



**ACUTE PAIN MANAGEMENT IN METHADONE
MAINTENANCE TREATMENT**

by

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degree of Doctor of Philosophy
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DECLARATION

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

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ABSTRACT

Pain is a very complex process and presents great challenges for modern medicine and pharmacology. There seems to be a general consensus that in the treatment of pain, patients with a prior history of substance abuse (particularly opioid dependent individuals) appear to be at increased risk for mismanagement problems. There are increasing numbers of people who are receiving opioids as substitution treatment for dependence. There have been many reasons postulated as to why this population is more likely to receive sub-optimal treatment, with further ad hoc suggestions as to their opioid analgesic needs. There are discrepancies in the literature about the pain sensitivity of methadone maintenance patients. Further, there are few and conflicting data about the antinociceptive, physiological and subjective effects of additional opioids in these patients. This thesis had one broad aim, to produce data that would eventually help in the formulation of prescribing guidelines, improved policies, and more importantly help direct optimal acute pain management for methadone maintenance patients.

The first study compared the responses to pain induced by a cold pressor test and electrical stimulation in 16 methadone maintained patients and 16 drug-free healthy volunteers. It reconciled the discrepancies in the literature by ascertaining that the relative pain sensitivity of methadone maintenance patients is determined by the nature of the nociceptive stimulus (eg. cold pressor test vs. electrical stimulation), the concentration of methadone (trough vs. peak plasma concentration), and whether thresholds are determined for detection of pain or pain tolerance. Methadone maintenance patients are hyperalgesic to pain induced by the cold pressor test but not electrical stimulation. This hyperalgesia is particularly pronounced at times of putative trough plasma methadone concentrations. A low pain tolerance to detection ratio was highlighted as a marker of this hyperalgesia in methadone maintained patients.

In the second study, intravenous morphine was administered on two separate occasions to 4 methadone patients and 4 healthy volunteers to determine the antinociceptive effects. The data showed that methadone patients are cross-tolerant to the antinociceptive effects of morphine up to plasma concentrations of approximately 60ng/mL. They are hyperalgesic to a cold pressor test but not electrical stimulation, confirming the findings of the first study. A low pain tolerance to pain detection ratio for the cold pressor test was confirmed as a sensitive marker of hyperalgesia in this patient population. These findings suggest that plasma morphine concentrations, which have previously been reported as being adequate for

minimal to severe post-surgical pain relief, are likely to be ineffective in managing episodes of acute pain amongst this patient group, and that large doses of morphine may be required to manage episodes of severe acute pain amongst individuals maintained on methadone. Further research is urgently needed to determine whether other drugs are more effective than morphine in managing acute pain in this patient population.

Data from the first and second studies were combined to determine the physiological and subjective effects of methadone alone, and in combination with morphine. These data indicate that methadone patients have a significantly lower respiratory rate compared with healthy control subjects. Further, additionally administered morphine produced no clinically significant cardiovascular or respiratory effects in the methadone patients. The data also suggest that in the context of acute pain management, methadone patients are unlikely to experience a classic “high” from the administration of additional opioids.

The final study investigated the antinociceptive effects, physiological and subjective effects, of (+)-(S)-ketamine alone and in combination with morphine in a sample of methadone patients and healthy volunteers. The data indicate that low dose (+)-(S)-ketamine alone, or in combination with low dose morphine is likely to be ineffective in managing episodes of acute pain in methadone maintenance patients. Despite a lack of antinociceptive effects, the findings show that even at very low doses (and plasma concentrations), (+)-(S)-ketamine produces pronounced subjective effects amongst methadone patients, and is likely to have high abuse potential in this patient group.

It was concluded that these data consistently show that methadone maintenance patients are hyperalgesic to pain induced by a cold pressor test but not electrical stimulation; methadone maintenance patients are cross-tolerant to the antinociceptive effects of conventional doses of morphine. In addition, low dose (+)-(S)-ketamine, alone, or in combination with low dose morphine, did not produce any significant antinociceptive effects amongst this patient group. Further research is urgently needed to determine whether other drugs such as gabapentin, tramadol, clonidine, or non-steroidal anti-inflammatory drugs, alone or in combination with morphine, are effective in managing acute pain in this patient population. Clinicians should aggressively treat complaints of pain amongst patients in this population, remembering importantly to treat the pain not the addiction.

