.

One aim of our study was to identify possible pharmacokinetic factors that might explain why some patients experience withdrawal symptoms and others do not, over part of a 24-hour inter-dosing interval. The AUC was equivalent in the holders and non-holders, indicating that racemic methadone total systemic clearance and bioavailability were not likely to be different between the two groups. The time to achieve maximum plasma concentration, the maximum concentrations and the peak to trough plasma concentration ratio were not significantly different between the two groups. The mean trough plasma methadone concentrations were virtually identical, and well within or above values which have been considered to indicate appropriate dosing in the majority of holders and non-holders (e.g. Bell et al., 1988; Dole, 1988; Holmstrand et al., 1977).

Previous research has suggested that trough methadone plasma concentrations may be lower in those clients who experience withdrawal symptoms (e.g. Loimer & Schmid, 1992). Bell and colleagues (1990) reported that methadone patients who persisted in

injecting heroin had high trough concentrations and interpreted the results as indicating that the failure of methadone to suppress their illicit heroin use was due to psychological or behavioural factors rather than pharmacological factors. Data from the present study, however, suggest that trough plasma methadone concentrations above 200 ng/mL cannot by themselves be used to determine the adequacy of the dosage regimen, since substantially higher concentrations were achieved in the majority of the holders and non-holders. Furthermore, in subsequent analyses it was found that methadone patients with trough plasma methadone concentrations of less than 200 ng/mL did not report more severe withdrawal severity than the other patients.

The only pharmacokinetic difference between the non-holders and holders in the present study was the significantly more rapid average hourly rate of decline in the plasma concentration during the period from the peak plasma concentration until the next dose. The maximum rate of plasma decline, that is, the largest decline in plasma methadone concentration that occurred in any hour between plasma peak and trough, was almost twice as large in the non-holders than in the holders. Further, it was also found that there was a significant correlation between the hourly rate of plasma decline and withdrawal severity in the period between plasma peak and trough. As such, it is likely that the rate of decrease in methadone plasma concentrations, rather than the absolute trough level, will determine whether or not a patient experiences significant withdrawal symptoms. Determining this rate requires repeated sampling over a period of at least 24-hours and this has not been done in previous studies.

Despite a significantly larger hourly rate of decline in plasma methadone concentration, non-holders had a peak to trough plasma concentration ratio that was similar to that of the holders. A possible explanation for this finding can be derived from consideration of the distribution phase of methadone among stabilised patients. The disposition of racemic methadone during chronic dosing has been shown to be best described by a two-

or more compartment pharmacokinetic model in various clinical situations (e.g. Inturrisi et al., 1987; Meresaar et al., 1981; Wolff et al., 1997; Nilsson et al., 1983). In opioid users on chronic oral methadone, the mean distribution half-life has been reported as 5.8 hours (Wolff et al., 1997) and thus the distribution phase would occupy a substantial portion of a 24-hour dosing interval.

Nilsson and co-workers (1983) compared eight methadone patients who complained of withdrawal and showed poor treatment progress, with 12 unselected patients who did not report these difficulties. There was no difference between the groups in the total clearance of methadone (mean (s.d.) of approximately 104(36) mL/min compared with 111(36) mL/min). However, it was found that the distribution volume at steady-state was smaller (3.1(0.1) L/kg compared with 4.6(1.0) L/kg) in those patients designated as therapeutic failures. This resulted in significant group differences in the terminal half-life values (24.5(2.6) hrs compared with 34.0(7.0) hrs). The average plasma concentration at steady-state was the same between the two groups. However, a smaller volume of distribution and terminal half-life of methadone, resulted in the therapeutic failure patients having a plasma concentration-time profile that was different to that of the control group. The authors postulated that these pharmacokinetic differences would result in higher peak concentrations and more rapid decline in plasma concentrations (during the distribution phase) to levels below an effective concentration, which in turn would translate into withdrawal towards the end of the dosing interval in the therapeutic failure group.

It was possible to apply the sigmoid E_{max} model to both objective and subjective responses in this chronic dosing study in sufficient patients to allow plausible conclusions to be drawn. There were large N values for withdrawal (mean (s.d.) of 5.5(0.9)), subjective direct opioid effect (5.1(1.1.)) and antinociception (2.9(0.8)), indicating very steep concentration versus effect relationships for these subjective

measures. In contrast, the slope factors for pupil diameter (1.2(0.1)) and respiration rate (1.0(0.2) were significantly less. These values were in accord with the slope factors for analgesia (2-4.4) and sedation (5.8) reported by Inturrisi and colleagues (1987; 1990).

The occurrence of withdrawal symptoms in the non-holders is likely to be the consequence of the very steep plasma concentration versus effect relationship for this response. Thus, a relatively small change in the plasma concentration during the initial decline in plasma concentration (distribution phase) would translate into a large clinical response. This would be exaggerated in the non-holders, whose rate of decline in the plasma concentration was almost twice as rapid as in the holders.

Finally, these pharmacokinetic analyses should be qualified by the fact that methadone is administered as the racemate and differences in the disposition of the two enantiomers have been previously described (e.g. de Vos et al., 1998; Schall et al., 1996). Differences in the time course of plasma concentrations of enantiomers may influence the measurement of distribution phase plasma concentrations a racemate. As such, caution is warranted when concluding a disposition mechanism for the difference between holders and non-holders in the present study. It may be more appropriate to conduct analyses involving the individual enantiomers of methadone, and in particular the unbound concentrations of the active enantiomer R-(-)-methadone (Kristensen et al., 1995; Schall et al., 1996).

5.3.3.4. Summary and Clinical Implications

The present study has demonstrated that subjective and physiological opioid responses were correlated with changes in plasma racemic methadone concentrations among methadone maintenance patients. Analyses of plasma concentration-effect relationships indicated that for the subjective responses, particularly withdrawal severity, small changes in plasma concentration translate into relatively large changes in effect. When compared with methadone patients who did not report significant withdrawal, self-identified non-holders reported significantly greater withdrawal severity, a significantly shorter period of direct opioid effect and more pronounced time-dependent changes in the subjective and physiological response to methadone. The difference in subjective withdrawal severity between these groups was not related to oral methadone dose, other drug use or trough methadone plasma concentrations, but rather to the significantly more rapid hourly rate of decline in plasma concentration in the period from the peak plasma concentration until the next dose. These findings translate into important clinical implications.

Firstly, previous authors (e.g. Bell et al., 1988; Whitehead, 1974) have maintained that self-reports of 'not holding' are merely an attempt to gain an increase in oral dose. The data in the present study, however, demonstrate that self-reports of subjective withdrawal, despite a seemingly adequate methadone dose, are associated with significant time-dependent physiological effects. The consistency of the findings presented in the present Chapter along with the findings presented in Chapter Three, suggest that self-reports of not-holding are valid and may well persist despite prescription of a seemingly adequate oral daily dose.

Secondly, the widely accepted once-daily dosage regimen may not be suitable for a significant proportion of methadone patients. A possible strategy for these patients may

be to divide the daily dose, rather than further increasing the dose. An increase in the daily methadone dose might increase peak plasma concentrations and so produce adverse direct opioid effects (such as respiratory depression), without reducing withdrawal severity as the decline in plasma concentration may continue to be rapid. Such an assertion is consistent with the conclusion of Nilsson and colleagues (1983) from their study of therapeutic failures:

> *"The smaller volume of distribution could lead to unacceptable high fluctuation of M(ethadone) ... and withdrawal symptoms during the latter part of the dosage interval. The appropriate treatment of this subgroup of patients is not to increase the dose but to shorten the dosage interval" (p497).*

The present study has presented the pharmacokinetic and pharmacodynamic basis for such a conclusion. However, there may be practical difficulties in dividing the daily dose such as requiring patients to report twice daily if they do not have take-home privileges, and might increase the cost of a methadone program.

Secondly, the standard clinical practice when responding to patients reporting subjectively uncomfortable opioid withdrawal symptoms is to use trough methadone plasma concentrations as a guide to adjusting the level of the daily methadone dose. Researchers have been divided about the utility of therapeutic monitoring, with some in favour (e.g. Bell et al., 1988; Loimer & Schmid, 1992; Wolff et al., 1991; Wolff & Hay, 1994) while others have noted the practical and theoretical limitations of such an approach (e.g. Horns et al., 1975; Kell, 1994; Nilsson et al., 1983). The present study has found that reports of the methadone dose 'not holding' were not associated with trough methadone plasma concentrations. As such, if a methadone dose increase has not alleviated a patient's withdrawal severity, then it may be appropriate to conduct repeated analyses of plasma methadone concentration over a 24-hour inter-dosing interval.

Thirdly, longer acting alternatives to methadone should be evaluated. Previous research has noted that LAAM produces less intense direct opioid effects (e.g. Freedman & Czertko, 1981) and withdrawal symptoms (e.g. Karp-Gelernter et al., 1976) during the inter-dosing interval than methadone Currently, buprenorphine, LAAM and slow - release morphine are under investigation in Australia. These evaluations should incorporate measurement of the inter-dosing interval withdrawal severity.

CHAPTER SIX

THE RELATIONSHIP BETWEEN MOOD STATE AND PLASMA METHADONE CONCENTRATION AMONG MAINTENANCE PATIENTS.

6.1. Introduction

In Chapter Five it was reported that subjective and objective opioid responses were correlated with changes in racemic plasma methadone concentrations among methadone maintenance patients. Analyses of plasma concentration-effect relationships indicated that for the subjective responses, in particular withdrawal severity, small changes in plasma concentrations translated into relatively large changes in effect. The difference in subjective withdrawal severity between patients self-reporting as 'holders' and 'non-holders' was not related to either oral methadone dose or trough methadone plasma concentrations, but rather to the significantly more rapid rate of decline in plasma concentration during the period from the peak plasma concentration until the next dose. Data on the mood state of participants were also collected during this study, using the Profile of Mood States (POMS)(McNair et al., 1971). The primary aim of this aspect of the study was to determine the mood changes that may be associated with changes in plasma methadone concentration. The present chapter presents the analyses of these data, and begins with a review of previous studies that have examined the effect of methadone upon mood state.

6.1.1. Methadone related changes in mood state

Withdrawal symptoms, enough to be subjectively assessed as uncomfortable, occur often among methadone maintenance patients and could potentially lead to other drug

use or poor treatment outcome. Mood states such as depression, anger and anxiety may also increase the perceived severity of subjective withdrawal symptoms and induce craving for opioids (Childress et al., 1994; Kleber, 1981; Phillips et al., 1986) and thus might increase the likelihood of a poor clinical outcome (Kanof et al., 1993; Nunes et al., 1994).

For the majority of patients, methadone ingestion is associated with immediate and positive changes in mood state, while signs of anxiety have been associated with trough methadone concentrations (Holloway, 1993; Kumor et al., 1993; Price et al., 1975). These mood changes have been recorded among patients entering methadone treatment and receiving an initial methadone dose as well as among those who have stabilised on a daily methadone dose within a methadone maintenance program. In an early study (Price et al., 1975) using the Profile of Mood States (POMS), 49 opioid users experiencing physiological signs of opioid withdrawal at entry to a methadone detoxification program described themselves as having considerable mood disturbance. Within 45 minutes of receiving methadone (range 20mg - 40mg with 78% receiving 40mg), all POMS sub-scales showed a significant decrease in mood disturbance. Specifically, Vigour increased by approximately 70%, while the negative moods, such as Depression and Anxiety, decreased by approximately 50% (see Table 6.1). More recently, Holloway (1993) assessed the subjective effects of methadone 30 minutes before and 90 minutes after the daily oral dose in patients who had participated in methadone treatment for a mean of nine months. After dosing, patients reported dramatic mood changes, including increased vigour, friendliness, arousal and positive mood, while anxiety, depression, anger and confusion all decreased.

Table 6.1: Data published by Price et al. (1975) of the mean scores on the sub-scales of the Profile of Mood States reported by 49 opioid users on admission to a methadone detoxification program and 45 minutes after receiving an initial methadone dose of between 20 and 40 mg. Values are mean (s.d.). The unit and percentage change in sub-scale scores have been calculated and are provided for information.

	Pre-methadone	45-minutes Post-methadone	Unit Change	% Change
Tension (0-36)*	22.7 (7.4)	11.1 (7.1)	11.6	51%
Depression (0-40)	26.2 (12.5)	13.8 (1.3)	12.4	47%
Anger (0-48)	15.0 (8.7)	6.9 (7.1)	8.1	54%
Vigour (0-32)	5.8 (5.2)	9.9(5.5)	4.1	70%
Fatigue (0-28)	17.6 (6.4)	9.3 (5.7)	8.3	47%
Confusion (0-28)	12.3 (5.3)	8.6 (4.5)	3.7	30%

* Values in parentheses under each sub-scale title indicate the possible range of scores for that sub-scale.

These studies suggest that oral doses of methadone result in changes in mood in a positive direction even among patients who have achieved a stabilised daily dose. However, the relationship between the degree of such positive changes in mood state and methadone dose level is unclear, with one study finding that higher doses (80mg/day) were no more effective than lower doses (40mg/day) in diminishing the psychological distress symptoms of patients (Banys et al., 1994).

Similarly, Kumor and colleagues (1993) hypothesised that methadone induced mood changes were dependent upon plasma methadone concentration level. In their study, methadone patients were subdivided into two sub-groups: responders (those not using other drugs and receiving take-away doses) and non-responders (those with positive urinalyses for other opioids). There were no differences between these sub-groups for age, methadone dose level or length of enrolment in the methadone program. Patients completed a positive affect scale, and responses were compared with plasma concentrations immediately prior to the methadone dose and 1 to 1.5 hours post-dose. Plasma methadone concentrations of the non-responders were significantly higher at trough and exhibited a trend for higher concentrations at the peak. For all patients, it was found that positive affect scores were significantly higher at plasma peak than at trough. However, there were no differences between the sub-groups in positive affect scores at either time period, suggesting that higher plasma methadone concentrations at either trough or peak were not related to higher degrees of positive mood changes.

Chapter Five presented plasma concentration-effect relationships for withdrawal severity that indicated that small changes in plasma methadone concentration translated into relatively large changes in withdrawal. The difference in subjective withdrawal severity between patients self-reporting as 'holders' and 'non-holders' was not related to either oral methadone dose or trough methadone plasma concentrations, but rather to the significantly more rapid rate of decline in plasma concentration during the period from the peak plasma concentration until the trough. It is therefore hypothesised that the intensity and temporal pattern of mood states reported by methadone patients will be similarly associated with changes in plasma methadone concentration, rather than absolute plasma methadone concentration levels. To the best of the author's knowledge, no studies have examined temporal changes in mood states in patients maintained on methadone and the relation between these changes and changes in plasma methadone concentrations throughout an entire inter-dosing interval.

6.1.2. The present study

In the present study the mood states of patients maintained on methadone were assessed over a complete inter-dosing interval. The aims were:

1. To evaluate mood state changes in methadone maintenance patients by comparing their Profile of Mood States (POMS) scores with those of non-opioid using controls.

2. To compare patients who reported significant withdrawal symptoms (non-holders) with a group who did not (holders), in order to determine whether the magnitude and temporal pattern of their mood states also differed.

3. To characterise the relationship between plasma racemic methadone concentration and mood.

Hypothesis:

1. That the intensity and temporal pattern of mood states reported by methadone patients will be associated with changes in plasma methadone concentrations during the inter-dosing interval.

6.2. Measures and Procedures

Data were collected using the sample, measures and procedures described in Chapter Five, with the addition of the Profile of Mood States (POMS) (McNair et al., 1971). The POMS was administered at the same time as the withdrawal scores, physiological and subjective opioid effects. This was before the daily dose and the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 9, 12 and 23 hours, resulting in a total of 11 measurement times. These times coincided with the corresponding blood sampling times. The control subjects were also tested over a single 24-hour period.

The POMS contains a list of 65 mood-related adjectives. Participants were instructed to rate each item on the list using a scale of 0 (not at all) to 4(extremely), based on how they were feeling at that moment (i.e. "Right Now"). The POMS is divided into six empirically derived sub-scales that reflect distinct types and qualities of identifiable affective state. Sub-scales include:

Vigour - a mood of ebullience and high energy;

Depression - depressed affect and a sense of inadequacy;

Tension - heightened musculo-skeletal tension;

Anger - irate mood and antipathy toward others;

Fatigue - weariness and low energy level;

Confusion - bewilderment and disorganised cognitive efficiency.

In addition to these sub-scales, the Total Mood Disturbance (TMD) score is a single global estimate of affective state, which is derived by summing the scores across all six factors, weighting Vigour negatively.

6.2.1. Analyses

Two-way repeated measures analyses of variance were used to determine differences in mood states between methadone patients and control subjects, and holders and non-holders. Tukey's HSD post-hoc tests were used when significant effects were found. The mean and maximum rate of decline in plasma methadone concentration during the period from peak concentration to trough were calculated for each patient. These data were analysed using SPSS for Windows (v. 6.0; Norusis, 1993).

Methadone plasma concentration-effect relationships were determined for the scores on the POMS sub-scales using the sigmoid E_{max} model described in Chapter Five. Student's t-test was used to compare the N and EC_{50} values between holders and non-holders. The relationship between the rate of decline of plasma methadone concentration and mean Total Mood Disturbance (TMD) scores from the POMS was evaluated by a Pearson's Product Moment correlation coefficient.

6.3. Results

6.3.1. Comparison between methadone patients and non-opioid using controls.

Table 6.2. presents the results of repeated measures analyses of variance for the comparison of mood states between methadone patients and controls. There were significant differences between methadone patients and controls for each sub-scale ($p<0.001$ for all sub-scales except anger where $p<0.05$). The group by time interaction was also significant for tension ($p<0.001$), depression ($p<0.001$), anger ($p<0.05$) and total mood disturbance ($p<0.001$).

Table 6.2.: Repeated measures analyses of variance for POMS sub-scales comparing methadone patients (n=18) with non-drug using controls (n=10).

Scale	Effect	df	F
Tension	Group	1,26	13.72 (2073.62) ***
	Hours since dose	10,260	5.62 (36.21) ***
	Group X Hours since dose	10,260	4.97 (32.01) ***
Depression	Group	1,26	10.19 (3297.09) ***
	Hours since dose	10,260	4.61 (43.09) ***
	Group X Hours since dose	10,260	3.74 (34.91) ***
Anger	Group	1,26	4.59 (846.37) *
	Hours since dose	10,260	2.17 (17.09) **
	Group X Hours since dose	10,260	1.94 (15.24) *
Vigour	Group	1,26	28.34 (6221.49) ***
	Hours since dose	10,260	5.77 (98.52) ***
	Group X Hours since dose	10,260	1.47 (25.17)
Fatigue	Group	1,26	12.55 (3435.06) ***
	Hours since dose	10,260	8.03 (97.61) ***
	Group X Hours since dose	10,260	1.11 (13.53)
Confusion	Group	1,26	17.11 (1375.95) ***
	Hours since dose	10,260	3.72 (23.06) ***
	Group X Hours since dose	10,260	1.06 (6.59)
TMD	Group	1,26	20.65 (93880.89) ***
	Hours since dose	10,260	9.21 (1272.18) ***
	Group X Hours since dose	10,260	2.90 (400.64) ***

Note: Values in parentheses represent mean square errors. * $p<0.05$; ** $p<0.01$; *** $p<0.001$

Mean scores on the Vigour sub-scale peaked approximately 3-4 hours post methadone dose and decreased throughout the remainder of the inter-dosing interval (see Figure 6.1.). Planned comparisons indicated that the controls scored significantly higher than the methadone patients at all time periods (See Table 6.3). All other sub-scales, including the TMD score, showed an inverse relation, peaking in the period immediately prior to the methadone dose (see Figures 6.2. through 6.7). Tables 6.4 through Table 6.9. present the planned comparisons between methadone patients and controls for the remaining sub-scales. Methadone patients scored significantly higher scores on each of these sub-scales than controls at each testing period during the 24-hour inter-dosing interval.

Table 6.3.: Comparison of mean scores on the Vigour sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 32.

Hours since dose	Controls	Methadone
Before dose	19.20 (7.44)	7.39 (7.10)***
1	18.60 (4.25)	11.72 (8.45)**
2	20.20 (3.01)	11.33 (4.62)***
3	20.40 (3.17)	11.17 (6.22)***
4	18.40 (5.56)	8.72 (7.54)***
5	18.60 (5.40)	8.39 (4.94)***
6	18.20 (4.87)	7.28 (6.09)***
7	17.20 (5.83)	6.83 (5.85)***
9	13.60 (6.52)	6.83 (5.16)**
12	13.20 (5.79)	6.78 (4.94)**
23	18.80 (7.00)	6.78 (5.84)***

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.1. Mean scores on the Vigour sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 32.

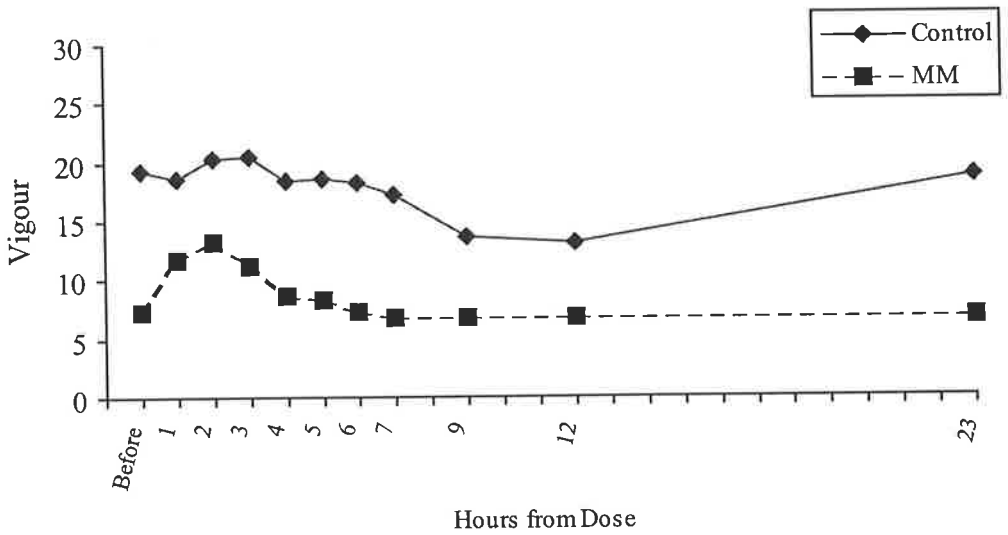


Table 6.4.: Comparison of mean scores on the Anger sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 48.

Hours since dose	Controls	Methadone
Before dose	0.60 (0.84)	6.11 (8.26) **
1	0.00	3.44 (5.68)**
2	0.00	2.06 (3.69)*
3	0.20 (0.42)	2.50 (3.55)**
4	0.20 (0.41)	2.89 (4.70)*
5	0.20 (0.42)	2.39 (4.16)*
6	0.20 (0.42)	2.72 (4.38)**
7	0.20 (0.42)	2.61 (4.87)*
9	0.20 (0.42)	3.94 (6.86)*
12	0.20 (0.42)	4.61 (7.39)**
23	0.00	6.78 (9.51)**

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.2.: Mean scores on the Anger sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 48.

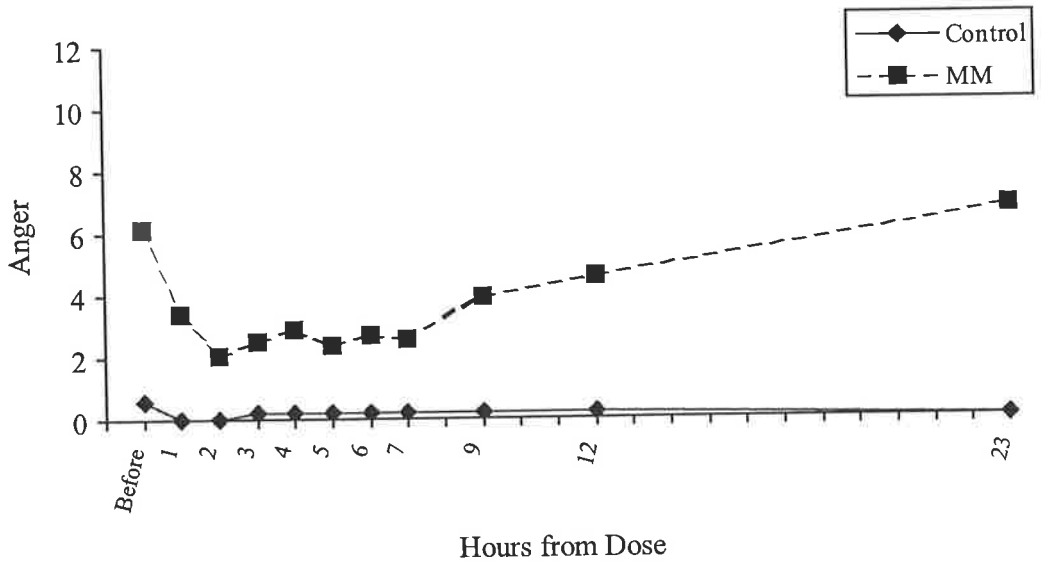


Table 6.5.: Comparison of mean scores on the Confusion sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 28.

Hours since dose	Controls	Methadone
Before dose	2.60 (1.43)	7.78 (3.99)***
1	1.40 (0.84)	5.00 (3.77)***
2	1.80 (0.42)	4.44 (3.76)***
3	1.60 (0.84)	5.56 (3.68)***
4	1.60 (0.52)	4.67 (3.56)***
5	1.60 (0.52)	6.06 (4.66)***
6	1.80 (0.42)	6.00 (4.77)***
7	2.00 (1.15)	7.06 (5.45)***
9	2.40 (0.52)	7.89 (5.30)***
12	2.80 (1.23)	8.50 (5.19)***
23	2.60 (1.43)	7.78 (3.61)***

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.3.: Mean scores on the Confusion sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 28.