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LIST OF ABBREVIATIONS

5HT	serotonin
AAG	α_1 -acid glycoprotein
AMPA	3-hydroxy-5-methyl-4-isoxazole-propionic acid
ANOVA	analysis of variance
Ca ⁺⁺	calcium
CKK	cholecystokinin
CNS	central nervous system
CO ₂	carbon dioxide
CPOC	chronic pain and opioid consuming
EAA	excitatory amino acid
EDDP	1,5-dimethyl-3,3-diphenyl-2-ethylidene-pyrrolidine
GABA	γ -aminobutyric acid
GCT	gate control theory
G-protein	glyco-protein
GDP	guanosine diphosphate
GTP	guanosine triphosphate
HPLC	high-performance liquid chromatography
IASP	International Association for the Study of Pain
IP ₃	1,4,5-triphosphate
i.v	intravenous
K ⁺	potassium
kg	kilogram
LAAM	levo-alpha acetylmethadol
LSD	lysergic acid diethylamide
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MBG	morphine benzedrine group
MG	morphine group
mGluR	metabotropic glutamate receptor
mg	milligram
Mg ⁺⁺	magnesium
mL	millilitre
MMT	methadone maintenance treatment
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
PARS	poly (ADP ribose) synthetase
PCP	phencyclidine
PKC	protein kinase C
POMC	pro-opiomelanocortin
SpO ₂	arterial oxygen saturation
VAS	visual analogue scales

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1.1 General introduction

The purpose of this review is to introduce the reader to the complex issue of pain and pain management, specifically in relation to people who are in methadone maintenance treatment (MMT). This will include (1) a review of the history of MMT, (2) a brief outline of the possible reasons for sub-optimal pain management in methadone maintenance patients, (3) an overview of previous studies examining pain sensitivity amongst methadone maintenance patients, and (4) a review of the relevant literature on the pain management needs of this patient population. It will also include (5) a brief overview of the physiology and pharmacology of pain, and (6) a brief overview of some methods of pain induction and measurement. Furthermore, the reader will be introduced to (7) the pharmacokinetic properties of methadone and morphine; (8) the clinical pharmacodynamics of opioid drugs, with (9) a detailed overview of tolerance, and (10) the pharmacokinetics and pharmacodynamics of (+)-(S)-ketamine.

1.2 Background: setting the scene

It is widely recognised that pain of all kinds, including acute pain, chronic cancer related pain and chronic pain of non-cancer origin, historically has been under-treated in the general population (Marks & Sacher, 1973; Morgan, 1985). Sub-optimal treatment of pain has been shown to increase morbidity following trauma and surgery in the general population (Wattil, 1989), whereas optimal pain treatment appears to shorten the length of hospital stay in similar contexts (Jackson, 1989).

It has been suggested that under-treatment of pain may create craving for pain-relieving medications, as well as anxiety, frustration, anger and other feelings which perpetuate addiction (McCaffery & Vourakis, 1992), and that under-treatment of pain leads to pseudoaddiction (Weisman & Heddox, 1986) which is drug seeking behaviour caused by a need for better pain relief. Frequently, medical practitioners prescribe opioids that are insufficient in dose magnitude and frequency due to lack of knowledge, lack of concern about pain management, or fear of exacerbating addiction (Cleeland, 1987; Rapp *et al.*, 1995). Furthermore, the choice of the opioid itself may be a complicating factor, ie. it may not be potent enough eg. codeine vs. morphine. Opiophobia, which has been cited as a factor in sub-optimal treatment of pain, is the phenomenon of failure to administer/prescribe opioid analgesics because of a fear of the power of these drugs to produce or exacerbate addiction (Morgan & Puder, 1989).

Although the use of opioid drugs for cancer pain is strongly endorsed globally (WHO, 1996), large surveys suggest that as many as 40% of cancer patients do not receive these drugs according to accepted guidelines (Cleeland *et al.*, 1994). Clinical surveys clearly demonstrate that routine orders for intramuscular injections of opioids “as needed” will result in unrelieved post-operative pain in over half of all patients due to undermedication (Agency for Health Care and Policy Research, 1992). Moreover, the risk of under treatment appears to be higher for individuals with a history of substance abuse (Fishbain *et al.*, 1992; Cleeland *et al.*, 1994; Portenoy *et al.*, 1997). Indeed, it has been suggested that “the outlook is even worse” for patients who have been receiving opioids for long periods of time (de Leon-Casasola, 1996).