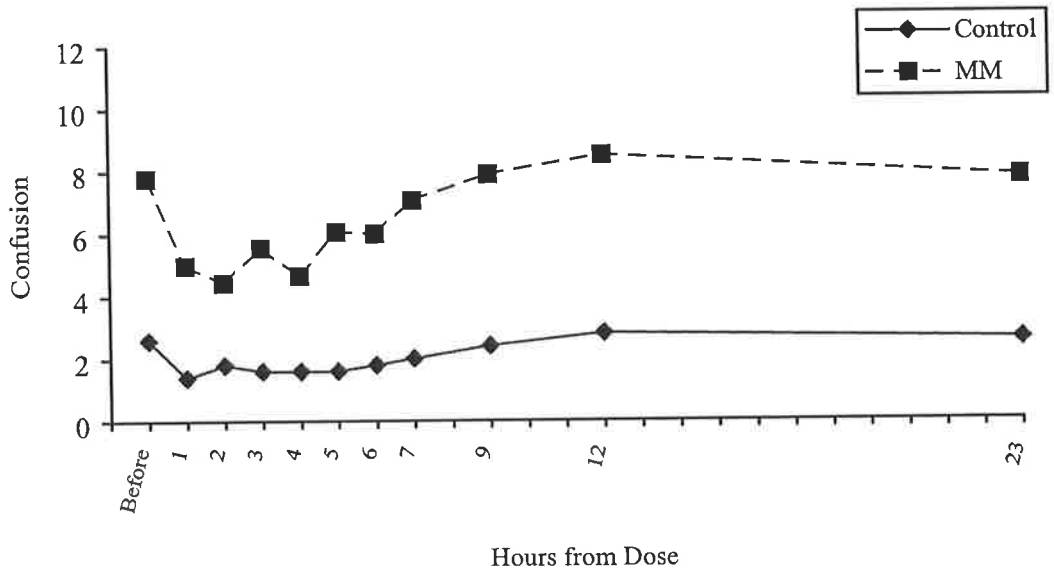


Table 6.6: Comparison of mean scores on the Depression sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 40.

Hours since dose	Controls	Methadone
Before dose	0.40 (0.52)	11.39 (9.95)***
1	0.00	7.83 (9.67)***
2	0.00	6.00 (7.15)***
3	0.00	3.78 (5.15)***
4	0.00	4.39 (6.12)***
5	0.00	6.11 (7.67)***
6	0.00	5.33 (6.17)***
7	0.20 (0.42)	5.61 (6.55)***
9	0.00	7.00 (1.71)***
12	0.00	7.61 (8.02)***
23	0.40 (0.51)	11.06 (8.57)**

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.4.: Mean scores on the Depression sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 40.

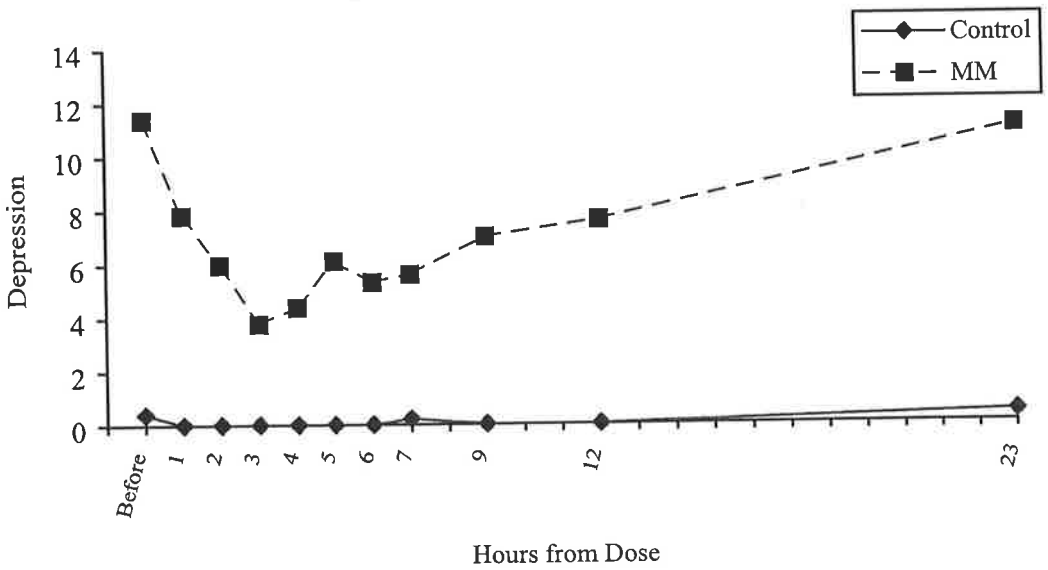


Table 6.7.: Comparison of mean scores on the Fatigue sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 28.

Hours since dose	Controls	Methadone
Before dose	4.00 (2.75)	10.89 (6.89) ***
1	1.00 (1.33)	6.00 (6.74) ***
2	0.20 (0.42)	4.72 (6.72) ***
3	0.60 (1.27)	6.56 (6.64) ***
4	1.40 (2.07)	8.44 (8.38) ***
5	1.20 (1.69)	8.89 (6.89) ***
6	3.00 (4.22)	9.44 (6.63) ***
7	1.60 (2.88)	9.89 (7.62) ***
9	2.80 (2.53)	12.17 (7.29) ***
12	4.80 (5.22)	11.94 (7.25) ***
23	3.40 (2.27)	11.72 (7.28) ***

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.5. Mean scores on the Fatigue sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 28.

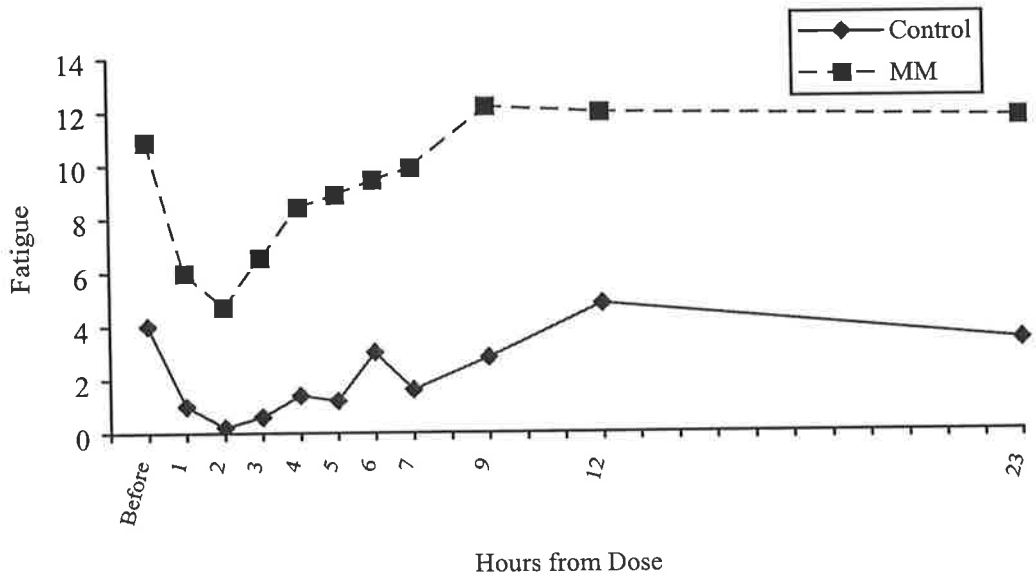


Table 6.8: Comparison of mean scores on the Tension sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 36.

Hours since dose	Controls	Methadone
Before dose	1.80 (1.23)	10.28 (6.95)***
1	1.20 (1.03)	6.17 (5.92)***
2	1.40 (0.84)	5.56 (3.68)***
3	1.20 (0.42)	4.11 (3.36)**
4	1.80 (1.23)	4.17 (4.97)*
5	1.80 (1.23)	6.06 (5.57)**
6	2.20 (2.04)	6.33 (5.06)**
7	1.80 (0.79)	7.17 (5.36)***
9	1.20 (0.79)	7.50 (5.46)***
12	1.40 (1.08)	8.61 (5.88)***
23	1.80 (1.23)	11.22 (6.26)***

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.6.: Mean scores on the Tension sub-scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 36.

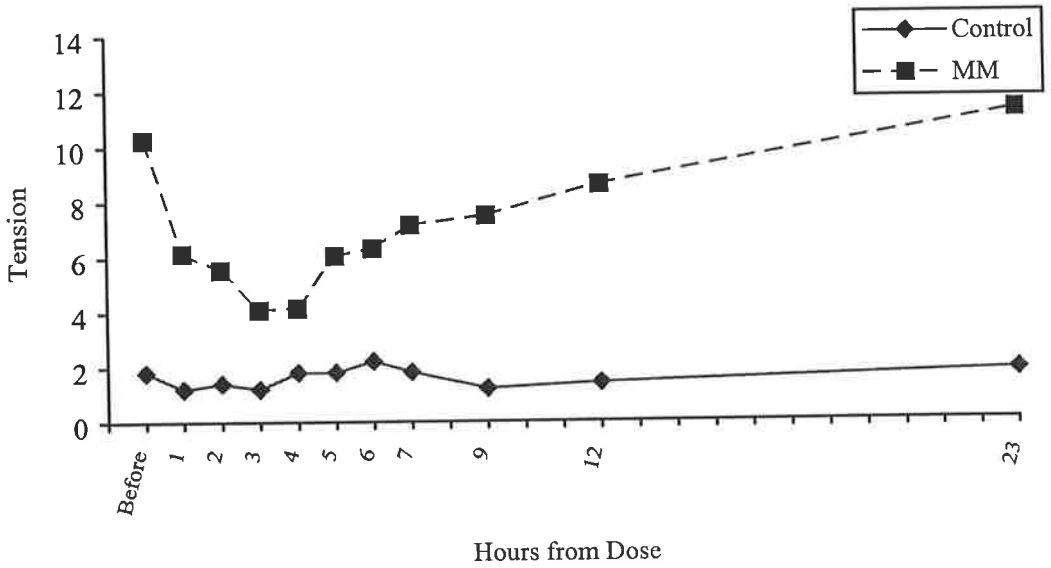
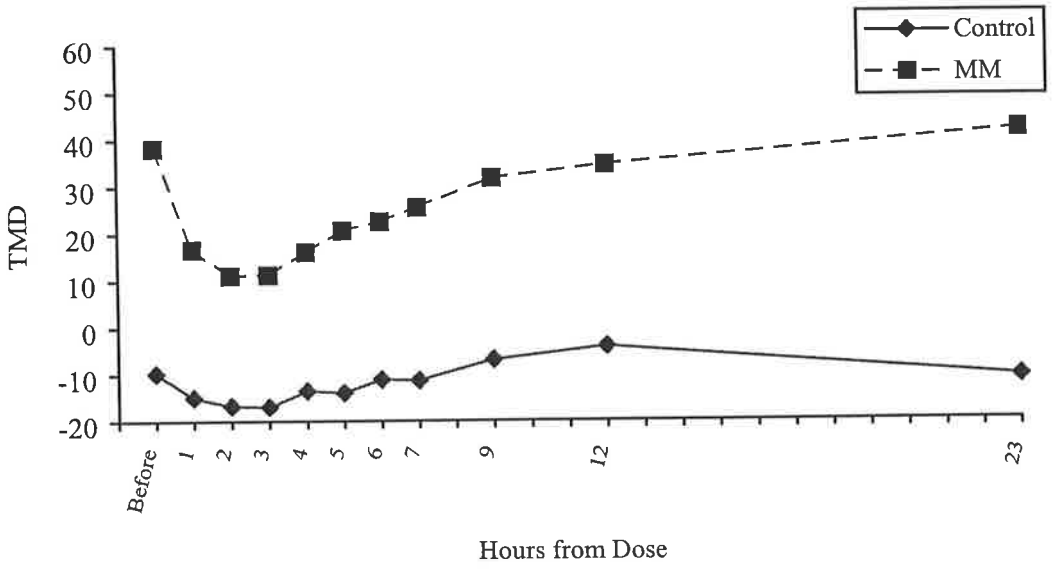


Table 6.9: Comparison of mean scores on the Total Mood Disturbance composite scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 168.

Hours since dose	Controls	Methadone
Before dose	-9.80 (10.98)	38.22 (35.56)***
1	-15.00 (4.32)	16.72 (32.64)***
2	-16.80 (3.16)	11.11 (22.26)***
3	-17.00 (3.20)	11.22 (18.55)***
4	-13.60 (7.79)	16.11 (24.80)***
5	-14.00 (7.21)	20.61 (25.71)***
6	-11.20 (9.17)	22.56 (24.34)***
7	-11.40 (8.66)	25.50 (27.18)***
9	-7.00 (8.08)	31.67 (29.48)***
12	-4.20 (10.55)	34.50 (30.91)***
23	-10.80 (9.69)	41.78 (33.07)***

* p<0.05; ** p<0.01; *** p<0.001

Figure 6.7.: Mean scores on the Total Mood Disturbance composite scale of the POMS of methadone patients (n=18) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 168.



6.3.2. Comparison between holders and non-holders.

The methadone patients were sub-divided according to whether they self-identified as non-holders (i.e. regularly experience significant opioid withdrawal; n=9) or holders (n=9), and comparisons were made between these groups, and also separately with the controls.

Table 6.10. presents the results of repeated measures analyses of variance for the comparison of mood states between the holders and controls. With the exception of the Confusion sub-scale, there were significant differences between the holders and controls for each sub-scale ($p<0.001$ for all sub-scales except vigour where $p<0.01$). The group by time interaction was significant for tension ($p<0.001$), but there were no significant interactions for the remaining sub-scales.

Table 6.11. presents the results of repeated measures analyses of variance for the comparison of mood states between the non-holders and controls. Unlike the comparisons with the holders, there were significant differences between the non-holders and the controls for every sub-scale ($p<0.001$ for all sub-scales). The group by time interaction was significant for all sub-scales ($p<0.001$ for all sub-scales except Fatigue where $p<0.05$).

Table 6.10: Repeated measures analyses of variance for POMS sub-scales comparing holders (n=9) with non-drug using controls (n=10).

Scale	Effect	df	F
Tension	Group	1,17	18.33 (380.70) ***
	Hours since dose	10,170	4.44 (19.11) ***
	Group X Hours since dose	10, 170	4.35 (18.73) ***
Depression	Group	1,17	10.60 (689.00) ***
	Hours since dose	10, 170	1.63 (6.53)
	Group X Hours since dose	10, 170	1.17 (4.66)
Anger	Group	1,17	3.50 (58.61)
	Hours since dose	10, 170	1.70 (2.68)
	Group X Hours since dose	10, 170	1.43 (2.25)
Vigour	Group	1,17	14.18 (2783.61) **
	Hours since dose	10,170	3.15 (60.53) ***
	Group X Hours since dose	10, 170	1.11 (21.32)
Fatigue	Group	1,17	8.97 (1286.89) ***
	Hours since dose	10, 170	5.99 (65.52) ***
	Group X Hours since dose	10, 170	1.63 (17.03)
Confusion	Group	1,17	20.06 (678.32) ***
	Hours since dose	10, 170	2.05 (8.89) *
	Group X Hours since dose	10, 170	0.53 (2.31)
TMD	Group	1,17	25.80 (28128.23) ***
	Hours since dose	10, 170	3.95 (415.97) ***
	Group X Hours since dose	10, 170	0.54 (56.37)

Note: Values in parentheses represent mean square errors. * $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 6.11: Repeated measures analyses of variance for POMS sub-scales comparing non-holders (n=9) with controls (n=10).

Scale	Effect	df	F
Tension	Group	1,17	26.78 (3441.69) ***
	Hours since dose	10,170	7.07 (38.54) ***
	Group X Hours since dose	10,170	6.00 (32.73) ***
Depression	Group	1,17	16.80 (5231.60) ***
	Hours since dose	10,170	10.62 (81.08) ***
	Group X Hours since dose	10,170	9.28 (70.89) ***
Anger	Group	1,17	9.01 (1788.41) ***
	Hours since dose	10,170	4.02 (36.20) ***
	Group X Hours since dose	10,170	3.77 (33.91) ***
Vigour	Group	1,17	34.85 (6831.73) ***
	Hours since dose	10,170	7.93 (98.51) ***
	Group X Hours since dose	10,170	2.38 (29.62) **
Fatigue	Group	1,17	17.17 (4192.15) ***
	Hours since dose	10,170	10.48 (96.95) ***
	Group X Hours since dose	10,170	2.00 (18.53) *
Confusion	Group	1,17	17.12 (1416.60) ***
	Hours since dose	10,170	6.12 (30.32) ***
	Group X Hours since dose	10,170	2.55 (12.63) ***
TMD	Group	1,17	32.11 (128385.76) ***
	Hours since dose	10,170	19.77 (1784.71) ***
	Group X Hours since dose	10,170	9.52 (859.92) ***

Note: Values enclosed in parentheses represent mean square errors. * $p<0.05$; ** $p<0.01$; *** $p<0.001$

When the holders were compared with the non-holders, two-way repeated measures analyses of variance showed significant between group main effects for the Tension ($p<0.001$), Depression ($p<0.05$), Anger ($p<0.001$), Vigour ($p<0.05$) and TMD ($p<0.01$) sub-scales (Table 6.12). There were also significant interaction effects for the Depression ($p<0.001$), Anger ($p<0.01$), Fatigue ($p<0.05$) and TMD ($p<0.001$) sub-scales suggesting that there were significant differences between the holders and non-holders in the manner that these mood states changed throughout the 24-hour period.

Table 6.12: Repeated measures analyses of variance for POMS sub-scales comparing holder (n=9) and non-holder (n=9) methadone patients

Scale	Effect	df	F
Tension	Group	1,16	9.68 (1456.41) ***
	Hours since dose	10,160	9.80 (93.48) ***
	Group X Hours since dose	10,160	0.85 (8.15)
Depression	Group	1,16	5.05 (2017.29) *
	Hours since dose	10,160	8.84 (108.73) ***
	Group X Hours since dose	10,160	3.72 (45.79) ***
Anger	Group	1,16	5.00 (1139.52) ***
	Hours since dose	10,160	4.03 (44.76) ***
	Group X Hours since dose	10,160	2.35 (26.04) **
Vigour	Group	1,16	4.46 (848.99) *
	Hours since dose	10,160	3.86 (71.63) ***
	Group X Hours since dose	10,160	1.42 (26.32)
Fatigue	Group	1,16	2.09 (792.00)
	Hours since dose	10,160	7.74 (115.21) ***
	Group X Hours since dose	10,160	1.99 (29.69) *
Confusion	Group	1,16	1.05 (127.68)
	Hours since dose	10,160	4.11 (37.12) ***
	Group X Hours since dose	10,160	1.10 (9.94)
TMD	Group	1,16	6.83 (34510.08) **
	Hours since dose	10,160	12.57 (2060.09) ***
	Group X Hours since dose	10,160	3.78 (619.17) ***

Note: Values enclosed in parentheses represent mean square errors.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Tables 6.13 through 6.19 present results from the post-hoc comparisons among the holders, non-holders and controls for each of the POMS sub-scales at each testing period during the 24-hour inter-dosing interval. Figures 6.9 through 6.15. display the mean scores on each sub-scale for the holders and non-holders at each testing period.

The post-hoc comparisons confirmed that the non-holders reported significantly greater intensity of mood disturbance than the controls, while the holders reported mood changes that were less intense than those of the non-holders. The holders reported significantly less Vigour than the controls immediately prior to each dose and between 2 and 7 hours post-dose. In contrast, the non-holders reported significantly less Vigour than the controls at every testing period during the 24-hour period. Non-holders also reported significantly less Vigour than the holders from 9 hours post-dose.

The non-holders reported significantly more Anger, Confusion, Depression, Fatigue. Tension and Total Mood Disturbance than the controls at every testing period during the inter-dosing interval. In contrast, there were no significant differences between the holders and the controls for scores on the Anger and Depression sub-scales at any testing period. For the remainder of the sub-scales, holders reported significantly more Anger than the controls immediately prior to dosing and from 3 to 5 hours post-dose; significantly more Fatigue at 5 and 9 hours post-dose; and significantly more Tension only in the period immediately prior to dosing. There were no significant differences between the holders and controls for these sub-scales for the remaining time-periods.

When compared with the holders, non-holders experienced a greater intensity of Anger, Tension and Total Mood Disturbance at each point of the inter-dosing interval. Non-holders also experienced significantly greater levels of Depression, Fatigue, and Confusion, and significantly lesser levels of Vigour, in the periods immediately prior to the oral methadone dose than the holders.

Table 6.13: Comparison of mean scores on the Vigour sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 32.

Hours since dose	Controls	Holders	Non-Holders
Before dose	19.20 (7.44)	11.44 (7.13) *	3.33 (4.39) *** ✠✠
1	18.60 (4.25)	14.22 (8.41)	9.22 (8.18) **
2	20.20 (3.01)	12.44 (4.64) **	10.22 (4.58) ***
3	20.40 (3.17)	11.78 (6.91) **	10.56 (5.81) ***
4	18.40 (5.56)	9.56 (9.34) *	7.89 (5.64) ***
5	18.60 (5.40)	9.11 (5.01) ***	7.67 (5.05) ***
6	18.20 (4.87)	8.89 (6.85) **	5.67 (5.10) ***
7	17.20 (5.83)	9.11 (6.09) **	4.56 (4.90) ***
9	13.60 (6.52)	9.33 (4.39)	4.33 (4.82) *** ✠
12	13.20 (5.79)	9.44 (4.03)	4.11 (4.43) *** ✠
23	18.80 (7.00)	10.67 (5.10) **	2.89 (3.52) *** ✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 6.9. : Mean scores on the Vigour sub-scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 32.

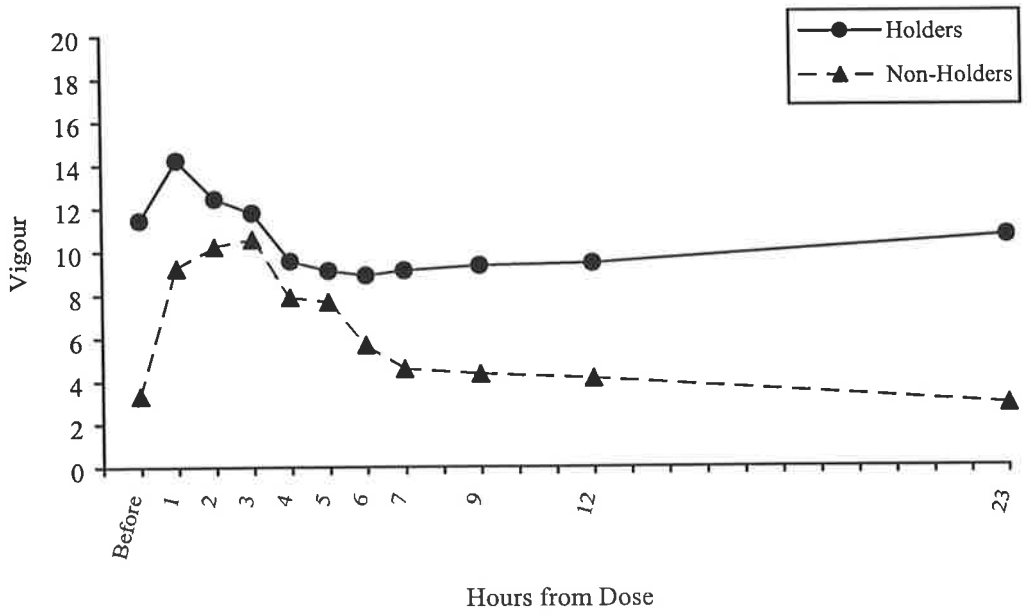


Table 6.14 : Comparison of mean scores on the Anger sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 48.

Hours since dose	Controls	Holders	Non-Holders
Before dose	0.60 (0.84)	2.33 (3.64)	9.89 (9.98) *** ✠
1	0.00	1.22 (2.99)	5.67 (6.96) **
2	0.00	1.11 (2.98)	3.00 (4.24) *
3	0.20 (0.42)	1.78 (2.86)	3.22 (4.18) *
4	0.20 (0.41)	1.44 (2.79)	4.33 (5.87) *
5	0.20 (0.42)	0.44 (0.88)	4.33 (5.24) ** ✠
6	0.20 (0.42)	0.67 (1.12)	4.78 (5.47) ** ✠✠
7	0.20 (0.42)	0.67 (1.41)	4.56 (6.31) * ✠
9	0.20 (0.42)	0.44 (1.33)	7.44 (8.41) *** ✠✠
12	0.20 (0.42)	1.11 (1.97)	8.11 (9.20) *** ✠✠
23	0.00	2.44 (3.21)	11.11 (11.83) *** ✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 6.10: Mean scores on the Anger sub-scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 48.

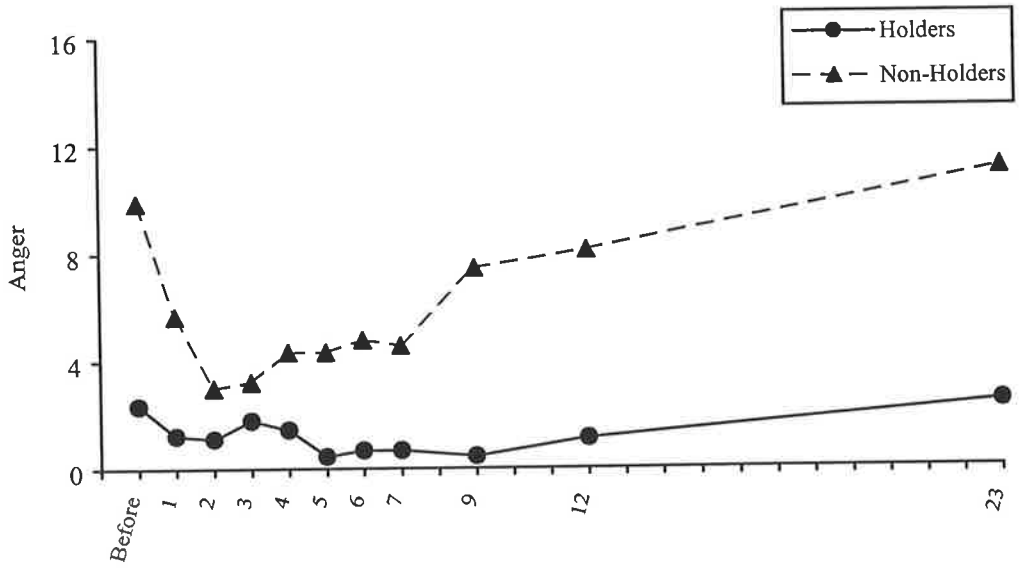


Table 6.15 : Comparison of mean scores on the Confusion sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 28.