In the United States there has been some degree of official recognition that chemically dependent patients are under-treated with narcotics when they have surgery (U.S. Department of Health and Human Services, 1993). This has been augmented with uniform concern amongst nursing professionals over the pain management of the chemically dependent patient (McCaffrey & Vourakis, 1992; Ferrell & McCaffrey, 1992; MacKay, 1993; St. Marie, 1996). St. Marie (1996) recommended that nurses must listen to the patient and recognise that comfort is inherent in human dignity and is essential for healing.

The transfer of research findings on pain management into clinical practice has been a widely recognised challenge for medical professionals (Ravenscroft & Schneider, 2000). In spite of a substantial body of research on opioids, pain control is still a problem for patients in our hospitals. Millions of people needlessly suffer from agonising pain because physicians have been reluctant to use opioids (Crain & Shen, 2000). Moreover, there seems to be a general consensus that individuals with a history of drug addiction are at most risk of suffering due to inadequate management of their pain (Cohen, 1980; Shine & Demas, 1984; Scimeca *et al.*, 2000). Many factors may be contributing to this, including inadequate training in pain management, fear of exacerbating addiction through the use of dependence-producing pharmacotherapies, lack of knowledge about addictive behaviours, tolerance, and societal prejudices against addicts (Savage, 1998; Scimeca *et al.*, 2000). In addition, anecdotal and empirical evidence suggests that, in particular, people who are on MMT are most at risk of having their pain under-treated.

1.3 Methadone maintenance treatment

Methadone is a synthetic opioid analgesic drug, with a relatively long duration of action (Ghodse, 1995; Reisine & Pasternak, 1995). It was created in 1938 by two German scientists, Böckmuhl and Erhart, and called 'Hoechst 10820' and later re-named polamidon (Preston, 1996). After World War 2, the Hoechst factory, where this drug was created, fell into the hands of the American military. In 1945 the US Department of Commerce Intelligence documented the findings of Böckmuhl and Erhart, that despite having a different chemical structure, polamidon closely mimicked the pharmacological action of morphine (May & Jacobsen, 1989). Isbell and colleagues published a paper describing their pharmacological experiments, which assessed the abuse potential of methadone. They confirmed the observation that methadone was an analgesic, and also found that it produced sedation and euphoria when administered in single doses. Further, methadone was used as a substitute for morphine, in dependent subjects; Isbell and colleagues reported that methadone induced tolerance and physical dependence when it was administered chronically in large doses. They concluded that methadone had high addiction potential (Isbell *et al.*, 1947).

It was not until 1964, when Dole and Nyswander, who were investigating suitable treatment options for heroin addicts in New York, that methadone was "re-discovered". They used it in clinical trials amongst heroin addicts in New York. Soon after, methadone maintenance treatment (MMT) was introduced as a substitution treatment for heroin addiction (Dole & Nyswander, 1965; Payte, 1991,1997; Joseph *et al.*, 2000). The clinical pharmacology of methadone makes it a useful agent for the treatment of opioid dependence, especially heroin (Dole & Joseph, 1978). MMT is recognised nationally and internationally as an effective method for treating opioid dependence and reducing the individual and social harms associated with illegal opioid use (Ball & Ross, 1991; Hall *et al.*, 1998; Lowinson *et al.*, 1997; Payte, 1997; Joseph *et al.*, 2000). MMT was first introduced into Australia as a treatment for opioid addiction in 1969. Between 1969 and the mid-1980s treatment grew very gradually to approximately 3000 individuals nation wide. However, since the onset of HIV/AIDS, there has been a substantial growth in the number of people receiving methadone treatment in Australia (Hall *et al.*, 1998). Currently, there are over 30,000 people in methadone treatment (with an average annual growth of approximately 15% since the mid 1980s).