Hours since dose	Controls	Holders	Non-Holders
Before dose	2.60 (1.43)	6.22 (3.93) *	9.33 (3.61) *** ✠
1	1.40 (0.84)	4.44 (3.36)	5.56 (4.28) **
2	1.80 (0.42)	3.67 (3.32)	5.22 (4.21) *
3	1.60 (0.84)	5.78 (3.96) **	5.33 (3.61) **
4	1.60 (0.52)	5.11 (4.20) *	4.22 (2.99)
5	1.60 (0.52)	5.89 (4.18) *	6.22 (5.33) *
6	1.80 (0.42)	5.44 (3.68)	6.56 (5.83) *
7	2.00 (1.15)	5.44 (3.32)	8.67 (6.80) **
9	2.40 (0.52)	6.44 (3.43)	9.33 (6.58) ***
12	2.80 (1.23)	7.11 (3.95)	9.89 (6.11) ***
23	2.60 (1.43)	6.33 (3.57) **	9.22 (3.19) *** ✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 6.11: Mean scores on the Confusion sub-scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 28.

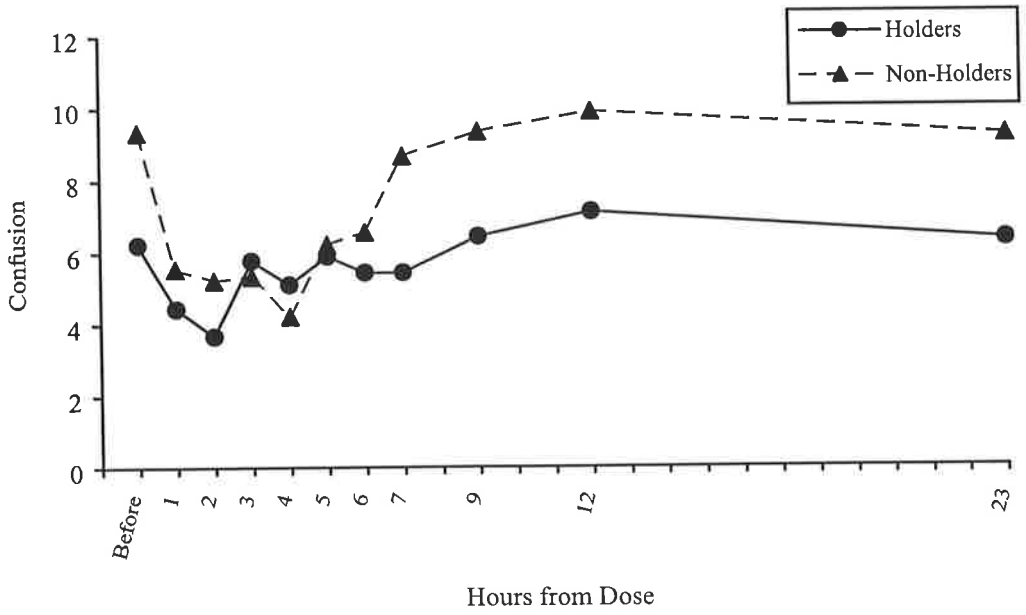


Table 6.16.: Comparison of mean scores on the Depression sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 40.

Hours since dose	Controls	Holders	Non-Holders
Before dose	0.40 (0.52)	5.33 (5.63)	17.44 (9.81) *** ✠✠✠
1	0.00	5.22 (5.61)	10.44 (12.33) **
2	0.00	3.67 (5.39)	8.33 (8.20) ***
3	0.00	3.11 (4.34)	4.44 (6.04) *
4	0.00	2.33 (3.00)	6.44 (7.81) **
5	0.00	3.44 (4.72)	8.78 (9.31) ***
6	0.00	2.67 (2.78)	8.00 (7.57) *** ✠
7	0.20 (0.42)	2.67 (3.08)	8.56 (7.88) *** ✠
9	0.00	3.44 (4.28)	10.56 (8.03) *** ✠✠
12	0.00	4.00 (4.39)	11.22 (9.39) *** ✠
23	0.40 (0.51)	5.11 (5.01)	17.00 (7.18) *** ✠✠✠

Tukey's HSD post-hoc comparisons with Control Group: * $p<0.05$; ** $p<0.01$; *** $p<0.001$
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ $p<0.05$; ✠✠ $p<0.01$; ✠✠✠ $p<0.001$

Figure 6.12: Comparison of mean scores on the Depression sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Maximum score is 40.

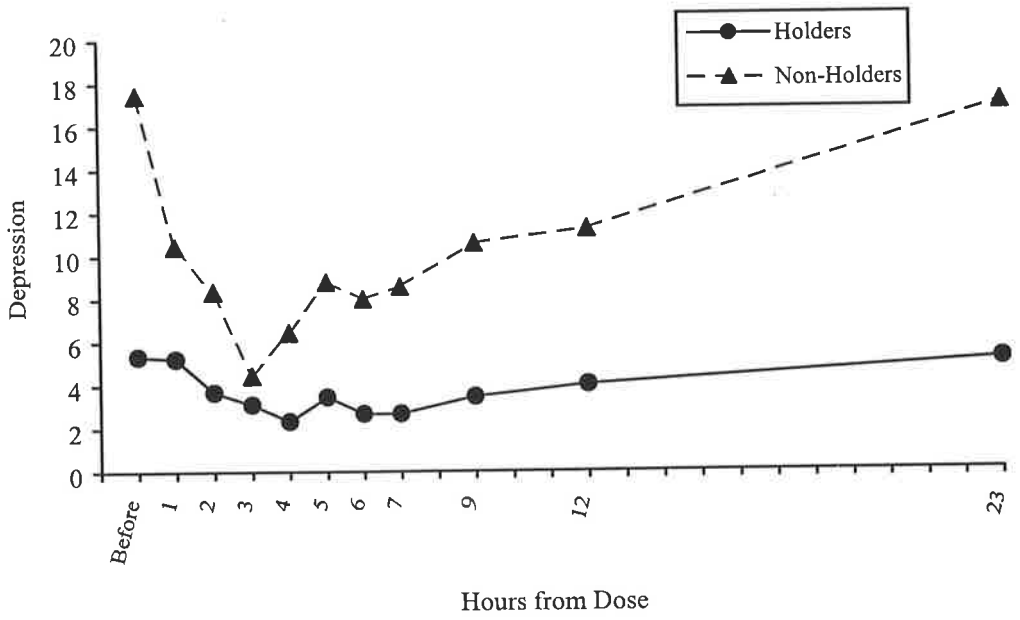


Table 6.17.: Comparison of mean scores on the Fatigue sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 28.

Hours since dose	Controls	Holders	Non-Holders
Before dose	4.00 (2.75)	7.56 (6.00)	14.22 (6.30) *** ✠
1	1.00 (1.33)	3.67 (3.20)	8.33 (8.60) **
2	0.20 (0.42)	2.00 (2.50)	7.44 (8.55) ** ✠
3	0.60 (1.27)	6.11 (5.46)	7.00 (7.97) *
4	1.40 (2.07)	8.78 (8.89)	8.11 (8.36)
5	1.20 (1.69)	8.33 (8.22) *	9.44 (5.70) **
6	3.00 (4.22)	7.11 (6.60)	11.78 (6.12) ***
7	1.60 (2.88)	7.11 (5.97)	12.67 (8.40) ***
9	2.80 (2.53)	10.33 (7.16) *	14.00 (7.37) ***
12	4.80 (5.22)	9.78 (6.52)	14.11 (7.66) **
23	3.40 (2.27)	7.89 (5.60)	15.56 (6.95) *** ✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 6.13. Mean scores on the Fatigue sub-scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 28.

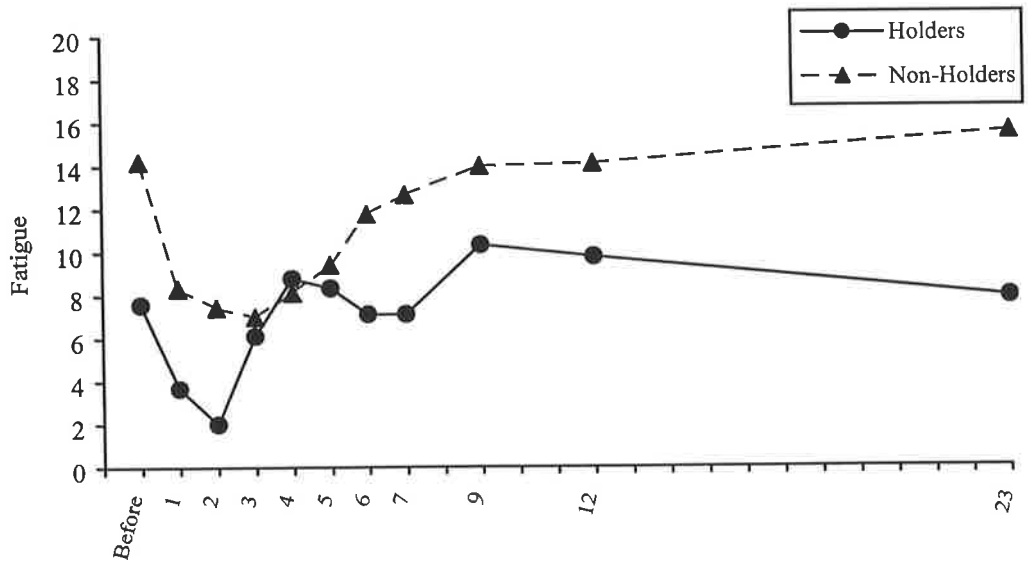


Table 6.18: Comparison of mean scores on the Tension sub-scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 36.

Hours since dose	Controls	Holders	Non-Holders
Before dose	1.80 (1.23)	6.78 (3.99)	13.78 (7.69) *** ✠✠
1	1.20 (1.03)	3.56 (3.36)	8.78 (6.92) *** ✠
2	1.40 (0.84)	3.67 (2.92)	7.44 (3.50) *** ✠✠
3	1.20 (0.42)	2.78 (2.68)	5.44 (3.57) *** ✠
4	1.80 (1.23)	1.78 (2.95)	6.56 (5.57) ** ✠
5	1.80 (1.23)	2.78 (2.68)	9.33 (5.87) *** ✠✠✠
6	2.20 (2.04)	3.11 (2.15)	9.56 (5.15) *** ✠✠✠
7	1.80 (0.79)	3.89 (2.47)	10.44 (5.55) *** ✠✠✠
9	1.20 (0.79)	5.11 (4.34)	9.89 (5.62) *** ✠
12	1.40 (1.08)	5.44 (4.22)	11.78 (5.76) *** ✠✠
23	1.80 (1.23)	8.44 (3.61) **	14.00 (7.26) *** ✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

Figure 6.14.: Mean scores on the Tension sub-scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 36.

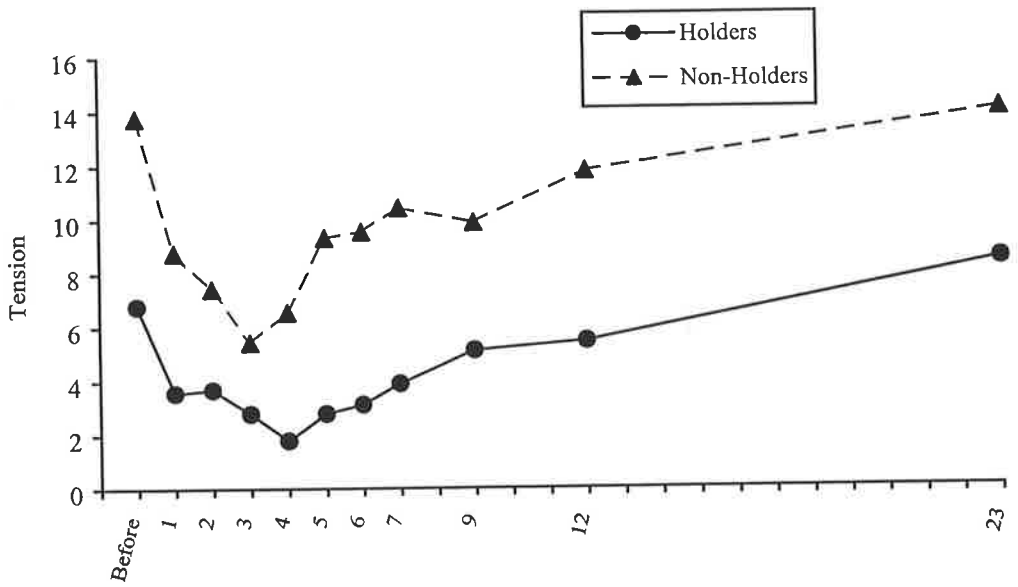
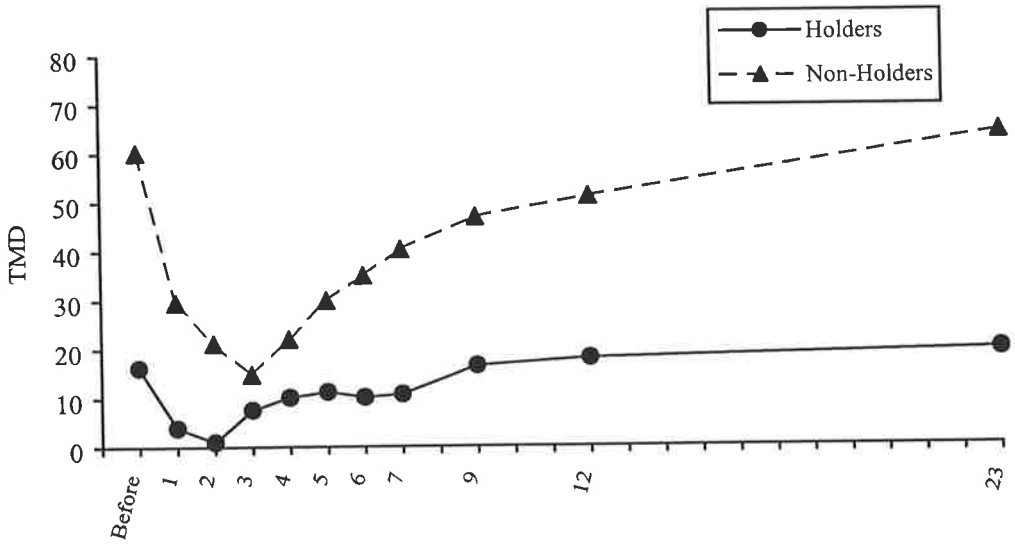


Table 6.19. Comparison of mean scores on the Total Mood Disturbance (TMD) composite scale of the POMS of holders (n=9), non-holders (n=9) and non-opioid controls (n=10) during one 24-hour inter-dosing interval. Values are mean (s.d.), maximum score is 168.

Hours since dose	Controls	Holders	Non-Holders
Before dose	-9.80 (10.98)	16.22 (22.01)	60.22 (33.36) *** ✠✠✠
1	-15.00 (4.32)	3.89 (20.11)	29.56 (38.58) *** ✠
2	-16.80 (3.16)	1.00 (15.12) *	21.22 (24.37) *** ✠
3	-17.00 (3.20)	7.56 (17.99) **	14.89 (19.43) ***
4	-13.60 (7.79)	10.11 (24.13) *	22.11 (25.37) ***
5	-14.00 (7.21)	11.22 (20.40) *	30.00 (28.12) ***
6	-11.20 (9.17)	10.11 (16.24) *	35.00 (25.44) *** ✠✠
7	-11.40 (8.66)	10.67 (15.03) *	40.33 (29.14) *** ✠✠✠
9	-7.00 (8.08)	16.44 (17.23)	46.89 (32.06) *** ✠✠
12	-4.20 (10.55)	18.00 (16.46)	51.00 (33.86) *** ✠✠
23	-10.80 (9.69)	19.56 (16.30) **	64.00 (30.79) *** ✠✠✠

Tukey's HSD post-hoc comparisons with Control Group: * p<0.05; ** p<0.01; *** p<0.001
Tukey's HSD post-hoc comparisons between Holders and Non-Holders:
✠ p<0.05; ✠✠ p<0.01; ✠✠✠ p<0.001

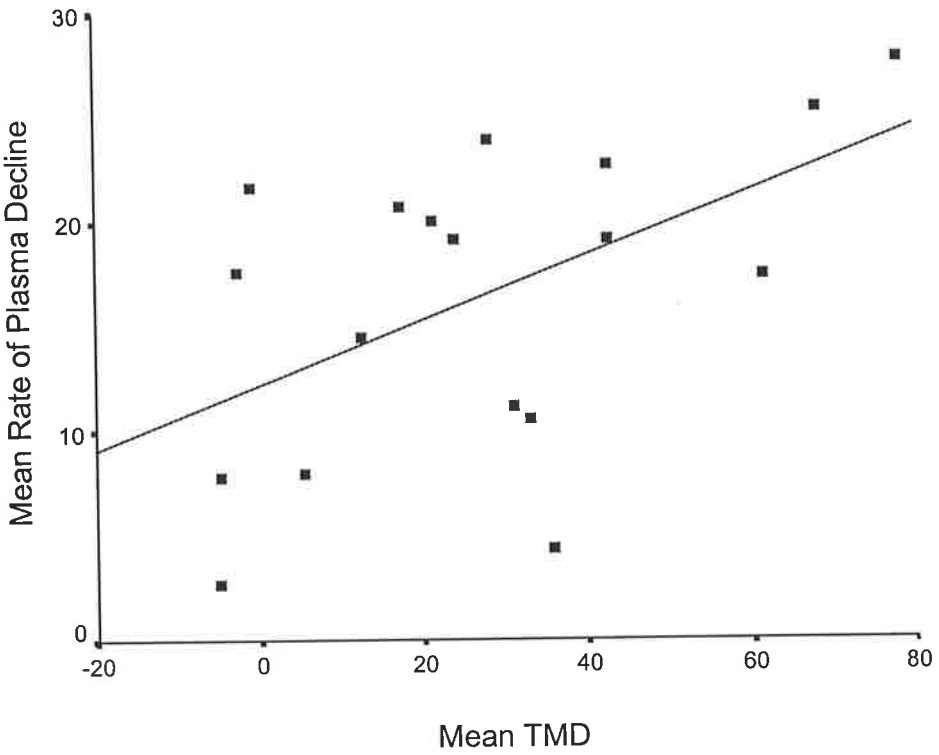
Figure 6.15.: Mean scores on the Total Mood Disturbance (TMD) composite scale of the POMS of holders (n=9) and non-holders (n=9) during one 24-hour inter-dosing interval. Maximum score is 168.



6.3.3. The relationship between plasma nethadone concentration and mood disturbance.

Figure 6.16. presents the significant correlation ($r=0.52$, $p<0.01$) between the mean rate of decline in plasma concentration and the mean score on the TMD sub-scale during the period from peak plasma concentration to the trough for all patients This correlation was increased when the two patients who had used additional opioids were excluded ($r=0.63$, $p<0.01$). The correlation between the maximum rate of decline in plasma concentration and the mean TMD score was also significant when the two patients were excluded ($r=0.46$, $p<0.05$).

Figure 6.16: Correlation between the mean rate of decline in plasma methadone concentration and the mean score on the Total Mood Disturbance scale of the Profile of Mood States from peak plasma concentration to trough (n=18).



6.3.4. Plasma concentration effect relationship for mood disturbance.

Table 6.20. presents the mean slope factors (N) and the EC_{50} values for the POMS sub-scales, including the TMD composite scale, for those patients in whom the model could be satisfactorily applied to the data. This applied to 12 of the patients for Vigour, 3 for Anger, 4 for Fatigue, 7 for Confusion, 8 for Depression and, 9 for Tension.

Table 6.20: Slope factors (N) and EC_{50} values derived from plasma racemic methadone concentration-effect relationships for all patients (n=18) and seperately for the holder (n=9) and non-holder (n=9) groups. Mean ± s.d..

	All Patients	Holders	Non Holders
Anger			
N	2.37 ± 1.19	-	2.37 ± 1.19
EC_{50}	206.35 ± 89.28	-	206.35 ± 89.28
	n=3	-	n=3
Confusion			
N	1.95 ± 0.28	2.09 ± 0.46	1.90 ± .37
EC_{50}	195.87 ± 52.82	195.06 ± 75.91	196.19 ± 72.68
	n=7	n=2	n=5
Depression			
N	5.56 ± 0.87	7.19 ± 1.47	5.20 ± 1.02
EC_{50}	199.17 ± 45.68	104.47 ± 22.28	230.73 ± 55.36
	n=8	n=2	n=6
Fatigue			
N	2.84 ± 0.53	1.48	3.29 ± 0.39
EC_{50}	229.29 ± 89.60	57.27	286.63 ± 97.37
	n=4	n=1	n=3
Tension			
N	3.20 ± 0.44	3.86 ± 0.99	2.87 ± 0.46
EC_{50}	235.08 ± 55.02	269.88 ± 117.88	217.68 ± 65.61
	n=9	n=3	n=6
Vigour			
N	4.22 ± 0.95	4.25 ± 1.62	4.20 ± 1.26
EC_{50}	561.81 ± 72.66	643.10 ± 63.15	503.80 ± 115.53
	n=12	n=5	n=7
Total Mood Disturb.			
N	2.16 ± 0.30	2.12 ± 0.76	2.18 ± 0.25
EC_{50}	289.36 ± 50.43	201.87 ± 68.25	337.96 ± 65.63
	n=14	n=5	n=9

The model could be applied to the TMD scores for 14 of the patients, including all(100%) of the non-holders and 5(56%) of the holders (Fisher's exact $p<0.05$). There was also a non-significant trend for the model to be applied for more of the non-holders than holders for the remaining sub-scales. There were no further significant differences between the patients for whom the model could or could not be applied with respect to gender, age, drug use or time enrolled on the program.

The values for N and EC_{50} were not significantly different between the two groups for any of the responses presented in Table 6.18.. The values for N were greater than 4 for the Depression and Vigour sub-scales indicating very steep plasma methadone concentration-effect relationships for these mood states. The values for N were significantly different between the Confusion and Depression sub-scales ($t=-3.51$, $p<0.01$). There were no significant differences among the remainder of the POMS sub-scales including between Confusion and Tension ($t=-2.10$, $p=0.08$), Confusion and Vigour ($t=-1.77$, $p=0.13$), Depression and Tension ($t=1.83$, $p=0.11$), Depression and Vigour ($t=1.53$, $p=0.17$) and Tension and Vigour ($t=0.64$, $p=0.54$). Statistical differences were not analysed for the remainder of the mean slope factors as the model could be fitted to only a small number of patients.

6.4. Discussion

The present study has found that the intensity and temporal pattern of mood states reported by methadone maintenance patients were associated with plasma methadone concentrations during the inter-dosing interval. To the best of the author's knowledge this is the first time that data have been reported comparing methadone plasma concentration and mood state over an entire inter-dosing interval.

The inclusion of a sample of drug-free controls, and the absence of mood changes in these participants, indicates that the changes in mood that were recorded among the methadone patients can be reasonably interpreted as resulting from methadone ingestion. In comparison with the relatively stable intensity of mood states reported by the controls, methadone patients experienced significant time dependent changes in the intensity of mood states throughout the 24-hour period. Specifically, it was found that peak plasma methadone concentrations were associated with an increase of approximately 51% from baseline for Vigour, and reductions in Anger (59%), Confusion (40%), Depression (67%), Fatigue (40%) and Tension (60%). These changes were in accord with the previously published work of Price and colleagues (1975)(see section 6.1.1).

For methadone patients, the period in which Vigour scores were closest to those of the control subjects corresponded with peak methadone plasma concentrations, and then declined throughout the remainder of the day, returning to baseline levels approximately 6 hours after the dose. The negative mood states showed an inverse pattern, reaching a nadir at the time of the peak plasma methadone concentration and peaking towards the end of the inter-dosing interval. However, even at peak methadone plasma concentrations, methadone patients reported significantly less Vigour and significantly

more disturbance of the other mood states than drug-free controls, indicating that patients' mood state never attained control values.

The methadone program in which these patients were enrolled has a policy of allowing considerable patient control over dose (DASC, 1997). Thus, it is unlikely that the effects noted here were due to inadequate dosing. The mean dose of 65 mg/day amongst the study participants is consistent with recommended clinical practice (Ward et al., 1998). Furthermore, the mean trough plasma methadone concentrations were within or above values considered appropriate (e.g. Bell et al., 1988, Dole, 1988 - see Section 5.1.2.).

One aim of this study was to further determine the characteristics differentiating patients who respond well to methadone (the holders) from those who report persistent opioid withdrawal symptoms (the non-holders). Post-hoc analyses demonstrated that the non-holders reported significantly greater mood disturbance, and significantly lesser Vigour, throughout the 24-hour period than the non-opioid using controls, while the holders displayed mood changes that were less intense. Specifically, holders' scores on the Anger, Depression, Fatigue and Tension sub-scales were not statistically different from control values, while non-holders differed from controls on all sub-scales at all times. When compared to the holders, non-holders experienced a consistently greater level of negative affect and a lesser degree of vigour during the inter-dosing interval. This was consistent with their higher levels of opioid withdrawal and lesser direct opioid effect previously reported in Chapter Five. Demographic variables, other drug use, oral methadone dose, and trough or peak methadone plasma concentrations could not differentiate the groups. The only significant difference between these patients was the significantly more rapid rate of decline in plasma concentration from peak to trough of the non-holders.

The hourly rate of decline in plasma concentration during the period from the peak plasma concentration until the next dose was significantly associated with the mean Total Mood Disturbance (TMD) during that period. Thus, the occurrence of negative mood states in the non-holders is likely to result from the very steep plasma concentration versus effect relationship for these responses. This was supported by the application of the Hill equation to the data. It was possible to fit the sigmoid Emax model to sufficient patients to allow plausible conclusions to be drawn. The mean N values for the Anger (2.4 ± 1.2), Confusion (2.0 ± 0.3), Depression (5.6 ± 0.9), Fatigue (2.8 ± 0.5), Tension (3.2 ± 0.4) and Vigour (4.2 ± 1.0) sub-scales, as well as for the Total Mood Disturbance composite scale (2.2 ± 0.3) indicate relatively steep concentration-effect relationships. This would suggest that relatively small changes in plasma methadone concentration would translate into a significant mood change. The likelihood of clinically significant mood changes will be exaggerated in the non-holders because their rate of decline in plasma concentration was almost twice as rapid as in the holders.

These observations are of considerable clinical relevance as negative mood states have been found to be associated with relapse to drug use (Cummings et al., 1980; Unnithan et al., 1992). It has been suggested that negative mood states are a background factor which increase the likelihood of relapse when coupled with a specific precipitant or cue (e.g. Childress et al., 1994; Greeley et al., 1992; Sherman et al., 1989). As such, it is possible that the non-holders in particular may have an elevated risk of relapse and therefore poor treatment compliance.

6.4.1. Summary and Clinical Implications

A principal objective of methadone is to help the patient feel physically comfortable without producing significant euphoria. Methadone patients' complaints of persistent withdrawal symptoms, despite seemingly adequate oral methadone doses and trough plasma concentrations, can represent a challenge to treatment staff. The present study has shown that methadone patients are most similar to, but not equivalent with, drug-free individuals only when that are experiencing the peak effect of methadone (i.e. at peak methadone plasma concentrations). The intensity of negative mood states, which was greater in the non-holders, was found to accompany the decline of methadone plasma concentration during the inter-dosing interval. These findings have a number of important clinical implications.

Firstly, once daily dosing may not be suitable for those methadone patients who experience significant mood disturbance in the latter part of the inter-dosing interval. An increase in the oral dose is unlikely to be of benefit as this would increase peak plasma concentrations but would not necessarily reduce the rate of change. Dividing the daily methadone dose may be an effective strategy. However, there may be practical difficulties in applying such a strategy to a large number of patients because of the need for supervised dosing in the majority of cases, and the expense involved in methadone dose preparation. An alternative may be the use of alternative opioid pharmacotherapies. With its longer half-life, LAAM may be suitable for patients with a more rapid hourly rate of decline in plasma concentration, while buprenorphine, with its potential role as an anti-depressant (Bodkin et al., 1995) may also be suitable for patients with significant depressed affect. Criteria for evaluating these alternative maintenance pharmaco-therapies should incorporate evaluation of the degree to which they produce mood disturbances.

The second clinical implication from this study relates to the diagnosis and treatment of mood disorders among methadone patients. Clinically significant levels of psychopathology have been observed in opioid users in treatment and non-treatment settings. The most common specific diagnoses in opioid users include depression and anxiety (e.g. Banys et al., 1994; Cicogni et al., 1996; Campbell & Stark 1990; Darke et al., 1992b; Kosten & Rounsaville, 1986; Mason et al., 1998; Milby et al., 1996; Miller et al., 1996; Mintz et al., 1979). Induction and maintenance on methadone has been associated with a reduction in the prevalence of these disorders as well as positive changes in overall mood state (Gibson et al., 1992 Musselman & Kell, 1995; Rounsaville et al., 1986, 1982a, 1982b; Shilony et al., 1996; Steer & Kotzer, 1980; Steer & Schut, 1980; Strain et al., 1991). However, Steer & Kotzer (1980), who measured general levels of mood over the first four months of methadone treatment, found that while there was a general improvement, the recorded mood states remained at levels measured in psychiatric outpatients.

The present study has demonstrated that methadone patients, and in particular non-holders, report significantly more mood disturbance than non-opioid using University students. However, comparisons with appropriate normative data are required for determination of whether the changes noted in the POMS within this sample are equivalent with those of psychiatric samples. The POMS can be used to measure mood states over varying time periods depending on the requirements of a particular study. Time periods that have been used successfully range from "*During the past week including today*", through much shorter periods such as "*Today*" and "*Right Now*". Different rating periods will yield different item and scale means and variances. The normative data provided by the authors of the POMS (McNair et al., 1971) are based on the one-week rating period, and as such, cannot be considered applicable for the shorter time-period ("*Right Now*") utilised in this study. In the absence of normative data it is difficult to determine whether the intensity of mood state changes reported by the

methadone patients in the present study are clinically significant. However, it was possible to locate suitable data (means and standard deviations) from two previously published studies that used the POMS for the "Right Now" time-period: one assessed the impact on mood of a naloxone challenge among opioid users, and the second involved a psychiatric sample of patients diagnosed with a Borderline Personality Disorder.

Handelsman and colleagues (1992) report data from 54 male opioid users administered an initial dose of 20mg methadone, followed 100 minutes later by a subcutaneous injection of 0.4mg naloxone. The TMD score rose from a mean of 29.7 (s.d.=46.1) after methadone to a mean of 43.2 (s.d.=49.2.) after naloxone. Thus, naloxone was associated with an approximate increase of 31% in TMD score.

In a study of a non-opioid using psychiatric sample, Steinberg and colleagues (1997) compared the Depression scores of patients diagnosed with a borderline personality disorder (BPD) before and after receiving an injection of the cholinesterase inhibitor physostigmine. Scores on the Depression sub-scale were recorded at baseline (mean (s.d.) of 15.7 (10.1)) and following an intravenous injection of physostigmine, 14 μg/kg (4.8(8.6)). Administration of physostigmine was associated with a decrease in Depression scores of 10.9 units, or 69%, among patients diagnosed with BPD.

Table 6.21 presents the mean scores on the TMD scale of opioid users receiving a naloxone challenge (Handelsman et al., 1992), and patients diagnosed with BPD (Steinberg et al., 1997). For comparison, scores for these sub-scales are also provided for the sample of methadone patients in the present study, and separately for the holders and non-holders, recorded at peak and trough plasma methadone concentrations.

Table 6.21: Mean Depression and TMD scores from the POMS for all patients in the current study (n=18) and separately for holders (n=9) and non-holders (n=9) at the time of peak and trough plasma methadone concentration compared with published data from 10 Borderline Personality Disorder patients before and after receiving 14 μg/kg physostigmine (Steinberg et al., 1997), and 38 opioid users receiving a 0.4mg naloxone challenge 110 minutes after receiving a 20mg oral methadone dose (Handelsman et al., 1992). Values enclosed in parentheses are standard deviations.

	Borderline Personality Disorder Patients Steinberg et al. (1997) (n=10)		**Treatment Entry Methadone Patients** Handelsman et al.(1992) (n=38)		**Current Study: Stabilised Methadone Patients**					
					All patients (n=18)		Holders (n=9)		Non-holders (n=9)	
	Pre-physostigmine	Post-physostigmine	Pre-naloxone	Post-naloxone	3 hrs post-dose	23.5 hrs post-dose	3 hrs post-dose	23.5 hrs post-dose	3 hrs post-dose	23.5 hrs post-dose
Depression	4.8 (8.6)	15.7 (10.1)	-	-	3.8 (5.2)	11.1 (8.6)	3.1 (4.3)	5.1 (5.0)	4.4 (6.0)	17.0 (7.2)
TMD	-	-	29.7 (46.1)	43.2 (49.2)	11.2 (18.6)	41.8 (33.1)	7.6 (17.9)	19.6 (16.3)	14.9 (19.4)	64.0 (30.8)

While extreme caution is required in making comparisons across these populations, it appears that the sample of methadone patients in the present study demonstrated a change in Depression from plasma peak (3.8(5.2)) to trough (15.7(10.1) that was generally equivalent with the changes observed in BPD patients. Specifically, Depression scores at trough were within one standard deviation of BPD patients before receiving physostigmine, while Depression scores at peak plasma concentration were within one standard deviation of medicated BPD patients. Further, the holders generally reported less Depression (mean (s.d.) of 3.1(4.3) at peak and 5.1(5.0) at trough), and a lesser degree of change in Depression scores (39%) than the BPD patients. In contrast, the non-holders reported levels of Depression that were equivalent with the BPD patients (4.4(6.0) at peak and 17.0(7.2) at trough), as well as an equivalent degree of change (74%). Similarly, in comparison with the TMD scores of opioid users before and after a naloxone challenge, it appears that the holders in the present study reported lesser scores on the TMD scale (7.6(17.9) at peak and 19.6(16.3) at trough). In contrast, the non-holders reported a larger percentage change in TMD score (77%) and at plasma trough reported a TMD score (64.0(30.8)) that was higher than that that of opioid users receiving a naloxone challenge (43.2(49.2)). While caution is warranted, these comparisons suggest that the negative mood disturbance recorded in non-holders in the present study is within the range of scores found in a psychiatric sample and within an opioid using sample experiencing naloxone induced opioid withdrawal. Thus, the mood disturbance of non-holders appears to be clinically significant. However, further research on this area is clearly warranted.

Finally, the DSM-IV (APA, 1994) utilises a hierarchical process of exclusion in diagnostic decision making. A diagnosis of mood disorder, for example, will only be valid if the presenting symptoms can not be explained by another syndrome such as substance use. It has been noted previously that symptoms of opioid withdrawal coincide with negative mood states, making a diagnosis difficult in the context of opioid

dependence (Handelsman et al., 1992). In response to this, several authors have suggested that an important strategy for distinguishing primary mood disorders from the mood effects of opioid withdrawal is the persistence of mood disturbance over time in treatment. Therefore, waiting for a period of time, ranging from a few weeks (e.g. Strain et al., 1991) to a few months (Nunes et al., 1994), is necessary before a valid diagnosis of a mood disorder is possible. The rationale being that stabilisation on an appropriate methadone dose will occur during this time. However, the findings from the present study suggest that methadone patients, and in particular non-holders, have considerable mood disturbance, with the severity of this disturbance being associated with the rate of decline in plasma concentration, rather than a function of time in treatment. As such, the present findings indicate that it is important to differentiate primary mood disorders from the mood disturbances that are associated with changes in plasma methadone concentrations, particularly in non-holders. These two causes of mood change require very different therapeutic strategies.

CHAPTER SEVEN

A SINGLE CASE STUDY OF THE EFFECT OF A DIVIDED METHADONE DOSE REGIMEN UPON OPIOID WITHDRAWAL.

7.1. Introduction

The standard practice of once daily dosing among methadone programs is based upon the premise that methadone has a duration of action of at least 24 hours. As such, it is generally held that the daily "high" to "sick" fluctuations experienced by individuals dependent upon heroin do not occur among methadone patients (e.g. Gerstein, 1992; O'Brien, 1993). However, this is not the case for a substantial proportion of methadone patients. Results from the study presented in Chapter Two, as well as more recent surveys conducted in Europe (Schall et al., 1996; Torrens et al., 1998), suggest that approximately one-third of methadone patients will report opioid withdrawal during the 24-hour inter-dosing interval.

Chapters Five and Six presented plasma concentration-effect relationships that indicated that for subjective responses, particularly withdrawal severity, small changes in plasma concentration translated into relatively large changes in effect. Patients who reported significant opioid withdrawal demonstrated a significantly shorter period of direct opioid effect, a greater intensity of mood disturbance, and more pronounced time-dependent changes in the subjective and physiological response to methadone, than patients who were responding well to methadone. The difference in withdrawal severity between these groups was not related to the oral methadone dose, other drug use or trough plasma methadone concentrations, but rather to the significantly more rapid hourly rate of decline in plasma concentration in the period from peak plasma concentration until the next dose. It was concluded that those patients reporting significant withdrawal, despite

seemingly adequate oral doses and trough plasma methadone concentrations, were at risk of a poor treatment outcome. It was recommended that alternatives to once-daily methadone dosing be explored for these patients.

Nilsson and colleagues (1983) concluded that patients considered 'therapeutic failures' would have higher peak plasma methadone concentrations, and thus more intense subjective direct effect, due to a smaller volume of distribution. This in turn would shorten the terminal half-life, producing a shortened period of feeling 'normal' and withdrawal in the latter part of the 24-hour inter-dosing interval. The authors argued that a methadone dose increase would not change this situation, and might expose the patients to adverse direct opioid effects. It was hypothesised that the answer might be to either shorten the dosage interval or prescribe a longer acting opioid such as LAAM (Nilsson et al., 1983); a conclusion also presented in Chapter Five.

Walton and colleagues (1978) presented a case study of two methadone patients who displayed subjective and objective evidence of opioid withdrawal. Serial plasma methadone concentrations were collected and it was found that these patients experienced a dramatic decline in plasma levels 2 to 6 hours after methadone ingestion. Both patients were prescribed 100mg of methadone per day. One patient (KP) displayed a trough concentration of 400ng/mL, a peak of 1600ng/mL, and a decline in plasma methadone concentration of approximately 1100ng/mL 2 to 3 hours after dosing. The other patient (RP) had a trough concentration of approximately 220ng/mL, a peak concentration of 1000ng/mL and a decline in plasma concentration of approximately 800ng/ml 2 to 6 hours after dosing. Both patients were subsequently prescribed an increased daily methadone dose (180mg/day for KP and 260mg/day for RP) divided thrice daily. The divided dosage regimen resulted in no major fluctuations in plasma methadone concentrations for either patient, with concentrations stabilising between 150 and 200 ng/mL throughout the inter-dosing interval for both patients. No clinical

evidence of opioid withdrawal was observed in the patients on the divided dosage regimen.

The present study represents the third phase of the study documented in Chapters Five and Six. One female patient (KM), who self-identified as a non-holder in the main experiment, was subsequently prescribed a split methadone dose (twice per day) by the medical officer at the public methadone program clinic as part of her standard treatment program. As such, the opportunity was taken to re-test KM after she had been stabilised on the divided dosage regimen for two months. Re-testing occurred 8 months after she had first participated in the study.

7.1.1. The present study

In the present study the effect of a divided dosage regimen was evaluated in one methadone patient. The aim was to:

1. Determine the effect of a divided dosage regimen upon plasma methadone concentration, and subjective and objective opioid response in a patient experiencing opioid withdrawal.

Hypothesis:

1. That a divided dosage regimen will modify the plasma methadone concentration-time profile and thereby reduce the intensity, and alter the temporal pattern, of both direct opioid effects and opioid withdrawal for this patient.

7.2. Method

The patient (KM) first participated in the main experiment in February 1995. She had been enrolled on the methadone program for 10 years. At that time she had a body weight of 65.0 kg, and she was prescribed a daily methadone dose of 120.0 mg/day (1.85mg/kg). Urinalyses results were positive for cannabinoids and benzodiazepines. KM reported that she used cannabis on 8 occasions and benzodiazepines (Rhohypnol) on 16 occasions in the past month. She also self-reported the use of thyroxine (Oroxine, 150mg/day) and smoked 15 cigarettes per day. KM self-identified as a non-holder at this time.

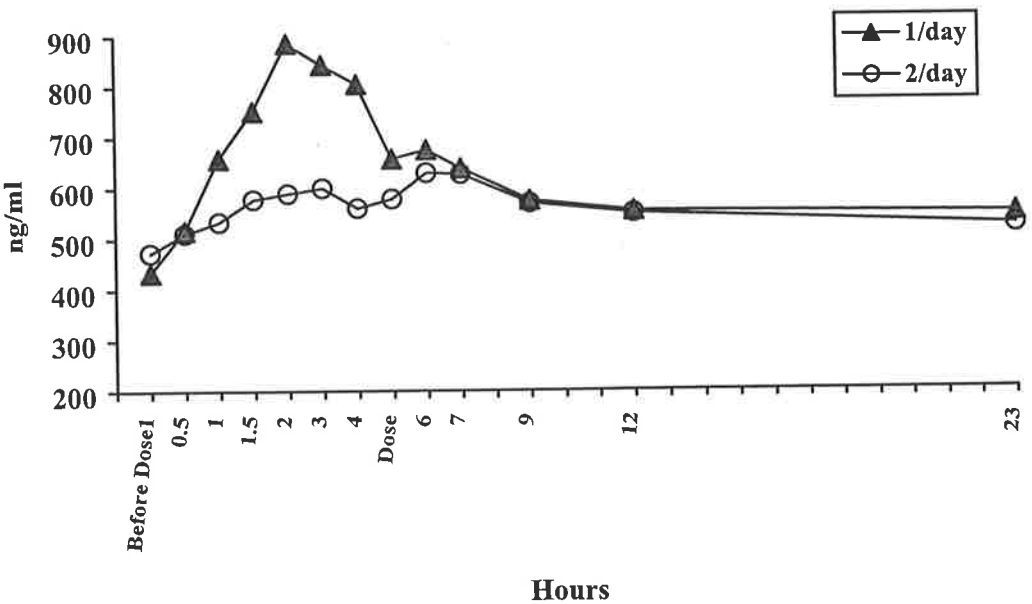
She was prescribed a divided daily methadone dose in August 1995 and was re-examined for this study in October 1995. Her body weight had remained relatively stable (67.50kg). Her total daily methadone dose had been reduced to 112.5 mg/day (1.67 mg/kg), with 60mg taken at 10:30am and 52.5mg taken at 2.45pm. Urinalyses results were positive for cannabinoids and benzodiazepines. KM reported that she used cannabis on 16 occasions and benzodiazepines (flunitrazepam; Rohypnol) on 10 occasions in the past month. She had smoked 20 cigarettes per day in the past month. She also self-reported the use of thyroxine (Oroxine, 150mg/day) and a small amount of dextropropoxyphene with paracetamol (Digesic 2 by 2mg/day), although urinalyses did not reveal the presence of opioids other than methadone. She self-identified as a holder during this testing period.

Ethical approval to conduct this re-test was obtained from the Royal Adelaide Hospital Research Ethics Committee and the Research Review Committee of the Drug & Alcohol Services Council. Data for this natural experiment were collected and analysed using the same methods and procedures described in Chapters Five and Six. The patient was reimbursed AUS$50.00 each time she participated in these analyses.

7.3. Results

The plasma methadone concentrations of KM during the two dosage regimens are presented in Figure 7.1. During the once daily dosage regime peak concentration was 885.49ng/mL, occurring approximately 2 hours after the dose, and the trough concentration was 546.39 ng/mL.. During the divided dosage regime, peak concentration from the first dose was 599.22ng/mL, approximately 3 hours after the dose and the trough was 472.19 ng/mL immediately prior to first dosing and 559.42ng/mL immediately prior to the second dose. During the second dosing interval the peak concentration was 628.27ng/mL, approximately one hour after the second dose, and the trough concentration was 521.86 ng/mL.

Figure 7.1.: Comparison of 24-hour plasma methadone concentrations (ng/mL) of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day.



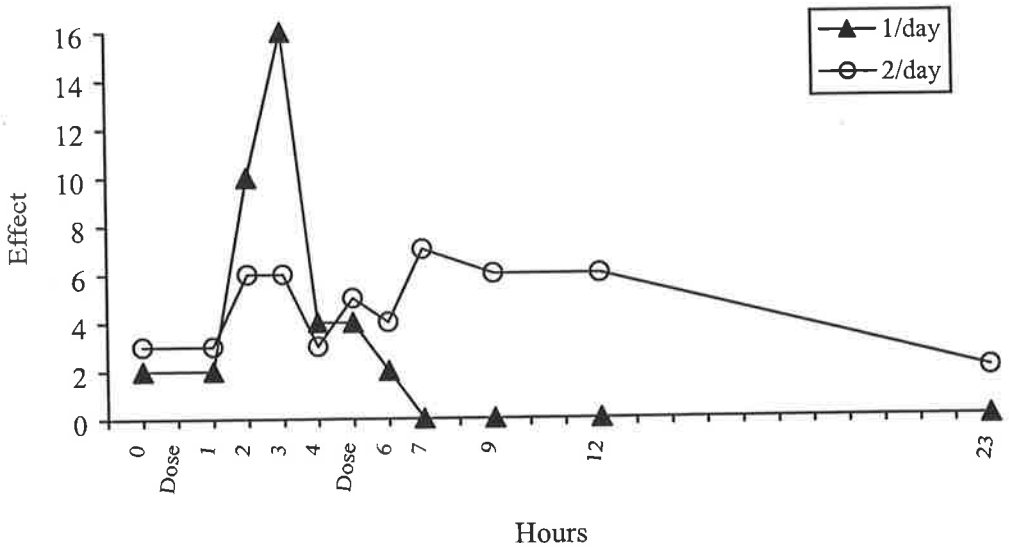
Pharmacokinetic data for KM during the two dosage regimes are presented in Table 7.1. During the once daily dosage regimen the AUC was 13.97 mg.h/L and the peak to trough concentration ratio was approximately 1:6. These values were reduced during the divided dosage regimen, such that the AUC during the entire 24-hour inter-dosing interval was 12.76 mg.h/L (2.25mg.h/L during the first 5 hour dosage interval and 10.51mg.h/L during the remaining 18 hour dosage interval) and the total peak to trough concentration ratio was 1:2 (approximately 1:3 during the first 5 hours and 1:2 during the remaining 18 hours).

Table 7.1.: Pharmacokinetic data of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day.

	Dosing Schedule		
	Once/Day	Twice/Day	
	0-24 hours	0-5 hours	6-24 hours
Dose (mg)	120	60	52.50
AUC (mg.h/L)	13.97	2.25	10.51
Peak Conc. (ng/mL)	885.49	599.22	628.27
Trough Conc. (ng/mL)	546.39	472.190	521.86
Peak to trough ratio	1.62	1.27	1.20

During the once-daily dosing regimen, KM experienced significant fluctuations in subjective direct opioid effect (Figure 7.2.). MBG scores peaked at the maximum of 16 after 3 hours, and declined to zero within 7 hours of dosing. In contrast, the divided dosing regimen produced more stable direct effects, reaching a peak level of 7 after 2 hours from the second dose, before falling to 3 in the periods immediately prior to dosing.

Figure 7.2.: Comparison of direct opioid effect scores, as measured by the MBG scale, of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. Maximum possible score is 16.



The number of opioid withdrawal symptoms, and the severity of those symptoms, reduced after KM had been prescribed a divided daily dose are shown in Figure 7.3. and Figure 7.4. respectively. During the once daily dosage regime, KM reported a minimum of 2 symptoms between 1 and 2 hours after dosing, and a maximum of 15 symptoms immediately prior to dosing. During the divided dosage regime the maximum number of withdrawal symptoms observed was 8, which occurred 19 hours after the second daily dose.

Figure 7.3. Comparison of opioid withdrawal symptoms of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. Maximum possible score is 16.