1.4 Opioids and pain sensitivity

Concerns have been raised that long term opioid exposure may increase pain perception in some individuals. Clinical studies and observations suggest that some individuals with pain who use opioids on a long-term basis experience improvement in pain following simple withdrawal of opioids without the institution of other pain interventions (Brodner & Taub, 1978; Rapaport, 1988; Schofferman, 1993). These studies included observations of patients with pain and opioid dependence in both pain treatment and addiction treatment settings. Further, there are a growing number of reports of the development of hyperalgesia (increased pain sensitivity) in some patients in the presence of high dose parenteral and intrathecal opioid administration (Ali, 1986; De Conno *et al.*, 1991; Sjørgen *et al.*, 1993, 1994; Stillman *et al.*, 1987). Interestingly, there is evidence from recent animal studies that chronic administration of opioids leads to increased pain sensitivity and/or decreased pain tolerance (Yaksh & Harty, 1988; Mao *et al.*, 1994; Dunbar & Pulai, 1998). In a series of animal experiments, Mao and co-workers demonstrated that molecular changes associated with the development of opioid tolerance in spinal cord dorsal horn neurons are the same as those associated with the development of central hyperalgesia following tissue injury and inflammation (Mao *et al.*, 1994, 1995a, 1995b); this is discussed in detail in section 1.21. Overall, these combined findings suggest that chronic opioid administration results in altered pain sensitivity. Hence, it is important to review the literature with regard to pain sensitivity of opioid addicts, in particular methadone maintenance patients.

1.4.1 Pain sensitivity of opioid addicts

There has been scientific interest in the pain responses of opioid addicts and ex-addicts dating back to the early 1940s. A pioneering study in the USA investigated the effect of various doses of morphine (ranging from 20-100mg) on pain threshold measurements in a group (number not specified) of post-addicts (ie. men who had been addicted to opiates but had not been using them for at least 6 months prior to the study) (Andrews, 1943). Experimental pain was induced using a heat lamp. The most striking result was that even doses of morphine as high as 100mg had minimal effects on increasing the pain threshold. The author suggested however that such measurements of pain threshold have little connection with the clinical relief of pain. He proposed that this is accomplished in the post-addict with considerably smaller doses of morphine. His final comments were not supported by specific documented evidence.

In the early 1960s a Canadian study investigated the relationships between pain tolerance, narcotic addiction and some aspects of personality (Martin & Inglis, 1964). The subjects were 24 formerly addicted female prisoners, with 24 non-addict female prisoners acting as a control group. Pain was induced by a cold pressor test, with subjects asked to immerse a hand in cold water (5 °C) until they could no longer tolerate the pain; at this point the hand was removed from the water, and the time of total immersion recorded as a measure of pain tolerance. Other measures included the Taylor Manifest Anxiety Scale (Taylor, 1953), which was designed to measure the degree of anxiety experienced, and the Maudsley Personality Test (Eysenck, 1959), which was designed to yield measures of introversion-extraversion and neuroticism. The results of this study showed significant differences between the groups for the cold pressor test. The group of former addicts was markedly less pain tolerant than the non-addict group (mean 73 seconds vs. 404 seconds). Interestingly, there were no significant differences for any of the psychological measures, suggesting that, albeit in a sample of prisoners, former opioid addicts were not significantly different psychologically from the non-addict group.

Ho and Dole (1979) investigated the pain threshold (pain detection) and pain tolerance of 10 drug-free ex-addicts (with previous history of heroin addiction), 10 methadone maintained patients on stable doses of methadone, and 10 never-addicted siblings of addicts. The mean daily dose of the methadone maintained patients was 80 mg (range 60-100mg), with an average of 18 months since any dose changes. Pain was induced using a cold pressor test (hand immersed in an ice-water bath, no temperature reported). All subjects were asked to verbally indicate when they first felt pain (pain threshold), and to remove their hand when the pain became too uncomfortable (pain tolerance). Pain threshold and tolerance were quantified in seconds. Their results showed that methadone maintained patients did not differ from drug-free ex-addicts with regard to pain threshold (mean 15.9 seconds vs mean 14 seconds, respectively) or pain tolerance (mean 27 seconds vs. mean 27.8 seconds, respectively); however, the methadone patients had significantly lower ($p < 0.01$) pain thresholds than the never-addicted group (mean 20.3 seconds), ie. they felt pain earlier. Pain tolerance of methadone patients was only slightly, but not markedly lower than the never-addicted group (mean 32.1 seconds). Ho and Dole concluded that methadone patients and ex-heroin addicts have a different physiological response to cold-induced pain compared to never-addicted controls. Blood samples were not collected in this study; hence it is unknown whether variations in plasma methadone concentrations made a difference to nociceptive response.