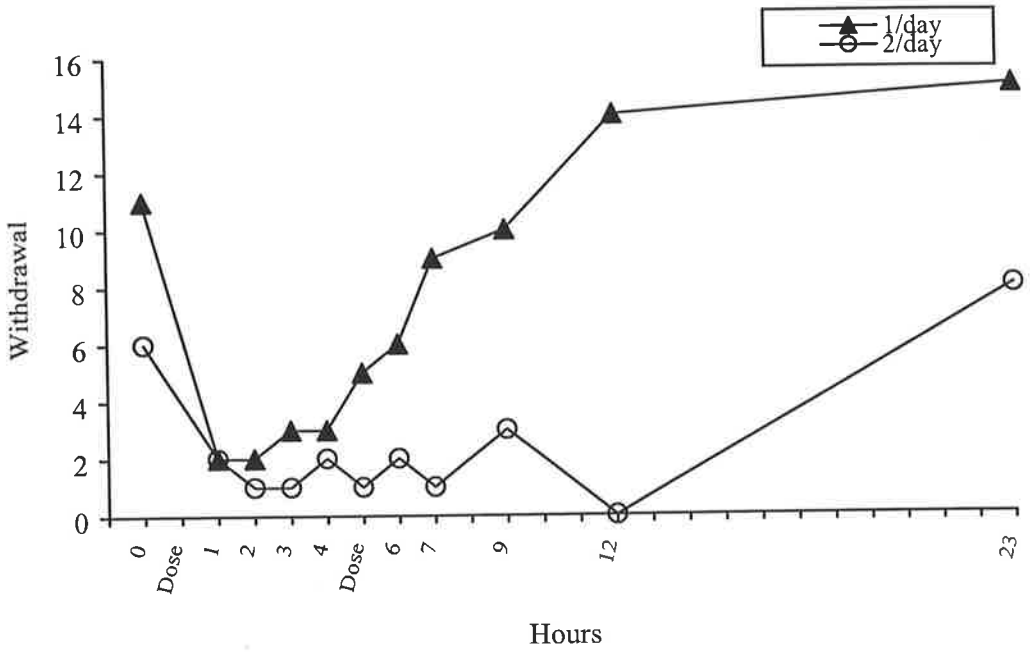
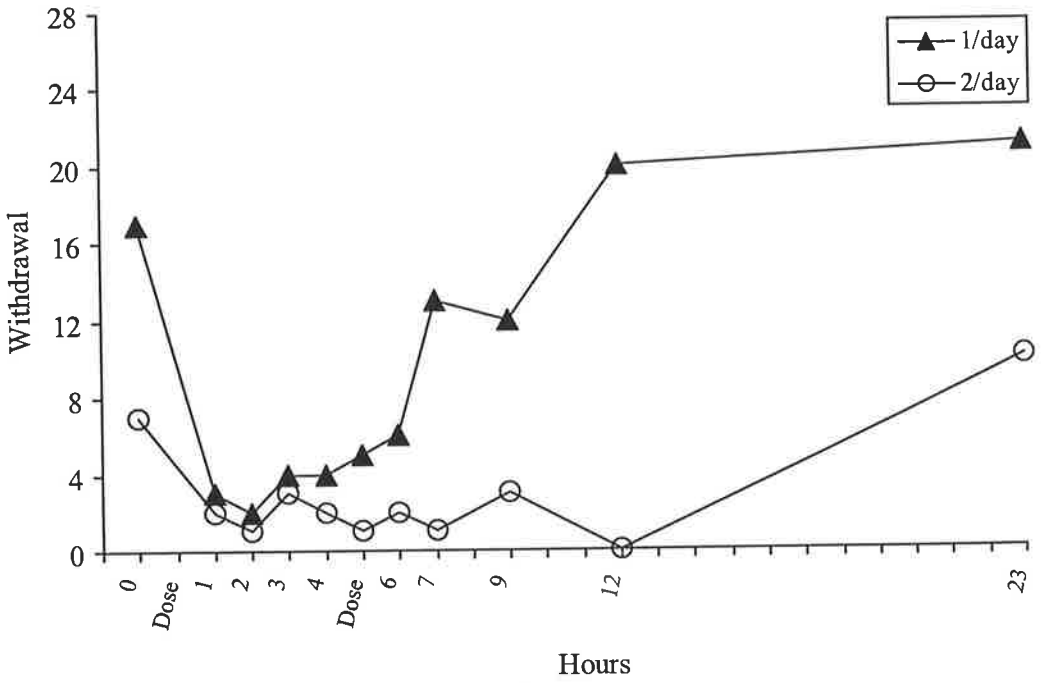
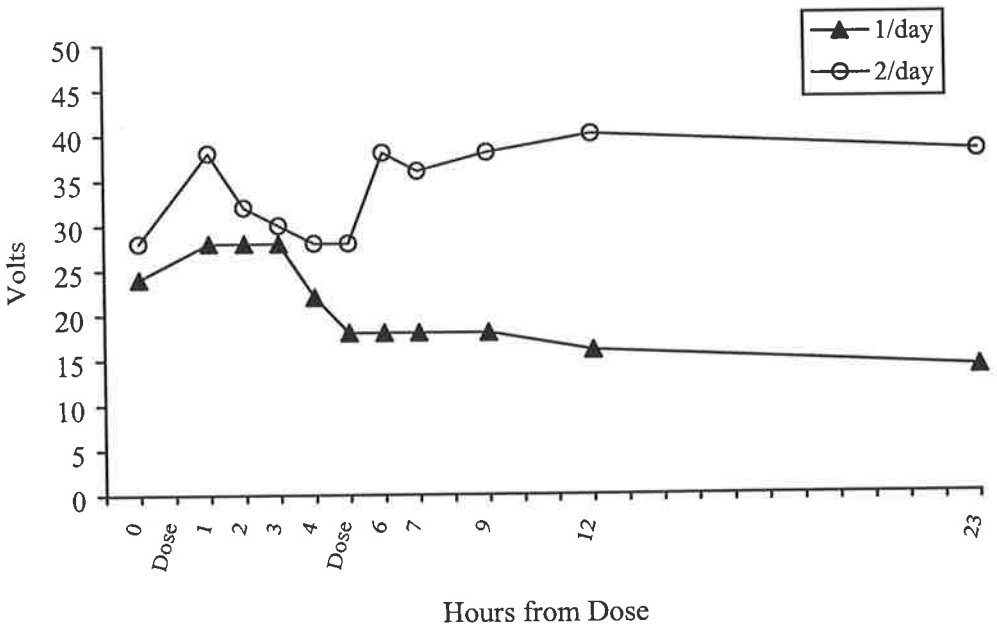


Figure 7.4.: Comparison of opioid withdrawal severity of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. Maximum possible score is 48.



The measure of analgesic effect, pain threshold, was consistently higher in KM during the divided dosage regimen (Figure 7.5). This was most apparent during the latter part of the day where the pain threshold remained relatively stable. During the once-daily dosage regimen, pain threshold peaked within one hour of dosing and lasted for three hours, before returning to baseline levels 5 hours after dosing. During the divided regimen, pain threshold peaked within one of the first dose, returned to baseline at the time of the second dosing, and then again increased during the next hour and continued at this level for the remainder of the dosage interval.

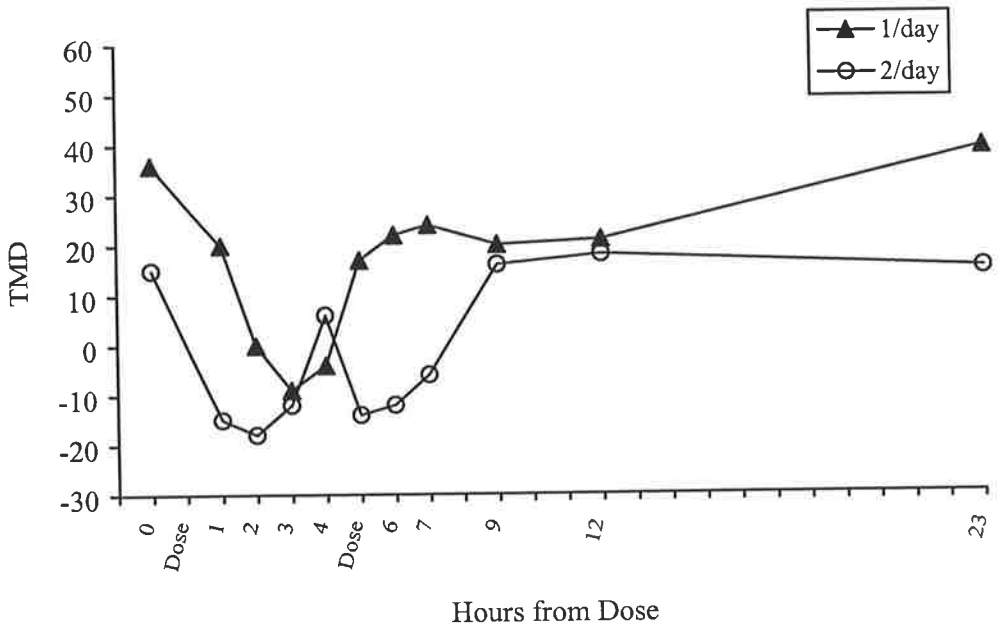
Figure 7.5. Comparison of pain threshold scores of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. (Volts)



The divided dosage regimen produced relatively little change in the scores on the Total Mood Disturbance scale of the Profile of Mood States (Figure 7.6.). For both dosage regimens, scores on this scale peaked in the period immediately prior to receiving the

methadone dose. However, the peak scores were lower in the divided dose regimen than in the once-daily regimen. Scores on the sub-scales of the POMS are provided in Appendix 7.

Figure 7.6. Comparison of Total Mood Disturbance scores from the Profile of Mood States of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. Maximum possible score is 168.



Of the objective indices, observable differences were noted in pupil size and saliva production for the different dosing regimens. During the once-daily dosage regimen, peak miosis occurred 2 hours after dosing, and then increased to near baseline levels during the next 2 hours (Figure 7.7.). During the divided dosage regimen, peak miosis occurred 5 hours after the first dose. This coincided with the second dose, and resulted in KM's pupil size remaining at this level for the next 4 hours before increasing steadily during the remainder of the 24-hour interval. Finally, KM produced greater amounts of saliva at each testing period during the divided dosage regimen (Figure 7.8.). Values for the remaining objective indices are also provided in Appendix 7.

Figure 7.7. Comparison of pupil size of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. (mm).

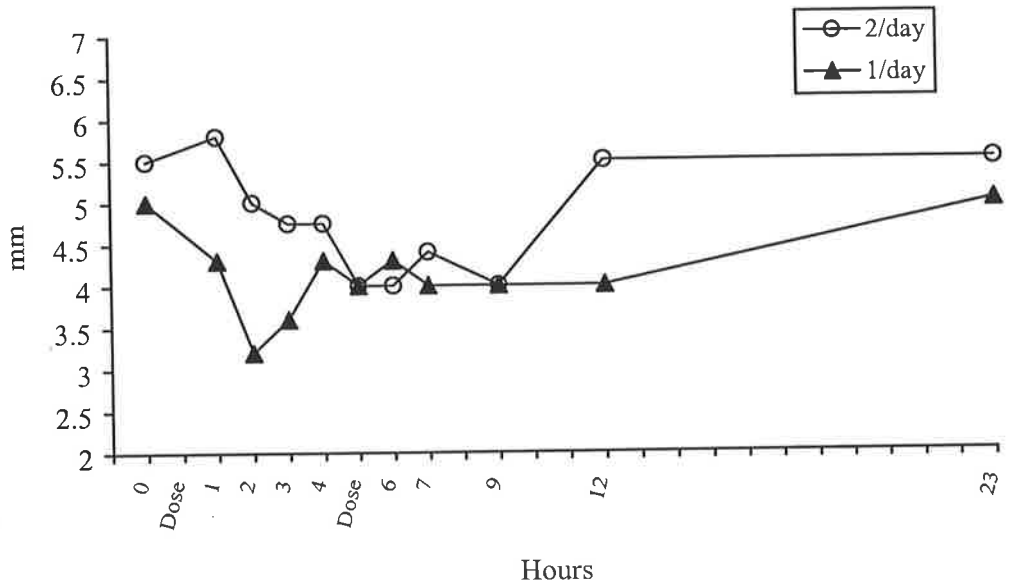
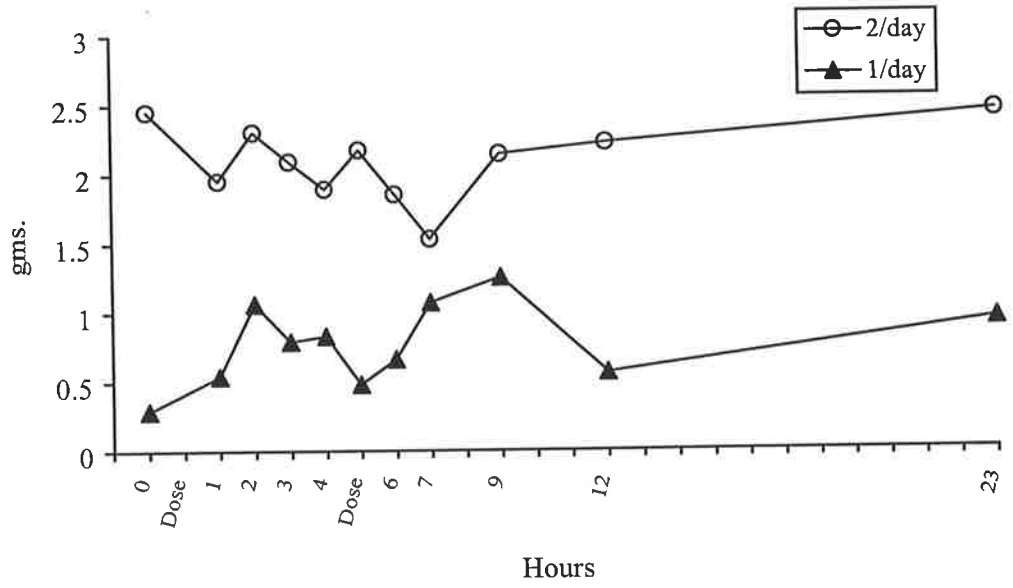


Figure 7.8. Comparison of saliva production of one methadone patient (KM) prescribed 120 mg of methadone once daily or 112.5 mg divided over two occasions per day. (grams).



7.4. Discussion

It was demonstrated in Chapter Five and Chapter Six that the intensity and time course of direct opioid effects and withdrawal symptoms were strongly related to fluctuations in plasma methadone concentrations over a dosing interval. Patients reporting significant opioid withdrawal were shown to have a significantly more rapid hourly rate of decline in the plasma concentration during the latter stages of the inter-dosing interval than other patients. It was hypothesised that reducing the inter-dosing interval by dividing the daily dose would reduce the plasma methadone concentration time profile, thereby decreasing opioid withdrawal severity. The present single-case study has supported this hypothesis in that dividing the daily methadone dose reduced the withdrawal severity of one patient during the 24-hour period.

The results of the present case study are largely in accord with those of Walton and colleagues (1978), who showed a dramatic clinical improvement in two patients prescribed a thrice-divided daily dose and a significant flattening of the curve of plasma methadone concentrations. However, measures of physiological and subjective direct opioid effects were not recorded in that study, and the patients also received an increase in the total oral methadone dose prescribed in the 24-hour period. In contrast, the patient in the present study received a reduced methadone dose divided twice daily. Despite this difference, the divided dosage regimen resulted in less intense opioid withdrawal as well as less intense and more stable levels of subjective direct opioid effect.

The standard clinical practice when responding to patients reporting uncomfortable withdrawal symptoms is to increase the daily dose. Nilsson and colleagues (1983) argued that for a significant proportion of patients such as strategy was likely to be ineffective and that shortening the dosage interval would be more appropriate. The present case study provides further support to this assertion in that withdrawal severity

was reduced by a divided-dose regime, despite the patient receiving a smaller daily dose. As such, the present study has provided pharmacokinetic and pharmacodynamic data to support the conclusion of Nilsson and colleagues (1983).

Although the patient in this study felt more comfortable on the divided dosage regimen, there was only a relatively small change in mood disturbance, and relatively little change in the physiological measurements between the two dosage regimens. There are possible explanations for these findings. Firstly, the mood disturbance reported by this patient on either dosage regimen was less than the mean mood disturbance of the non-holders previously reported in Chapter Six. The patient was prescribed a benzodiazepine during both testing periods and this may have has a greater effect on her overall mood disturbance than her plasma methadone concentration.

It has been suggested that patients with a rapid rate of plasma concentration decline may cope with their discomfort by using illicit drugs, benzodiazepines or dropping out of treatment (Walton et al., 1978). This was not noted in the current study in that there was not a decline in the patient's use of cannabis. Bell and colleagues (1990) reported that the failure of high methadone trough concentrations to suppress illicit heroin use was the result of behavioural rather than pharmacological factors. It should be noted that the patient in this study used cannabis recreationally and did not use illicit heroin. However, it may be the case that this patient continued cannabis use due to a liking for the drug effect rather than as a means of medicating uncomfortable withdrawal symptoms. As such, this patient may require additional counselling to reduce illicit drug use.

Methadone patients complaining of opioid withdrawal despite seemingly adequate methadone doses (i.e. 'the dose is not holding') have been previously reported (e.g. Bell et al., 1988). The standard clinical response to such reports has been to use trough plasma methadone concentrations as a basis for dose reassessment. However, previous

research utilising serial plasma methadone concentrations have indicated that a proportion of methadone patients display aberrant metabolism (e.g. Nilsson, 1983; Tennant, 1987). The patient described in the present study, displayed significant opioid withdrawal despite a large trough plasma methadone concentration. A reduction and division of this patient's daily methadone dose reduced the plasma methadone concentration-time profile and thereby reduced opioid withdrawal severity. The present case study has used analyses of serial methadone concentrations to demonstrate the effectiveness of dividing the daily-dose in a patient who reports withdrawal. As such, aberrant metabolism should be considered when patients complain of non-holding and display withdrawal despite seemingly adequate doses. Although the present findings are based on one patient, and obviously more data are required, the results from the present study justify the collection of serial plasma methadone concentrations as a technique for the diagnosis and management of methadone patients who respond poorly to methadone.

CHAPTER EIGHT

GENERAL SUMMARY AND DISCUSSION

The principal aim of this thesis was to determine the factors associated with the occurrence of symptom complaints, especially opioid withdrawal, among methadone maintenance patients. To achieve this broad aim, specific objectives included:

- determining the prevalence of symptom complaints among methadone maintenance patients;
- determining the patient characteristics and treatment variables associated with the occurrence of symptom complaints;
- determining the relationship between plasma racemic methadone concentration and pharmacodynamic response during the inter-dosing interval;
- determining the factors that might explain why some patients report opioid withdrawal symptoms toward the end of the inter-dosing interval (i.e. the methadone is not holding) and others do not;
- determining the pharmacokinetic and pharmacodynamic factors that influence opioid withdrawal severity.

A particular focus of this thesis was examining methadone patients who reported that their daily methadone dose was consistently ineffective in suppressing opioid withdrawal symptoms (designated the non-holders). The following discussion will begin by summarising the effects of methadone upon maintenance patients, before focussing upon the determinants of withdrawal.

8.1. The effects of methadone upon maintenance patients

In the first study, a non-selected and representative sample of methadone patients who had participated in the methadone program for an average of approximately 11 months reported an average of 8 symptom complaints that they attributed to methadone treatment. All patients reported at least one symptom and the majority of specific symptoms surveyed were experienced by nearly one-third of the sample. The most frequently reported direct opioid effect symptoms were constipation and a dry mouth. Frequently reported opioid withdrawal symptoms included excessive sweating and muscle pain, while insomnia and reduced libido were also common. Methadone patients reported all symptoms to a far greater extent than non-opioid using controls. An assessment of the 7-day test re-test reliability among a randomly selected sample of these patients indicated the consistency of these self-reports.

As described in the introduction to this thesis (Chapter One) there are a number of possible individual and treatment regimen characteristics that may alter the pharmacological effectiveness of methadone. These may include clinical policies, particularly the setting of an adequate methadone dose, drug interactions, and individual variation in methadone half-life and clearance rate. Other factors associated with the occurrence of symptom complaints among maintenance patients may include clinical procedures, the degree of tolerance to the direct opioid effects of methadone and classical conditioning. In general, these factors were found to be less important for explaining the observed withdrawal symptoms than were methadone pharmacokinetics.

The South Australian Methadone Public Maintenance Program has adopted many of the clinical procedures associated with increased rates of treatment participation and retention. Most importantly, the program has a policy of setting individualised methadone doses, whereby patient complaints of withdrawal or craving are often

accompanied by dose increases. Despite such a policy, symptom complaints, particularly opioid withdrawal symptoms, were common among these patients.

There were no correlations between treatment length and the overall frequency of symptoms, or more specifically with the intensity of direct opioid effects or withdrawal symptoms. While it is possible that tolerance to direct opioid effects such as constipation and a dry mouth develops over longer periods of time than were measured in this thesis, insufficient tolerance would not explain the occurrence of withdrawal symptoms.

It was found in the first study that, after controlling for methadone dose level, benzodiazepine use was associated with higher levels of direct opioid effects but not opioid withdrawal symptoms. It has been reported that when taken within one hour of dosing, benzodiazepines enhance the methadone effect, while chronic use has been suspected to lower plasma methadone concentrations and produce withdrawal (see section 1.7.2.2.). The findings from the present study were in accord with those of Preston and colleagues (1984), and suggest that the direct opioid effects of methadone were enhanced by concurrent administration of benzodiazepines. Attention should be directed to limiting the use of benzodiazepines among patients, as this might decrease the frequency of symptom complaints for at least this subset of methadone patients.

In another study, conditioned responses to opioid-related stimuli were assessed among methadone patients. It was demonstrated that some reports of withdrawal might represent a conditioned response to cues found in the environment during drug taking. The intensity of subjective opioid withdrawal reported by a small sample of methadone patients increased after presentation of a drug-related stimulus. Higher methadone dose levels have been associated with reduced signs and symptoms of opioid withdrawal among many patients (see section 1.13). Childress and colleagues (1986a; 1986b) postulated that methadone would also generally attenuate the incidence and intensity of

conditioned withdrawal responses among methadone patients, although statistics demonstrating such a dose-response relationship were not reported. This assertion was confirmed in that the size of the increment in subjective withdrawal was negatively associated with the methadone dose level, such that patients prescribed higher methadone doses exhibited smaller changes in conditioned withdrawal severity. It was unlikely that the subjective withdrawal severity reported by the patients after presentation of the drug-related stimulus, which were almost double baseline levels, was the result of inadequate dosing. Rather, it appeared that methadone doses of at least 65mg/day were sufficient to alleviate daily opioid withdrawal in many patients, while higher dose levels also reduced the severity of the conditioned opioid withdrawal response.

It appeared that the most important factor associated with the occurrence of symptom complaints among maintenance patients might have been the magnitude of the daily dose. However, it was found that the total number of symptoms reported in the first study was only moderately correlated with methadone dose. Specifically, methadone dose level was moderately correlated with direct effects but not with withdrawal severity. The mean methadone dose among study participants was consistent with the level required to alleviate withdrawal symptoms in many patients (see section 1.13.2). This suggested that factors other than the absolute level of the oral methadone dose were important in symptom presentation.

A study was conducted to determine the time-dependent changes in self-reported symptom complaints during a 24-houir inter-dosing interval. It was found that the majority of symptom complaints varied in intensity throughout the inter-dosing interval. Direct opioid effects were maximal approximately 2-3 hours after dosing and opioid withdrawal was maximal immediately prior to dosing. This time course of effect and withdrawal suggested a relationship with plasma methadone concentrations.

The plasma racemic methadone concentration-effect relationships for subjective and objective responses were assessed. The inclusion of a sample of non-opioid using controls, and the absence of significant changes in subjective and objective responses among these participants, suggested that the changes recorded among the methadone patients could be reasonably interpreted as resulting from methadone ingestion. There was an inverse relationship between plasma methadone concentrations and withdrawal severity, heart rate and respiration rate, as well as a direct relationship with subjective opioid effect, pain threshold and pupil diameter.

There were also substantial time-dependent changes in the mood state of the patients. In comparison with controls, methadone patients exhibited increased anger, depression, tension, confusion and fatigue, and decreased vigour. The mood states of methadone patients were most similar to, but not equivalent with, non-opioid using controls only at peak plasma methadone concentrations. To the best of the author's knowledge this is the first time that data have been reported comparing methadone plasma concentration and mood state over an entire inter-dosing interval.

It was possible to apply the sigmoid E_{max} model to both objective and subjective responses in this chronic dosing study in sufficient patients to allow plausible conclusions to be drawn. Analyses indicated that for the subjective responses, notably withdrawal severity and mood disturbance, small changes in plasma methadone concentrations translated into relatively large changes in effect. Withdrawal severity and mood disturbance were significantly associated with the rate of plasma decrease in the period from peak plasma concentrations to trough.

8.2. The non-holders

In the first study, it was found that over half of the sample reported having the experience of their methadone dose not 'holding' for the entire inter-dosage interval. It was of further concern to note that over one-third of patients report that their methadone dose was consistently ineffective in suppressing withdrawal symptoms despite the finding that these patients had a higher oral methadone dose than other patients. Patients who reported consistent opioid withdrawal during the inter-dosing interval were designated the 'non-holders' and comparisons were made with patients who did not report this experience (the holders).

In the second study, which analysed the time-dependent self-reported effects of methadone, it was found that the non-holders experienced a smaller degree of opioid effect, and a greater intensity of opioid withdrawal, throughout the 24-hour period than the other patients. Further, while changes in opioid effect intensity were similar between the two groups, changes in withdrawal intensity throughout the dosage interval were different. These differences could not be accounted for by differences in oral methadone dose. Furthermore, patients complaining of the dose 'not holding' were not more likely to use benzodiazepines, and could not be differentiated by any other drug use, health or treatment variables. Although these patients were consuming a significantly higher oral methadone dose, and had a higher dose to body weight ratio, withdrawal complaints persisted.

These findings suggested that there was a differential response to methadone between sub-groups of maintenance patients. The role of methadone pharmacokinetics and pharmacodynamics was assessed. While there were relatively few significant differences in the intensity of physiological responses between the groups, post-hoc analyses demonstrated that the non-holders displayed greater time-dependent changes in

physiological response than non-opioid using controls, while the holders displayed physiological changes that were less intense. The finding that the differences between the groups were greater for the subjective responses than for the physiological responses was consistent with the assertion that opioid withdrawal is subjectively severe but objectively mild (see Section 1.13). Further, the time dependent differences in physiological response between the holders and non-holders were consistent with the greater intensity and longer duration of opioid withdrawal, as well as the shorter duration of subjective opioid effect reported by the non-holders.

Post-hoc analyses also demonstrated that the non-holders reported significantly greater mood disturbance, and significantly lesser vigour, throughout the 24-hour period than the non-opioid using controls, while the holders displayed mood changes that were less intense. Specifically, holders' ratings of anger, depression, fatigue and tension were not statistically different from control values, while non-holders differed from controls on all sub-scales at all times. When compared to the holders, non-holders experienced a consistently greater level of negative affect and a lesser degree of vigour during the inter-dosing interval. This was consistent with their higher levels of opioid withdrawal and lesser direct opioid effect.

Demographic variables, other drug use, treatment length or oral methadone dose could not differentiate the patient groups. As a result, pharmacokinetic differences were analysed.

8.3. Pharmacokinetic determinants of withdrawal severity

When compared with methadone patients who did not report significant subjective opioid withdrawal, the non-holders exhibited a significantly shorter period of direct opioid effect and more pronounced time-dependent changes in the subjective and

physiological response to methadone. The mean area under the plasma concentration versus time curve was equivalent in the holders and non-holders, indicating that racemic methadone total systemic clearance and bioavailability were not likely to be different between the two groups. The time to achieve maximum plasma concentration, the maximum concentrations and the peak to trough plasma concentration ratio were not significantly different between the two groups. The mean trough plasma methadone concentrations were virtually identical, and well within or above values which have been considered to indicate appropriate dosing practices.

The only pharmacokinetic difference between the non-holders and holders was the significantly more rapid average hourly rate of decline in the plasma concentration during the period from the peak plasma concentration until the next dose. The maximum rate of plasma decline, that is, the largest decline in plasma methadone concentration that occurred in any hour between plasma peak and trough, was almost twice as large in the non-holders than in the holders. Further, it was also found that there was a significant correlation between the hourly rate of plasma decline and withdrawal severity in the period between plasma peak and trough among all patients. It is therefore likely that the rate of decrease in methadone plasma concentrations, rather than the absolute trough level, will determine whether or not a patient experiences significant withdrawal symptoms. Determining this rate requires repeated sampling over a period of at least 24-hours and this has not been done in previous studies.

Despite a significantly larger hourly rate of decline in plasma methadone concentration, non-holders had a peak to trough plasma concentration ratio that was similar to that of the holders. A possible explanation for this finding can be derived from consideration of the distribution phase of methadone among stabilised patients. The pharmacokinetic differences between patient groups were explained by the more rapid decline in the plasma concentration during the long distribution phase in the non-holders. Trough

concentrations, however, would be in the post-distribution phase and therefore, be equivalent in the two groups. As such, the occurrence of withdrawal symptoms in the non-holders is likely to be the consequence of the very steep plasma concentration versus effect relationship for this response. Thus, a relatively small change in the plasma concentration during the initial decline in plasma concentration (distribution phase) would translate into a large clinical response. This would be exaggerated in the non-holders, whose rate of decline in the plasma concentration was almost twice as rapid as in the holders.

The standard clinical practice when responding to patients reporting uncomfortable withdrawal symptoms is to increase the daily dose. Nilsson and colleagues (1983) argued that for a significant proportion of patients such as strategy was likely to be ineffective and that shortening the dosage interval might be more appropriate. A single-case study was conducted and provided support for this assertion. The patient displayed significant opioid withdrawal despite a large trough plasma methadone concentration. A division of this patient's daily methadone dose reduced the plasma methadone concentration-time profile and thereby reduced opioid withdrawal severity. This occurred despite a small reduction in the oral methadone dose. In total, this thesis has provided pharmacokinetic and pharmacodynamic data to support the conclusion of Nilsson and colleagues (1983).

8.4. Clinical and Research Implications

In summary, among these groups of long-term methadone maintenance patients, opioid responses were strongly correlated with changes in plasma racemic methadone concentrations. For the subjective responses, notably withdrawal and mood disturbance, small changes in plasma methadone concentrations translated into relatively large changes in effect. It was demonstrated that the differences between holders and non-

holders were not related to oral methadone dose, other drug use, trough plasma methadone concentrations or the mean area under the plasma concentration versus time curve, but rather to the significantly more rapid hourly rate of decline in the period from the peak plasma concentration until the next dose. Therefore withdrawal severity was a consequence of pharmacokinetic rather than pharmacodynamic differences. However, the pharmacokinetic analyses should be qualified by the fact that methadone was administered as the racemate and differences in the disposition of the two enantiomers, and, in particular, the unbound concentrations of the active enantiomer R-(-)-methadone, require further investigation. Nonetheless, a number of important clinical implications derive from this thesis.

Firstly, previous authors (e.g. Bell et al., 1988; Whitehead, 1974) have maintained that self-reports of 'not holding' may be merely an attempt to deceive the clinic for an increase in oral dose. The data in this thesis, however, demonstrate that self-reports of subjective withdrawal, despite a seemingly adequate methadone dose, are associated with significant time-dependent subjective and physiological effects. Differences in the time-dependent effects of methadone were observed in different settings, and among different groups of patients.

Secondly, the results of this thesis suggest that trough plasma methadone concentrations above 200 ng/mL cannot by themselves be used to determine the adequacy of the dosage regimen, since substantially higher concentrations were achieved in the majority of the holders and non-holders. Repeated analyses of plasma methadone concentration over a 24-hour inter-dosing interval identified the differences between the patient groups, and demonstrated the reduction of withdrawal severity resulting from a division of the daily methadone dose. As such, aberrant metabolism should be considered when patients complain of non-holding and display withdrawal despite seemingly adequate doses. The results from this thesis justify the collection of serial plasma methadone concentrations

as a technique for the diagnosis and management of methadone patients who respond poorly to methadone.

The widely accepted once-daily dosage regimen may not be suitable for a significant proportion of methadone patients. A possible strategy for these patients may be to divide the daily dose, rather than further increasing the dose. An increase in the daily methadone dose might increase peak plasma concentrations and so produce adverse direct opioid effects (such as respiratory depression), without reducing withdrawal severity as the decline in plasma concentration may continue to be rapid. The single-case study presented in this thesis supported such a strategy. However, there may be practical difficulties in dividing the daily dose of significant numbers of patients. These practical constraints might include requiring patients to report twice daily if they do not have take-home privileges, and increasing the cost of treatment delivery. Nonetheless, reducing the rate of plasma methadone concentration decline is effective in reducing withdrawal severity.

Finally, longer acting alternatives to methadone should be evaluated. These alternative opioids might reduce the rate of plasma concentration decline, without the practical difficulties of a divided methadone dosage regimen. Currently, buprenorphine, LAAM and slow-release morphine are currently under investigation in Australia. These evaluations should incorporate pharmacokinetic and pharmacodynamic measurements, particularly of subjective response, during the inter-dosing interval.

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LIST OF APPENDICES

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome.

The following summary is organised by the dependent, rather than independent, variable. The dependent variables studied are: retention, post-treatment outcome (usually drug use), drug use during treatment, employment during treatment, compliance with program rules and process (eg counselling appointments), and criminal behaviour during treatment. The majority of studies do not allow one to declare an independent variable as a predictor of outcome (ie regression analyses and discriminant function analyses were rare). As such the following discussion is in terms of positive or negative correlations with the outcome. Formulation of the list of variables declared to be associated with outcome was based upon the ratio of studies in support of that variable.

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Retention					
Ball et al, 1994	USA	1.gender (men) 2.education 3.age 4.race 5.marital status 6.homeless 7.treatment history 8.criminal history	retention	1.positive 2.positive 3.none 4.none 5.none 6.none 7.none 8.none	Treatment for different drugs & included in-/out-patients. Fixed demographic variables have little predictive power with respect to retention.
Calsyn et al, 1992	USA	personality disorder (MCMI)	retention	none	No correlation with comorbidity or any MCMI subtypes
Condelli, 1993	USA	1.age 2.ease of access	retention	1.positive 2.positive	Ease of access includes geographic convenience, convenient clinic hours and short waiting lists. Therefore, may be considered as tapping into motivation.

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Craig, 1980	USA	1.employment 2.number of arrests 3.age	retention	1.positive 2.negative 3.positive	
Dale & Dale, 1973	USA	1.age 2.race (white) 3.motivation 4.outside assistance for habit 5.court referral	retention (at 2mths)	1.positive 2.positive 3.negative 4.negative 5.negative	Tested at time of drop-out
Del Rio et al, 1997	Switzerland	1. duration of opioid use 2. employment 3. age	retention	1.positive 2.positive 3.none	1.Risk of dropping-out was greater for patients uring opioids for less than 7 years. 3.Age was not significant once duration of use had been controlled for.
Dolan et al, 1986	UK	treatment history	retention	positive	
Friedmann et al, 1994	USA	Interim treatment first	retention	postive	Not significantly different from comprehensive only.
Gerstein, 1992	USA	treatment motivation	retention	positive	Suggests program factors more influential than any initial differences in motivation or severity of problems.
Gill et al, 1992	USA	ASPD	retention	none	

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Hubbard et al, 1989	USA	1. marriage 2. poly drug use	retention	1. positive 2. negative	Only opioid users retained in treatment longer
Joe & Simpson, 1975	USA	treatment history	retention	positive	
Joe et al, 1991	USA	1. psychological adjustment 2. poly drug use	retention	1. positive 2. negative	More depressive symptoms associated with better retention.
Joe et al, 1994	USA	1.general problems 2.legal problems 3.medical problems 4.education problems 5.mental health problems 6.employment problems 7.family 8.financial 9.drug problems 10.age 11.gender 12.race 13.marital status 14.years of education 15.source of referral	retention & time until relapse	1.none 2.none 3.none 4.none 5.negative 6.positive 7.none 8.none 9.none 10.none 11.none 12.none 13.none 14.none 15none	Treatment environment most important predictor. No demographic variable predictor of relapse when considered singly. Sample had been enrolled for 3months+: perhaps demographic variables less important after client in treatment for a period of time.

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Joe et al, 1991	USA	1.race (black) 2.education 3.social security 4.self-referral 5.medical referral 6.mental health problems 7.depression 8.poly drug use 9. treatment history	retention	1.negative 2.positive 3.negative 4.positive 5.positive 6.negative 7.positive 8.negative 9.none	
Kosten et al, 1989, 1992	USA	1.opioid dependence (naloxone challenge 12 months after entry) 2.opioid history 3.previous treatment 4.cocaine dependence 5.age 6.non-white 7.self-report drug use	retention & drug use at 1 year	1.negative 2.none 3.none 4.negative 5.positive 6.negative 7.negative	1. For whites only 7. For non-whites only
Levine et al, 1972	USA	1.anxiety 2.depression 3.compliance	retention	1.positive 2.negative 3.positive	No objective tests used in psychiatric interview. Anxiety and depression may be a result of the pharmacological effects of heroin.

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Maddux et al, 1994	USA	1.treatment fees 2.gender 3.ethnic group 4.education 5.incarceration history 6.marital status 7.productive activity	retention	1.negative 2.none 3.none 4.none 5.none 6.none 7.none	
McLellan, 1983	USA	1.age 2. psychological adjustment	retention	1.positive 2. negative	Descriptive measures of personality and psycho-pathology not predictive of outcome but quantitative measures suggest negative correlation with retention.
Moffett et al, 1972	USA	1.legal problems 2.family problems 3.poly drug use 4.unemployment	retention	1.negative 2.negative 3.negative 4.negative	

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Nwakeze et al., 1997	USA	1.age 2.self-referral 3.heroin use only 4.poly-drug use 5.gender (female) 6.culture	retention	1.positive 2.positive 3.positive 4.negative 5.positive 6.positive	Variables (1. - 5.) were independent predictors of retention after controlling for clinic. 6. Hispanic patients had higher retention rates than non-white or whaite patients. However, this difference did not remain significant once clinic variables had been controlled for.
Perkins & Bloch, 1971	USA	1.employment 2.legal problems 3.drug use in treatment	retention	1.negative 2.negative 3.negative	
Rosenberg et al, 1972	USA	1.employment 2.living with family 3.opioid history	retention	1.positive 2.positive 3.positive	Tested at admission.
Saxon et al., 1996	USA	1.age 2.race (non-black) 3.legal problems	retntion	1. positive 2.positive 3.negative	
Schaffer & LaSalvia, 1992	USA	poly drug use	retention	negative	Noted that benzodiazepine use increased during 1st year of MM.

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Smart & Gray, 1978	USA	1.treatment motivation 2.drinking problems 3.life problems (money etc) 4.length of alcohol problem 5.treatment history	retention	1.curvilinear 2.negative 3.curvilinear 4.curvilinear 5.positive	Alcohol treatment program but raises question that most distributions will be curvilinear.
Strain et al, 1994	USA	1.cocaine (pre-treatment) 2.poly drug use (pre-treatment) 3.psychological problems (pre-) 4.medical problems (pre-) 5.employment problems (pre-)	retention	1.negative 2.negative 3.positive 4.positive 5.positive	180-da y Methadone programme.
Szapocznik & Ladne, 1977r	USA	1. employment 2. marriage 3. poly drug use 4. alcohol use	retention	1. positive 2. positive 3. negative 4. negative	1. Employment required before client able to leave MM voluntarily - so may be confounded.
Winburn et al, 1974	USA	1.legal 2.employment 3.drug use	retention	1.none 2.none 3.negative	Comparisons made at treatment entry and 6-months

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Post-Treatment Outcome					
Ball & Ross, 1991	USA	opioid use history	outcome	negative	
Bell et al, 1992	Aust	pre-treatment criminal history	outcome	negative	
Cushman, 1978, 1981	USA	employment	outcome	positive	
Dole & Joseph, 1978	USA	1.employment 2. pre-treatment criminal history 3. opioid use history	outcome	1.positive 2. negative 3. negative	
Hubbard et al, 1989	USA	1.pre-treatment criminal history 2. opioid use history 3. alcohol use	outcome	negative	
Judson & Goldstein, 1982	USA	1.pre-treatment criminal history 2. alcohol before and during 3. heroin use during treatment 4. living with an addict 5. minority ethnicity 6. alcohol use	outcome	1.negative 2. negative 3. negative 4. .negative 5. .negative 6. negative	All moderate correlations: highest r=.26.

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Judson et al, 1980	USA	prior treatment	outcome	positive	Comparisons at 1year before enter,4yrs and 5yrs after. Suggests some clients will require a number of attempts before succeeding
Longabaugh & Clifford, 1992	USA	1.age 2.poly drug use	outcome	1.positive 2.negative	
McGlothin & Anglin, 1981	USA	1.employment 2. pre-treatment criminal history	outcome	1.positive 2. negative	
McLellan, 1983	USA	1.employment 2. opioid use history	outcome	1.positive 2. negative	
Simpson & Sells, 1982	USA	1.pre-treatment criminal history 2. opioid use history	outcome	1.negative 2. negative	
Strain et al, 1994	USA	prioir treatment	outcome	positive	Used ASI

Appendix 1: Table A1. Patient characteristics associated with methadone maintenance retention rates and outcome(continued).

Author	Country	Patient Characteristics	Outcome Measure	Direction of Correlation	Comment
Saxon et al., 1996	USA	1.age 2.pre-treatment cocaine use 3.psychological functioning 4. legal pronblems	drug use	1.negative 2.positive 3.negative 4.positive	Authors note that the intensity of treatment provided and methadoen dose also influenced outcome.
Scaffer & LaSalvia, 1992	USA	1.benzodiazepines (10mth) 2.cocaine (3 mth) 3.amphetamine (7 mth) 4.Benzo (8mth)	drug use (12 mth)	1-4positive	Suggests that most drug use during MM predicts higher levels at end of 1st year. But some 1st year drug use is associated with a decline in drug use at 12 mth: suggest self-medication or occassional lapses.
Simpson et al, 1995	USA	1.race (white) 2.employment 3.motivation for treatment 4.self-confidence 5.self-esteem 1. prev arrests 2. employment 3. treatment history	1-5 compiance 1-3 crime	1.positive 2.positive 3.positive 4.positive 5.positive 1. positive 2. negative 3.positive	Claims engagement in treatment (attendance) is a pre-cursor of retention.
Spunt, 1993	USA	street-orientated identity	crime	positive	
Zanis et al, 1994	USA	1.depression 2.cocaine use 3.education 4.marital status (married)	employ	1.negative 2.positive 3.positive 4.positive	

Appendix 2: Table A2. Program policies and procedures associated with methadone maintenance retention rates and outcome.

	Author	Country	Variables assessed	Direction of association	Comment
Drug use during treatment					
Counsellor attitudes	Kang et al., 1997	USA	Attitude scale measured "tough-mindedness" about drug dependence, abstinence versus maintenance orientation, strictness to policy adherence, opinions of clients, medical knowledge of methadone, and satisfaction of work environment.	none	No correlation reported between counsellor attitudes and percent of patients testing positive for heroin or cocaine.
Counsellor education level	McLellan et al., 1991 Kang et al., 1997	USA USA	Years of training Drug or alcohol counselling certification	none none	
Counsellor patient management techniques	McLellan et al., 1991	USA	Techniques assessed included detail of patient notes, charting all pertinent aspects of patient contact, clearly formulated plan of rehabilitation that had been developed in consultation with colleagues and patient, plans documented throughout treatment, use of referral agencies, organised and consistent in approach.	negative	
Change in methadone formulation	Steels et al., 1992	UK	Methadone program changed methadone preparation from tablet to liquid form	positive	

Appendix 2: Table A2. Program policies and procedures associated with methadone maintenance retention rates and outcome. (continued)

	Author	Country	Variables assessed	Direction of association	Comment
Program policy	Bell et al., 1995	Aust.	Abstinence and time-limited orientation	positive	A higher rate of heroin use in clinic oriented toward abstinence was attributed to time-limited treatment and the low methadone doses.
	Saxon et al., 1996	USA	Philosophy re: higher methadone dose levels	negative	Clinics using higher methadone dose levels associated with diminished cocaine use.
Participation in treatment	Simpson et al., 1995	USA	Measured number of attendances with counsellor.	negative	Higher session attendance was associated with reduced cocaine and opiate use, higher psychological functioning, higher counsellor evaluation of rapport, motivation and self-confidence but was not associated with patient criminal involvement.
	De Leon et al., 1995	USA	Measured rate of attendance at a day-treatment program based on modified therapeutic community approaches.	negative	

Appendix 2: Table A2. Program policies and procedures associated with methadone maintenance retention rates and outcome. (continued)

	Author	Country	Variables assessed	Direction of association	Comment
Retention					
Program policy	Caplehorn et al., 1996, Caplehorn, 1994	Aust	Abstinence orientation.	negative	
Program policy	Maddux et al., 1993	USA	Assessed the following policy changes in a single program: fees had increased to US$6.00/day, outpatient induction, strict take-home dose policy, compulsory attendance at twice monthly counselling, observed urinalysis and continual illicit drug use was grounds for discharge	negative	
Counsellor attitudes	Brown et al., 1975	USA	Measured staff attitudes toward patients (e.g. methadone patients as inferior to abstinent peers) and abstinence orientation.	negative	
Contingency management	Rowan-Szalz et al., 1997	USA	Rewards provided to patients new to treatment (first 90 days) based on a token economy for attending counselling sessions and providing drug free urines.	positive	
Rapid admission	Maddux et al., 1995b	USA	Compared 1-day admission with 14-day admission	none	Rapid admission was associated with pre-treatment attrition but not retention in program.

Appendix 2: Table A2. Program policies and procedures associated with methadone maintenance retention rates and outcome. (continued)

	Author	Country	Variables assessed	Direction of association	Comment
Rapid admission	Dennis et al., 1994	USA	Assessed reduction of waiting lists from 49 days to 1 day, reduction of admission process from 2 weeks to 1 day, and increase of static capacity by 25%.	none	Procedure changes increased the numbers of patients on the program, attracted lower functioning patients but did not lead to a significant change in retention rates.
	Friedman et al., 1994	USA	Compared retention of patients first admitted via an interim program versus those admitted directly to a comprehensive methadone program.	none	
No treatment fees	Maddux et al., 1994	USA	Patients admitted to maintenance were randomly assigned to a fee-paying (US$2.50/day) or no-fee-paying condition.	positive	Elimination of fees significantly increased retention.
Optional Counselling	Maddux et al., 1995a Saxon et al., 1996	USA USA		positive positive	Higher levels of intervention had a moderate effect on retention and drug use during treatment.
Patient self-regulation of methadone dose	Maddux et al., 1995a	USA		none	

Appendix 2: Table A2. Program policies and procedures associated with methadone maintenance retention rates and outcome. (continued)

	Author	Country	Variables assessed	Direction of association	Comment
Patient knowledge of methadone dose level	Condelli, 1993	USA	Re-analysed TOPS data.	positive	
Participation in treatment	Maddux et al., 1995b	USA	Measured number of appointments per month with caseworker	negative	May be confounded with the level of problems experienced by patients who attended counselling more frequently.
Clinic accessibility	Payte & Khuri, 1993		Measured accessibility to clinic in terms of hours of opening.	positive	
Patient evaluations of the quality of ancillary services	Condelli, 1993	USA	Re-analysed TOPS data - patient evaluations of social services received during first month of treatment as high quality and ease of access.	positive	

Appendix Three - Methadone Symptoms Checklist - Version 1

These questions are designed to find out how methadone has made you feel since you joined the program. Please answer all of the questions.

Since joining the methadone program, have you experienced:

1. Constipation	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never
2. Sweating more than usual	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never
3. Trouble urinating (pissing)	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never
4. Reduced desire for sex	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never
5. Trouble having sex (erectile dysfunction,lubrication)	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never
6. Itchy skin	4. Yes, always	3. Yes, a lot.	2. Yes sometimes	1. Yes, rarely	0. No, never

7. Itchy nose

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

8. Nausea (feeling sick)

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

9. Vomiting (being sick)

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

10. Increased appetite (wanting more food, more often)

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

11. Dizziness

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

12. Trouble thinking clearly

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

13. Confusion

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

14. A dry mouth

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

15. Problems with your teeth (e.g. cavities)

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

16. Feeling tired (lethargic)

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

17. Trouble sleeping (insomnia)

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

18. Muscle aches and pains

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

19. Pains in your bones or joints

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

20. Have you found that your daily methadone dose does not 'hold' all day?

4.	3.	2.	1.	0.
Yes,	Yes,	Yes	Yes,	No,
always	a lot.	sometimes	rarely	never

21. Changes in weight since joining program Increase/Decrease/Same

If you are a **female:**

22. Have you noticed any irregularities in your menstrual cycle (periods)?

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

23. Have you noticed any other effects of methadone? _____

4.	3.	2.	1.	0.
Yes, always	Yes, a lot.	Yes sometimes	Yes, rarely	No, never

The checklist is now complete. Seal in an envelope.

Appendix Four

METHADONE SYMPTOMS CHECKLIST – version 2

Please indicate how you are feeling right now. Put a ✓ in the appropriate box for each symptom.

Time _____ am/pm

RIGHT NOW

	NONE	MILD	MODERATE	SEVERE	EXTREME
Constipation					
Sweating					
Trouble urinating					
Reduced desire for sex					
Nausea (feeling sick)					
Decreased Appetite					
Hallucinations					
Dry mouth					
Feeling tired					
Methadone dose not holding					
Chest pains					
Swelling of feet or ankles					
Diarrhoea					
Itchy skin					
Need to urinate					
Vomiting					
Increased appetite					
Nervousness					
Bleeding gums					
Bone / Joint pain					
Muscle aches					
Numbness in hands or feet					
Heartburn					
Itchy nose					
Want to drink alcohol					
Dizziness					

RIGHT NOW

	NONE	MILD	MODERATE	SEVERE	EXTREME
Headache					
Runny nose					
Want to drink (not alcohol)					
Trouble thinking clearly					
Yawning					
Feelings of coldness					
Stomach cramps					
Runny eyes					
Confusion					
Muscle spasms / twitching					
Blurred vision					
Feel energetic					
Heart pounding					
Tense muscles					
Goose pimples					
Pleasant feeling in stomach					
Feeling high					
Increased desire for sex					
Craving					
Feeling unhappy/depressed					
Feeling anxious					
Feeling irritable/angry					
Other (please write symptom)					

Appendix Five

MBG - Positive Opioid Effect

Please indicate how you are feeling right now.
Put a ✓ in the box if you agree with the statement.

Time _____ am/pm

RIGHT NOW

	Yes
I would be happy all the time if I felt as I feel now *	
My nose itches	
I am in the mood to talk about the feeling I have *	
My hands feel clumsy	
I am full of energy *	
My movements are free, relaxed and pleasurable	
I have been scratching myself	
Things around me seem more pleasing than usual *	
I have an unusual weakness in my muscles	
I feel less discouraged than usual *	
I feel very patient	
I fear that I will lose the contentment that I have now *	
I have some pins and needles sensations	
I feel as if something pleasant just happened to me *	
I feel anxious and upset	
Today I say things in the easiest possible way *	
I have a sentimental feeling	
I feel so good that I know other people can tell it *	
My speech is not as loud as usual	
I am more clear headed than dreamy *	
I can completely appreciate what others are saying when I am in this mood *	
I have a peculiar craving for icecream or something cold	
I feel as if I would be more popular with people today *	
I would like to sit and think	
I feel a very pleasant emptiness *	
I have been dozing occasionally for seconds or minutes	
I feel in complete harmony with the world and those about me*	
I have a pleasant feeling in my stomach *	
I feel high *	

* MBG items. Note that additional items were included on this page to reduce the likelihood of a response bias among the methadone patients. The additional items were not analysed.

Appendix 6 **Opioid Withdrawal Scale**

1*. Feeling Sick	None	Mild	Moderate	Severe
2*. Stomach cramps	None	Mild	Moderate	Severe
3*. Muscle spasms/twitching	None	Mild	Moderate	Severe
4*.Feelings of coldness	None	Mild	Moderate	Severe
5*. Heart pounding	None	Mild	Moderate	Severe
6*. Muscular tension	None	Mild	Moderate	Severe
7*. Aches and pains	None	Mild	Moderate	Severe
8*. Yawning	None	Mild	Moderate	Severe
9*. Runny eyes	None	Mild	Moderate	Severe
10. Runny nose	None	Mild	Moderate	Severe
11. Gooseflesh	None	Mild	Moderate	Severe
12. Perspiration	None	Mild	Moderate	Severe
13. Hot flushes	None	Mild	Moderate	Severe
14. Restlessness	None	Mild	Moderate	Severe
15. Salivation	None	Mild	Moderate	Severe
16. Feelings of weakness	None	Mild	Moderate	Severe

*: Short Opiate Withdrawal Scale (SOWS)

Appendix 7

Single case study of the effect of a divided methadone dosage regimen: Physiological and mood state changes

Figure A7-1: Comparison of systolic blood pressure of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (mmHg).

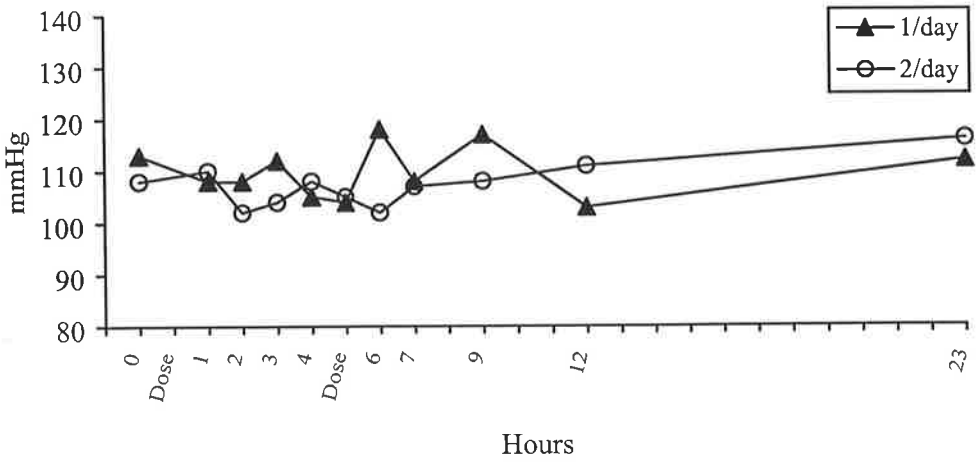


Figure A7-2: Comparison of diastolic blood pressure of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (mmHg).

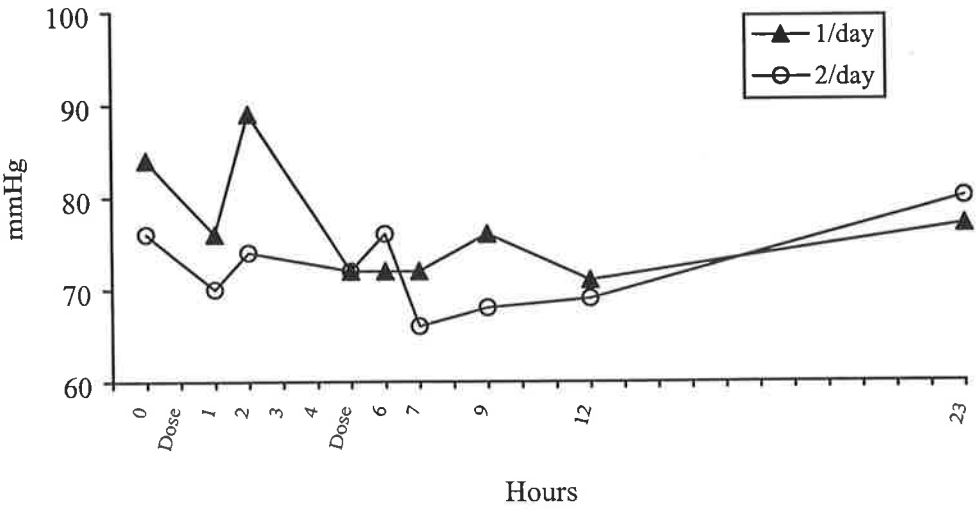


Figure A7-3: Comparison of heart rate of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (beats per minute).

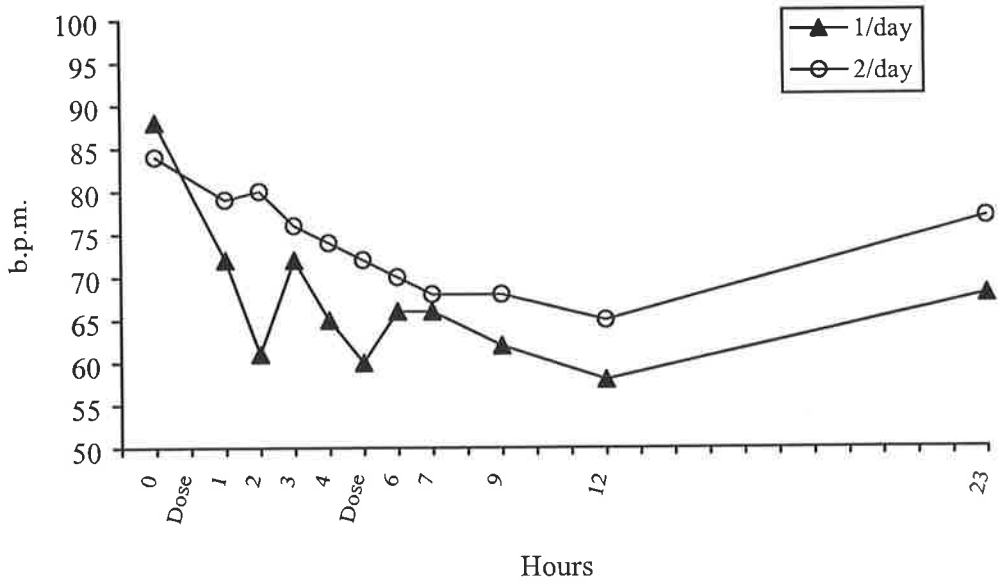


Figure A7-4: Comparison of pain detection of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (Volts).

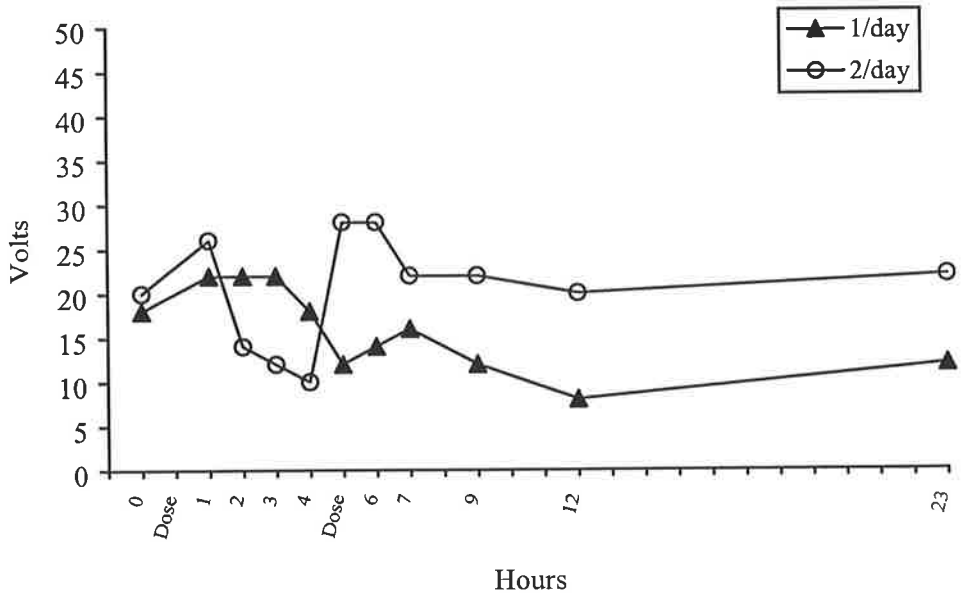


Figure A7-5: Comparison of respiration rate of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (breathes per minute).

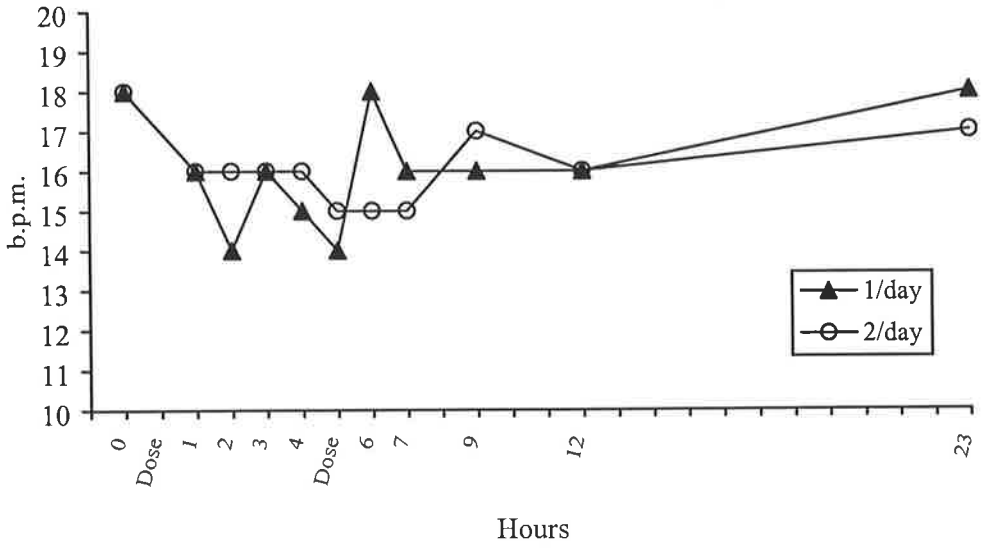


Figure A7-6: Comparison of sweating of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (%).

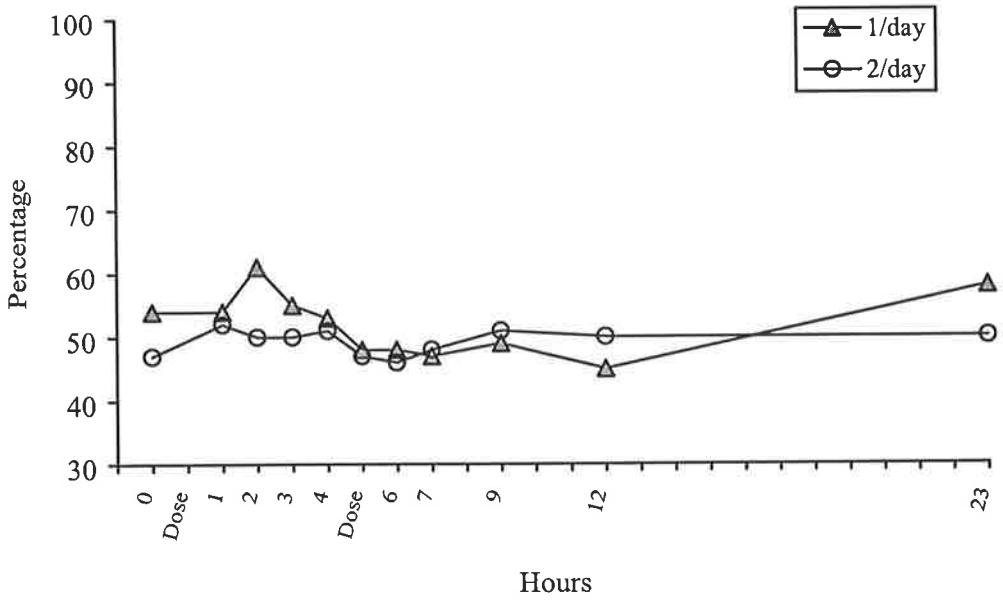


Figure A7-7: Comparison of skin temperature of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. (°C).

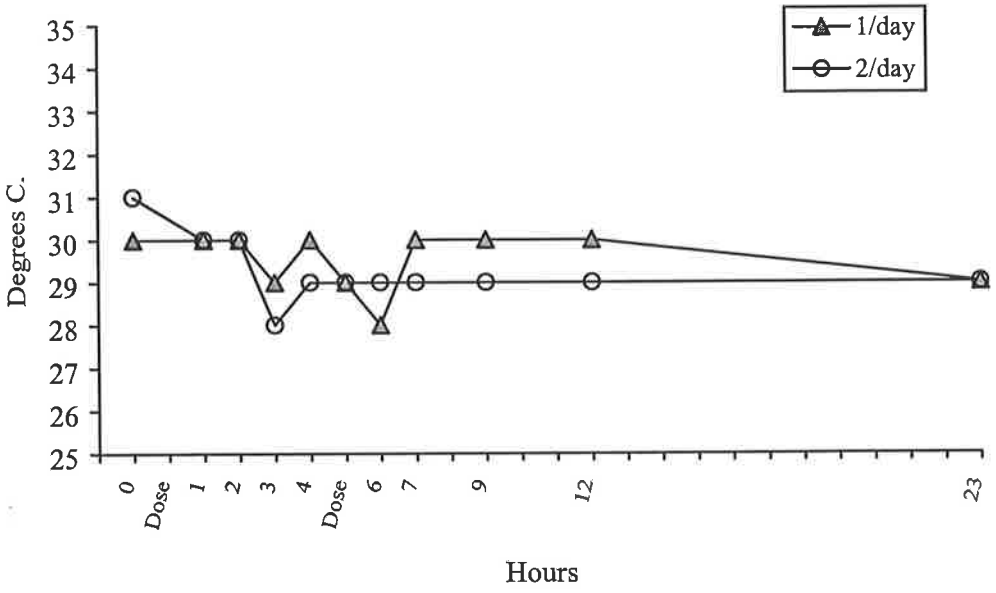


Figure A7-8: Comparison of scores on the Anger sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 48.

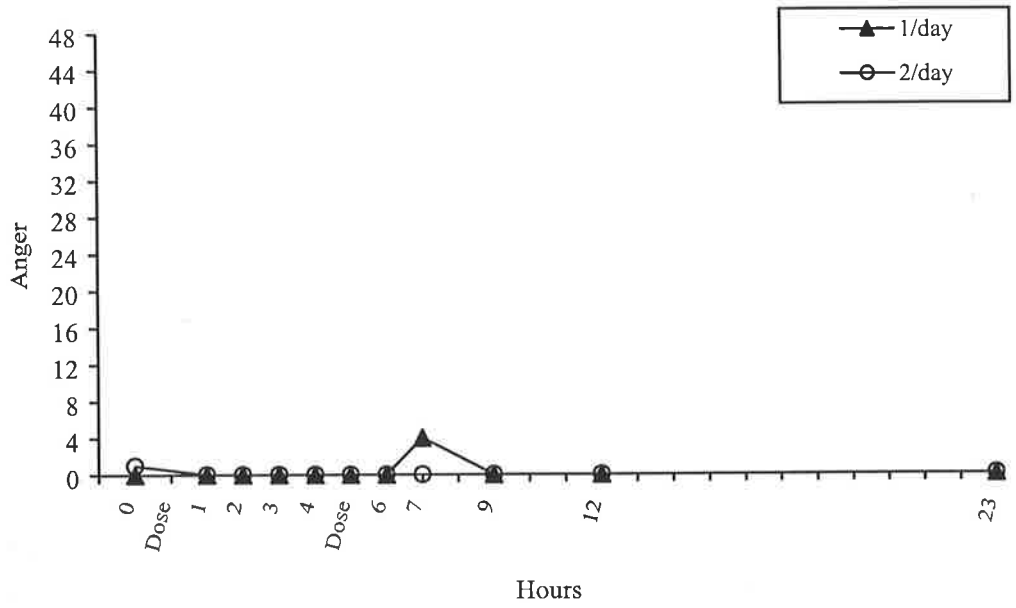


Figure A7-9: Comparison of scores on the Confusion sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 28.

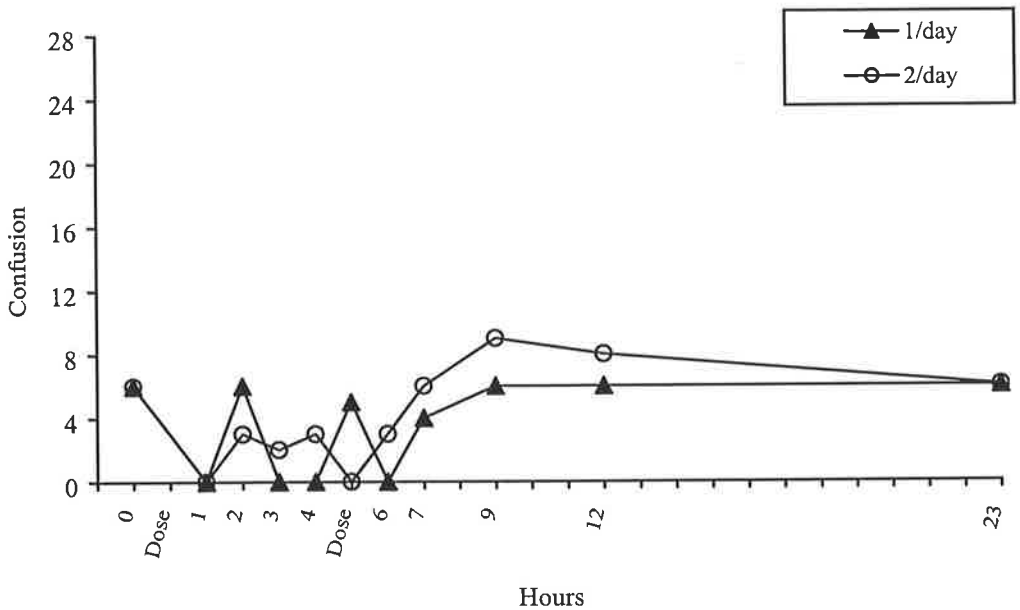


Figure A7-10: Comparison of scores on the Depression sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 40.

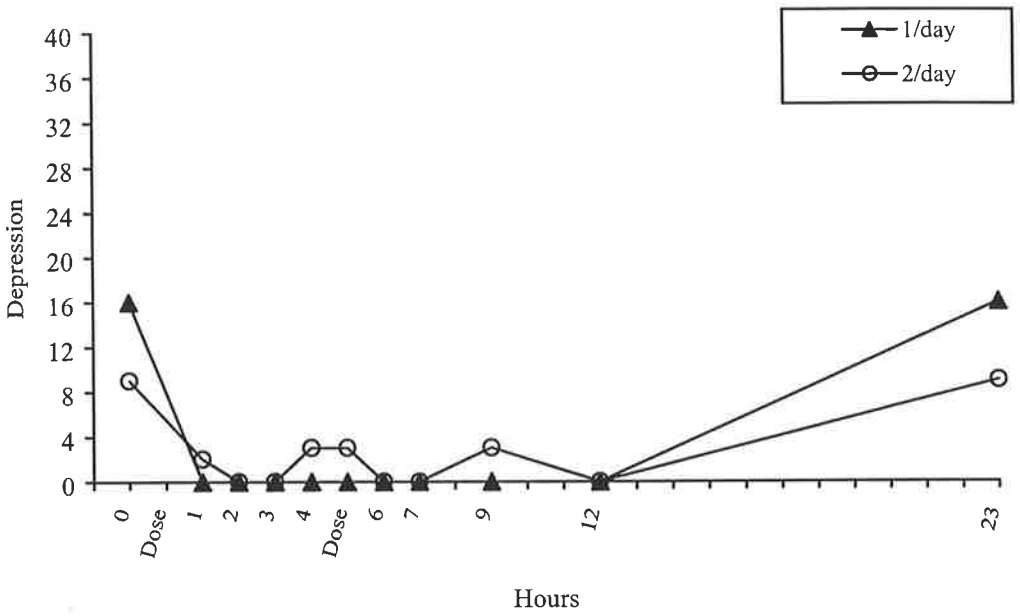


Figure A7-11: Comparison of scores on the Fatigue sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 28.

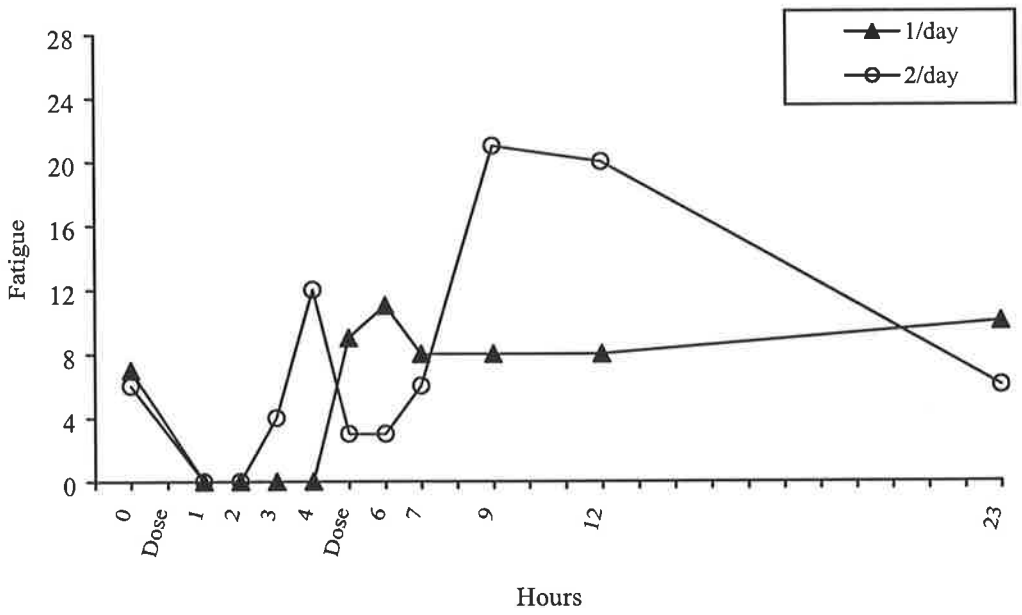


Figure A7-12: Comparison of scores on the Tension sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 36.

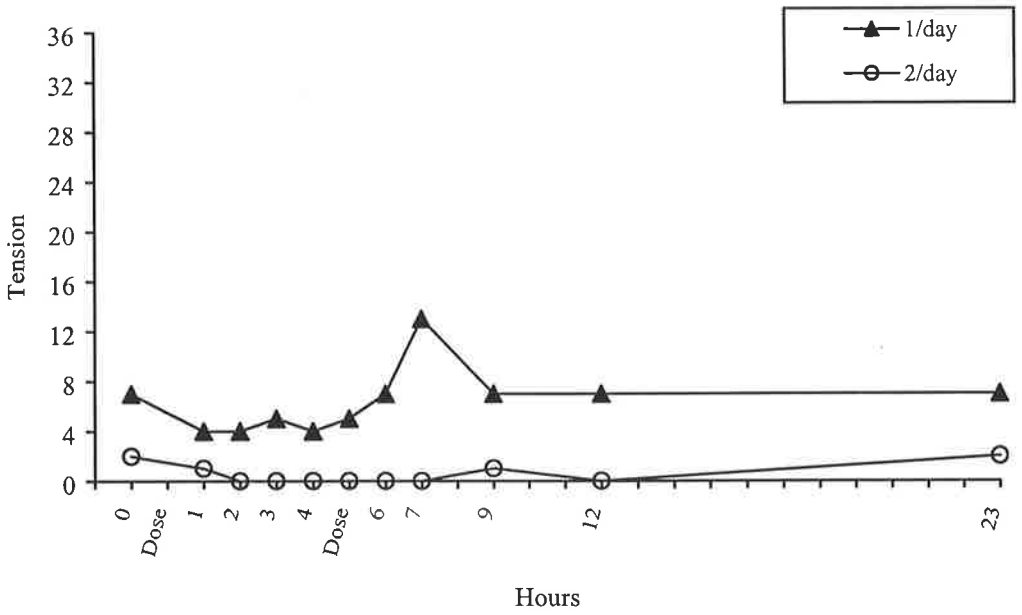
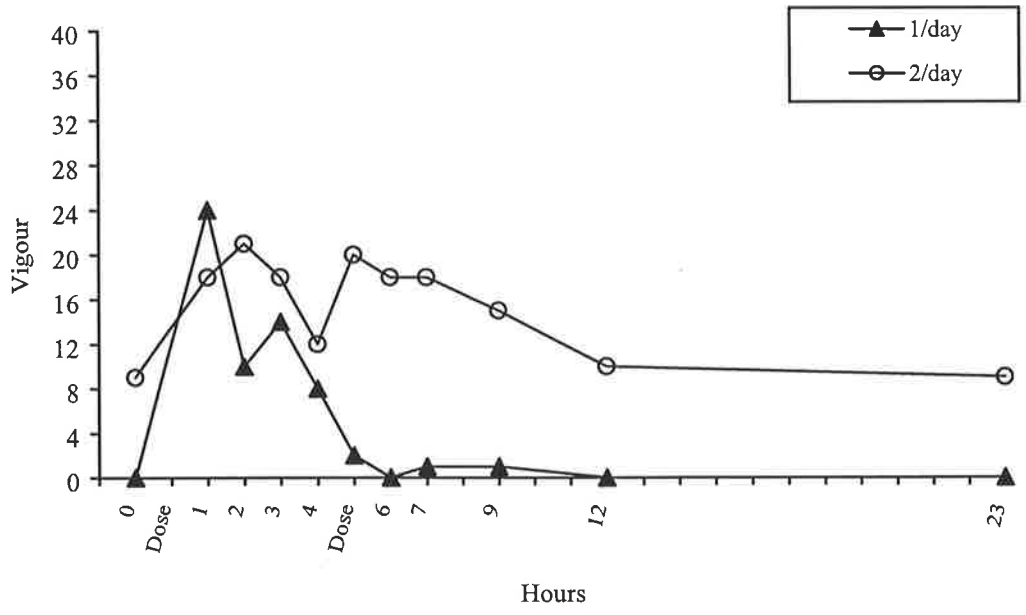


Figure A7-13: Comparison of scores on the Vigour sub-scale of the POMS of one methadone patient (KM) prescribed 120mg of methadone once daily and 112.5mg divided over two occasions per day. Maximum score possible is 32.



PEER REVIEWED PUBLICATIONS FROM THIS THESIS

Dyer, K.R., White, J.M. (1997) Patterns of symptom complaints in methadone maintenance patients. *Addiction, 92(11), 1445-1455.*
Dyer, K.R., Foster, D., White, J.M., Somogyi, A., Menelaou, A., Bochner, F. (1999) Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: Comparison of those who do and do not experience withdrawal and concentration-effect relationships. *Clinical Pharmacology & Therapeutics, 65(6), 685-694.*
Dyer, K.R., White, J.M., Foster, D., Bochner, F., Menelaou, A., Somogyi, A. (In Press) The relationship between mood state and plasma methadone concentration in maintenance patients. *Journal of Clinical Psychopharmacology. Accepted for publication November 1999.*

Dyer, Kyle R. and White, Jason M. (1997) Patterns of symptom complaints in methadone maintenance patients.
Addiction, v. 92 (11), pp. 1445–1455, November 1997

Kyle R. Dyer, David J. R. Foster, Jason M. White, Andrew A. Somogyi, Andrew Menelaou and Felix Bochner (1999) Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: Comparison of those who do and do not experience withdrawal and concentration-effect relationships.
Clinical Pharmacology & Therapeutics, v. 65 (6), pp. 685–694, June 1999

THE RELATIONSHIP BETWEEN MOOD STATE AND PLASMA METHADONE CONCENTRATION IN MAINTENANCE PATIENTS

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Abstract

While methadone maintenance is designed to stabilise opioid dependent patients, some experience significant withdrawal in the latter part of the 24-hour inter-dosing interval. The present study was designed to determine the mood changes that maybe associated with such withdrawal. Eighteen methadone patients, 9 of whom experienced significant withdrawal, were tested over a single inter-dosing interval. During this time 13 blood samples were collected to measure plasma racemic methadone concentrations, and the Profile of Mood States (POMS) was administered on 11 of these occasions. The POMS was also administered on 11 occasions over 24 hours to 10 drug-free healthy controls. In comparison with controls, methadone patients showed increased anger, depression, tension, confusion and fatigue, and decreased vigour. For all scales, maximal differences from controls occurred at times of trough methadone concentration and minimal differences around the time of peak concentration. Changes in mood over the inter-dosing interval were more exaggerated in the 9 patients who experienced significant withdrawal compared to those who did not. The composite Total Mood Disturbance (TMD) scores were calculated for each subject at each time point. The sigmoid Emax model was used to relate plasma concentrations to these data and to calculate the slope factor (N). This model could be fitted for 14 of the 18 patients with a mean±SEM N value of 2.2±0.5. TMD was also shown to be inversely related to the rate of decline in methadone concentration from peak to trough. These results show that significant mood changes occur in response to changes in methadone concentration and these are more pronounced in those who experience withdrawal. The concentration-effect relationships

suggest that relatively small changes in plasma concentration will result in significant mood change. Differences in degree of mood change between those who do and do not experience significant withdrawal may be explained by variation in rate of decline in plasma concentration from peak to trough.

The rationale for methadone maintenance programs is to stabilise the pharmacological condition of illicit opioid users, thereby providing an opportunity to normalise health and social functioning.[1] The extent to which this is effective for any given individual will be governed by the degree to which methadone prevents opioid withdrawal symptoms in the absence of significant direct opioid adverse effects. In an earlier study[2] we found that approximately one-third of a representative sample of patients in a large public methadone maintenance program, stabilised on oral doses averaging 60 mg/day, regularly experienced withdrawal symptoms at the end of each inter-dosing interval (these were designated non-holders). These patients could not be differentiated from those who did not experience withdrawal symptoms (holders) by demographic, health, other drug use or treatment variables.

In a subsequent study[3] of methadone maintained patients, subjective (withdrawal score, MBG Scale of the Addiction Research Center Inventory[4], pain threshold) and objective (pupil diameter, respiration rate) opioid responses were correlated with plasma racemic methadone concentration. Analysis of plasma concentration-effect relationships for withdrawal severity indicated that small changes in plasma methadone concentration will translate into relatively large changes in withdrawal. Further, the difference in withdrawal severity between patients self-reporting as holders and non-holders was not related to either oral methadone dose or trough plasma methadone concentration demographic or other individual characteristics, but, rather, to the significantly more rapid rate of

decline in plasma concentration during the period from the peak plasma concentration until the trough.

Withdrawal symptoms, sufficient to be subjectively assessed as uncomfortable, occur often and could potentially lead to other drug use or poor treatment outcome. Mood changes such as depression, anger and anxiety may also increase the perceived severity of withdrawal and induce a craving for additional opioids[5-7] and thus might be associated with a poorer clinical outcome[7]. In an early study[9] using the Profile of Mood States[10] (POMS), opioid users experiencing physiological signs of withdrawal at entry to a methadone detoxification program described themselves as having considerable mood disturbance. However, within 45 minutes of receiving methadone, all POMS scales showed changes indicative of a significant decrease in mood disturbance. To our knowledge, no studies have examined temporal changes in mood states in patients maintained on methadone and the relation between these changes and plasma methadone concentrations.

In the present study patients maintained on methadone were assessed over a complete inter-dosing interval. The aims were, firstly, to evaluate mood state changes in methadone maintenance patients by comparing their POMS scores with those of controls; secondly, to compare POMS scores of holder and non-holder patients; thirdly, to characterise the relation between plasma racemic methadone concentration and mood.

Methods

Ethical approval to conduct this study was obtained from the Royal Adelaide Hospital Research Ethics Committee . Eighteen patients (9 self-reported holders and 9 self-reported non-holders), previously described[3], freely consented to participate. The non-holder group were previously shown to have substantially higher withdrawal scores than the non-holders. Exclusion criteria included positive HIV serology and pregnancy. The patients had been enrolled in the South Australian Public Methadone Maintenance Program for periods of six months to ten years with no methadone dose change for at least two months prior to the study. The patients, 11 males and 7 females, weighed from 60 to 94 kg and were aged from 21 to 45 years. Their daily methadone dose ranged from 0.12 to1.9 mg/kg (7.5-130 mg). Urinalysis showed ten were positive for cannabinoids, two for opioids other than methadone, two for amphetamines and one for barbiturates. The majority smoked cigarettes and four consumed alcohol regularly in quantities of less than 40 grams daily. Control subjects (previously described[3]), 6 males and 4 females, weighed 54 to 90 kg and were aged from 24 to 32 years; they had not taken any psychoactive drug (other than alcohol, nicotine or caffeine) within two months of the study.

Procedure and Measures

All methadone patients were admitted to an inpatient ward one hour before the scheduled daily methadone dose and remained in the unit under the supervision of the chief investigator for the subsequent 24 hours. After providing a urine sample, an 18 gauge indwelling venous catheter (Jelco™, Criticon Corp., Tampa,

FL) was inserted into a forearm vein 30 minutes before the scheduled daily methadone dose. The catheter was kept patent with a teflon stylet (Jelco™). A 5 mL blood sample was collected pre-dose to determine the trough plasma methadone concentration. Patients then completed the POMS (see below). They then took their normal daily oral methadone dose. Blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 12 and 23 hours after their dose. All blood samples were centrifuged and the plasma stored at -20°C prior to the assay for the quantification of plasma racemic methadone concentrations by a reverse phase HPLC method with UV detection[3]. The POMS was administered 1, 2, 3, 4, 5, 6, 7, 9, 12 and 23 hours after dosing. The control participants were not admitted to the inpatient ward, did not receive methadone and no blood samples were collected, but they were otherwise treated in the same manner as the patients.

Profile of Mood States

Subjects were instructed to rate each item on a list of 65 adjectives on a scale of 0 (not at all) to 4 (extremely), based on how they were feeling at that moment (i.e. "right now"). The POMS is divided into six empirically derived sub-scales that reflect distinct types and qualities of identifiable affective states. The sub-scales include: Vigour - a mood of ebullience and high energy; Depression - depressed affect and sense of inadequacy; Tension - heightened musculo-skeletal tension; Anger - irate mood and antipathy toward others; Fatigue - weariness and low energy level; Confusion - bewilderment and disorganised cognitive efficiency. In addition to these sub-scales, the Total Mood Disturbance (TMD) score, a single global estimate of affective state, was derived by summing the scores across all

six factors weighting Vigour negatively. The maximum possible TMD score is 168. The mean TMD score from the time of peak to the trough plasma methadone concentration was also calculated.

Data Analysis

Two-way repeated measures analyses of variance were used to determine differences in pharmacodynamic response between methadone patients and control subjects, and between holders and non-holders. Tukey's post-hoc tests were used when significant effects were found. These data were analysed using SPSS for Windows v 6.0[11]. The mean and the maximum rate of decline in plasma methadone concentration during the period from peak plasma concentration to trough were calculated for each patient.

Plasma methadone concentration-effect relationships were determined for the TMD score. An inverted sigmoid E_{max} model was used to relate the intensity of effect (E) to the plasma methadone concentration by employing an adaptation of the Hill equation:

$$E = E_{max} - \frac{E_{max} \times C^N}{EC_{50}^N + C^N}$$

where E_{max} is the maximum attainable effect, C is the plasma methadone concentration, EC_{50} is the plasma methadone concentration which produces 50% of the maximum effect and N is the sigmoidicity or slope factor, which determines the steepness of the curve. The equation was fitted to unweighted

data using non-linear least-squares regression analysis (Regression, Blackwell Scientific Publications, Oxford, U.K.) to yield estimates of EC_{50} and N. Values of the coefficient of determination (r^2) were not statistically significant at the 0.05 level for 4 patients and these were not included in the analyses. Student's t-test was used to compare the N and EC_{50} values between holders and non-holders. The relationships between the mean and maximum rates of decline of plasma methadone concentration and mean TMD scores were evaluated by linear regression to yield values for Pearson's r. All data are expressed as mean±SEM.

Results

Fig. 1 shows the the mean plasma methadone concentration-time profile for all patients and Fig. 2 the comparison of mood states between methadone patients and control subjects. Mean scores on the Vigour sub-scale peaked approximately 3-4 hours after the dose and decreased throughout the remainder of the inter-dosing interval. All other sub-scales, including the TMD score, showed an inverse pattern, in which the maximum response occurred prior to the methadone dose. Results from two-way repeated measures analyses of variance for each sub-scale showed significant differences between methadone patients and controls ($p<0.001$ for all sub-scales except Anger, where $p<0.05$). The group by time interaction was also significant for Tension ($p<0.001$), Depression ($p<0.001$), Anger ($p<0.05$) and Total Mood Disturbance ($p<0.001$), but not for Confusion, Fatigue or Vigour.

Comparisons of POMS scores for holders and non-holders are shown in Fig. 3. Results from two-way repeated measures analyses of variances showed significant between group effects for the Tension ($p<0.001$), Depression ($p<0.05$), Anger ($p<0.001$) and Vigour ($p<0.05$) sub-scales and the TMD ($p<0.01$) score. There were also significant interaction effects for the Depression ($p<0.001$), Anger ($p<0.01$) and Fatigue ($p<0.05$) sub-scales and the TMD ($p<0.001$) score. For all sub-scales, there were significant differences between holders and non-holders at each of the trough times (-0.5 and 23 hours).

There was a significant positive correlation ($r=0.52$, $p<0.01$) between the mean rate of decline in plasma methadone concentration and the mean TMD score during the period from peak plasma concentration to the trough across all patients. The correlation between the maximum rate of decline in plasma methadone concentration and the mean TMD score was only significant when the two patients whose urinalysis indicated the use of other opioids were excluded ($r=0.46$, $p<0.05$).

The inverted sigmoid E_{max} model was able to be fitted for the TMD score for 14 of the 18 patients : all 9 of the non-holders and 5 of the holders. For the other 4 patients, the plasma concentration versus time profiles were too flat and/or the TMD scores changed relatively little over the inter-dosing interval when compared to the 14 whose data could be filled, the remaining 4 did not differ with respect to dose, age, gender, body weight, drug use or other variables. Table 1 shows the N and EC_{50} values for the 14 patients and separately for the holder and non-holder groups. These values were not significantly different ($p>0.05$)

between the two groups. Fig. 4 shows examples of fitted curves from one subject in each of the holder and non-holder groups for total mood disturbance. The non-holder subjects exhibit a somewhat steeper curve compared to the subject reporting that their methadone dose 'held' for the full 24 hours.

DISCUSSION

The present study has found that the intensity and temporal pattern of mood states reported by methadone maintenance patients are related to plasma methadone concentrations during the inter-dosing interval. The absence of changes in the drug-free controls indicates that the changes in mood amongst methadone patients can be reasonably interpreted as resulting from methadone ingestion. In comparison with the relatively stable intensity of mood states reported by the controls, the patients experienced significant time-dependent changes in the intensity of mood states throughout the 24-hour period. Specifically, for patients, the period in which Vigour scores were closest to those of the control subjects corresponded with peak plasma methadone concentrations, and then declined throughout the remainder of the day, returning to baseline levels approximately 6 hours after the dose. The other mood states showed an inverse pattern, reaching a nadir at the time of the peak plasma methadone concentration and peaking towards the end of the inter-dosing interval. However, even at peak plasma methadone concentrations, patients reported significantly less vigour and significantly more disturbance of the other mood states than drug-free controls, indicating that patients' mood state never attained control values. The methadone program in which these patients were enrolled has a policy of allowing considerable patient control over dose. Thus, it is unlikely that the

effects noted were due to inadequate dosing. The mean dose of 65 mg/day amongst the study participants is consistent with recommended clinical practice[12]. Furthermore, the mean trough plasma methadone concentrations were within or above values considered appropriate[3,13-15].

One aim of this study was to further determine the characteristics differentiating patients who respond well to methadone (the holders) from those who report persistent opioid withdrawal symptoms (the non-holders). Compared to the holders, non-holders experienced a consistently greater level of negative affect and a lesser degree of vigour during the inter-dosing interval. This was consistent with their higher levels of opioid withdrawal and lesser direct opioid effects previously reported[3]. Non-holders could not be differentiated by demographic variables, other drug use, oral methadone dose, trough or peak plasma methadone concentrations. The only difference between these patients was the significantly more rapid rate of decline in plasma concentration from peak to trough.

We were able to fit the sigmoid Emax model to sufficient patient data to allow plausible conclusions to be drawn. The slope factor (N) for TMD (2.2±0.5) indicates a relatively steep concentration-effect relationship so that a relatively small change in the plasma concentration will translate into a significant mood change. The likelihood of clinically significant mood changes will be exaggerated in the non-holders because their rate of decline in plasma concentration was greater than holders. These observations are of considerable

clinical relevance because negative mood states have been found to be associated with relapse to drug use[16,17].

A principal objective of the methadone maintenance program is to help the patient feel physically comfortable without producing euphoria. Methadone patients' complaints of persistent withdrawal symptoms, despite seemingly adequate oral methadone doses and trough plasma concentrations, can represent a challenge to treatment staff. Our findings have several important clinical implications. Firstly, once daily dosing may not be suitable for those methadone patients who experience significant mood disturbance in the latter part of the inter-dosing interval. An increase in the dose would increase peak plasma concentrations, but would also increase undesirable direct opioid effects[3]. Dividing the methadone dose for twice daily administration may be a possible strategy, but there are practical difficulties because of the need for supervised dosing in the majority of cases. The alternative is the use of other opioid maintenance medications such as LAAM or buprenorphine. The second implication is that it is important to differentiate primary mood disorders from the mood disturbances that are associated with changes in plasma methadone concentrations, particularly in the non-holders. These two causes of mood change require very different therapeutic strategies. Thirdly, criteria for evaluating maintenance pharmacotherapies should incorporate evaluation of the degree to which they produce mood disturbances. The present study has highlighted the substantial mood changes that occur in methadone patients, particularly those who experience withdrawal.

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Table 1

Slope factors (N) and EC_{50} values from fitting the modified Hill equation to Total Mood Disturbance score. Values are mean±SEM.

Total Mood Disturbance	All patients (n=14)	Holders (n=5)	Non-holders (n=9)
N	2.2±0.5	2.1±0.75	2.2±0.2
EC_{50} (ng/mL)	289±71	202±68	338±22

Figure Legends.

FIG.1. Mean plasma methadone concentration-time profile during a single 24-hour interdosing interval in 18 methadone patients.

FIG.2. POMS responses (vertical axes) during a single 24-hour inter-dosing interval in 18 methadone patients (closed square) and ten drug-free controls (open circles). Data are shown for the six POMS sub-scales (Anger, Confusion, Depression, Fatigue, Tension, Vigour) and the composite score (Total Mood Disturbance). Time 0 represents the time of methadone dosing. Values are mean ± SEM. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

FIG.3. POMS responses (vertical axes) during a single 24-hour inter-dosing interval in 18 methadone patients: 9 holders (closed squares) and 9 non-holders (open squares). Values are mean ± SEM. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

FIG. 4. Examples of the Hill equation fitted to the data of a non-holder subject (■) and a holder subject (□). The Total Mood Disturbance from the Profile of Mood States has been plotted against racemic methadone concentration (log scale).

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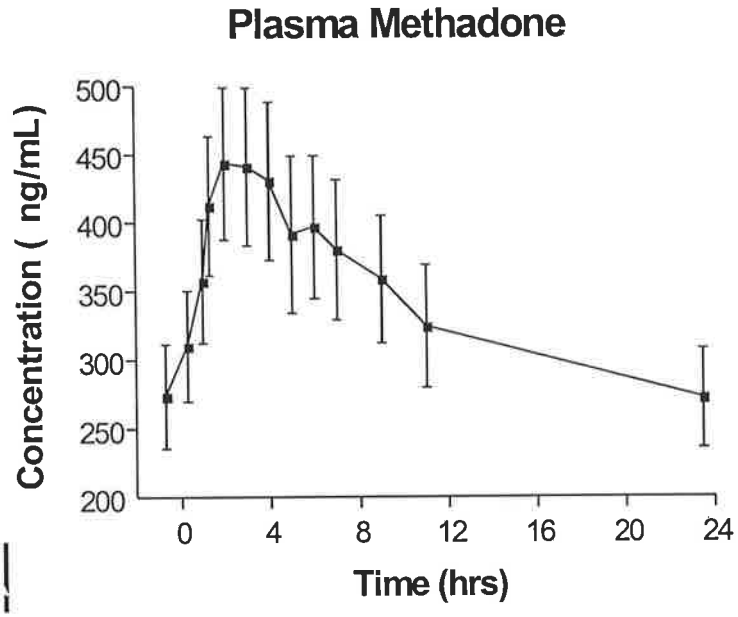
Plasma Methadone
Concentration (ng/mL)
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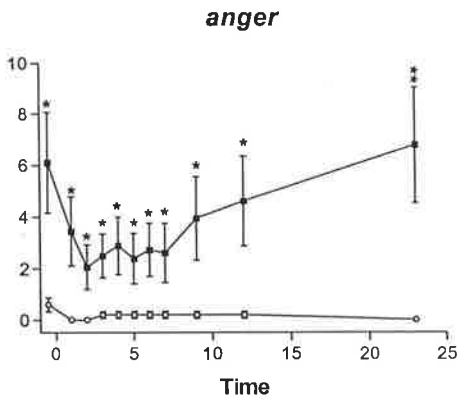
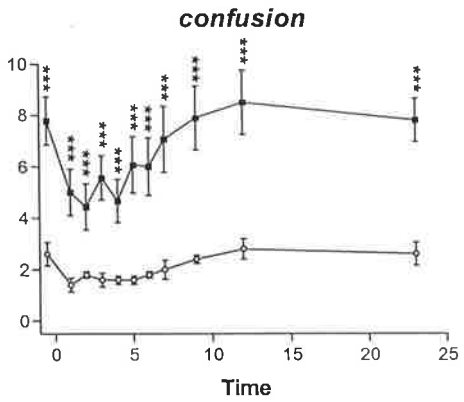
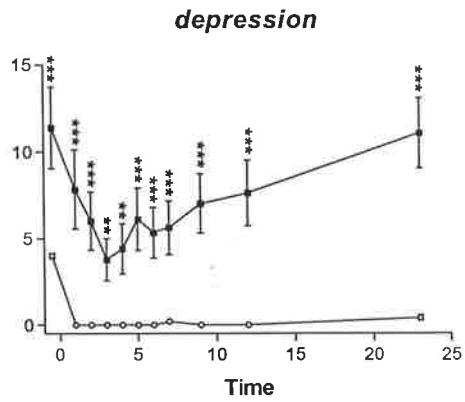
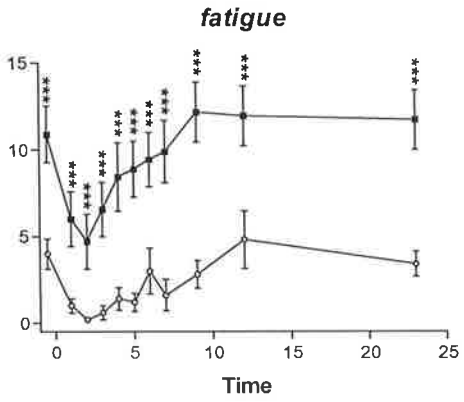
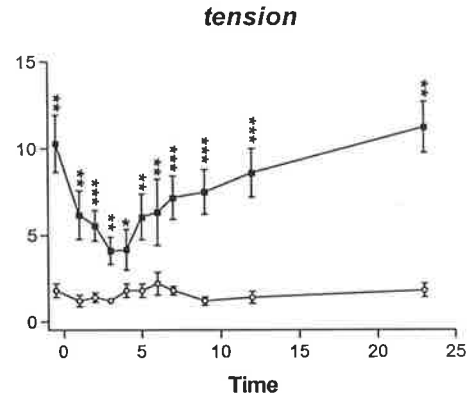
300
250
200
0
4
8
12
16
20
24
Time (hrs)

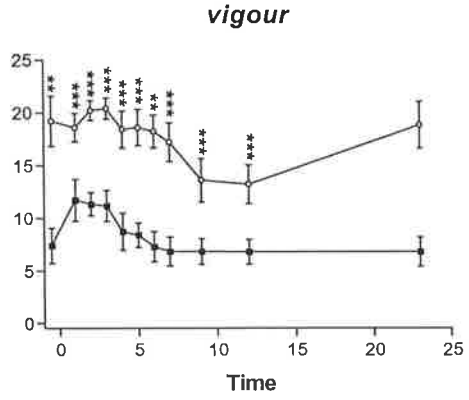


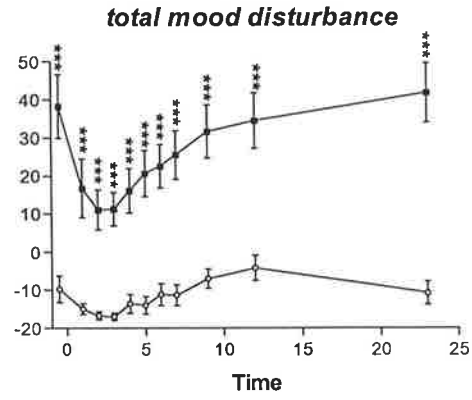








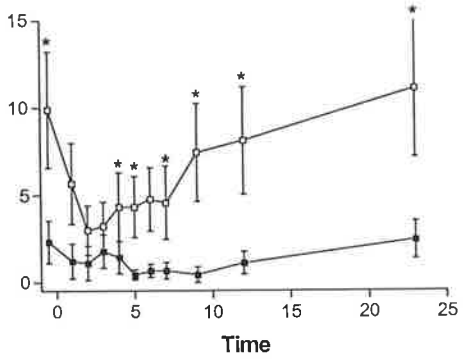




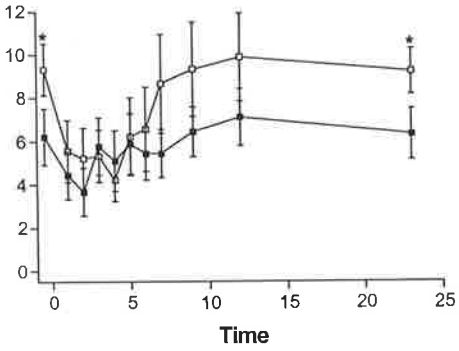
Methadone
Control

* = p<0.05
** = p<0.01
*** = p<0.001

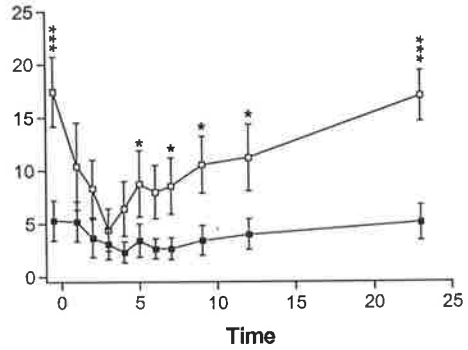
anger



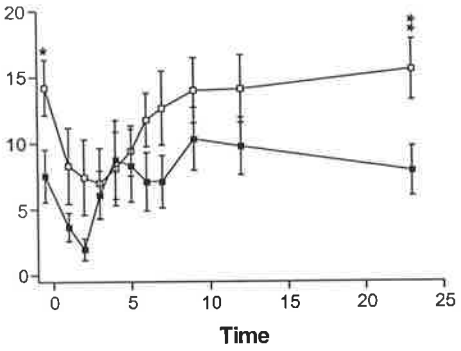
confusion



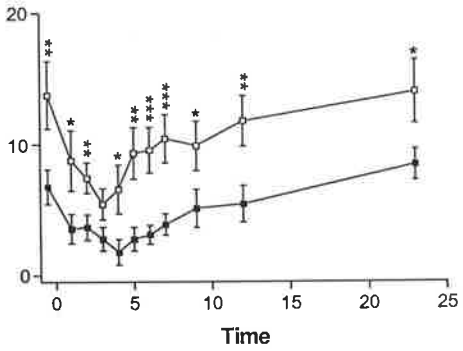
depression



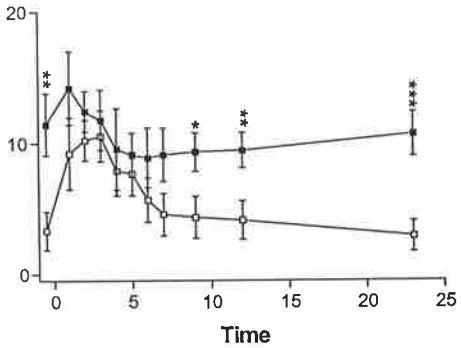
fatigue



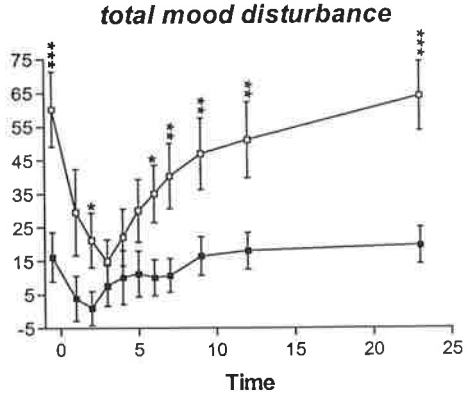
tension



vigour



total mood disturbance



Hold
Not Hold

* = p<0.05
** = p<0.01
*** = p<0.001

total mood disturbance