Compton (1994) investigated the pain tolerance of four groups of drug abusers: (1) abstinent opioid users (n=26, with no self-reported use of problem substance for at least 6 weeks), (2) current opioid users (n=43), all on methadone maintenance treatment (average dose 66mg/day), but may or may not have been using other substances), (3) abstinent cocaine users (n=32, with no self-reported use of cocaine for at least 6 weeks), and (4) current cocaine users (n=21). Pain was induced using a cold pressor test, with all subjects asked to immerse their dominant forearm in a cold water bath (0-2° C) until the pain became intolerable (pain tolerance measured in seconds). Opioid users (methadone maintained and abstinent) were significantly pain intolerant (mean $\pm$ S.D.: 65 $\pm$ 71 seconds and 71.5 $\pm$ 102 seconds) compared with abstinent cocaine users (167 $\pm$ 120 seconds).

Interestingly, Compton reported that amongst the patients on methadone, pain tolerance did not significantly vary with time since methadone ingestion. Blood samples were not collected during this study. Hence there were no plasma concentrations to correlate or associate with pain responses. Further, Compton also reported that, counter-intuitively, cold-pressor pain tolerance decreased as methadone dose increased ($r=-0.25$; $p=0.05$). Once again it would have been important scientifically if plasma methadone concentrations had been determined in this study, in order to determine if there was any relationship between plasma methadone concentrations and pain responses. Interestingly, from Compton's results it seems that drug-using status was significantly related to pain tolerance, such that abstinent drug abusers were able to tolerate cold-pressor pain almost twice as long as those still using the same drugs. Compton suggested that, with regard to opioid abusers, her finding of decreased pain tolerance with chronic drug abuse, as opposed to the analgesic effects of acute drug ingestion, is consistent with the concept of a negative reinforcer as described in the Opponent Process Theory (Solomon, 1980). This suggestion is only relevant to opioid drugs as cocaine does not have analgesic effects. Compton concluded that complaints of discomfort and pain associated with injury, illness or surgical intervention amongst drug abusers should be taken seriously and managed aggressively.

More recently, Schall et al., (1996) investigated pain perception of 42 methadone maintenance patients compared with 16 healthy, drug-free control subjects. The methadone patients (12 women and 30 men) had been in methadone maintenance treatment for periods ranging from 3 to 56 months; their average dose was 0.7mg/kg of methadone, with no dose changes in the 6 weeks prior to testing. Pain stimulation was induced by mechanical pressure, or, more specifically, pressure stimulation of the nociceptors located in the dorsal

extension-aponeurosis and the underlying periosteum (on each subject's non-dominant hand). This method of tonic pain induction was chosen by the investigators because it 'is as effective as the cold pressor test'. Methadone patients were tested immediately prior to receiving their methadone dose. Then they were randomly allocated into 3 groups: (a) 12 patients were re-tested one hour after the methadone dose was administered, (b) 14 patients were re-tested two hours after the dose, and (c) 16 patients re-tested 4 hours after the dose. Blood samples were taken from all methadone patients concurrently with pain induction, although plasma methadone concentrations were not reported. Results revealed that pain responses of methadone patients (prior to receiving their methadone dose) were not significantly different from those of the drug-free controls; however, the patients had an analgesic response to the administration of methadone (particularly 4 hours post-dose) resulting in a significant reduction in pain perception compared with the control group.

The findings of Schall and co-workers are supported by some of the results reported by Dyer et al. (1999). Although not specifically investigating the issue of pain sensitivity in methadone maintenance patients, Dyer and colleagues induced pain via cutaneous electrical stimulation of the ear lobe in a sample of 18 stable methadone maintenance patients (no dose changes in the previous 2 months). Their responses were compared to those of 10 drug-free volunteers acting as a control group. They found that the pain thresholds of methadone patients at trough plasma methadone concentrations within the inter-dosing interval were similar to the drug-free control group (29 versus 26 volts). However, Dyer and colleagues reported that the pain thresholds of methadone patients, at putative peak plasma methadone concentrations (ie. approximately 3 hours post-dose), were significantly higher than those of the control group (37 vs. 21 volts, respectively). Indeed, the increase in plasma methadone concentrations from trough to peak resulted in significant increases (approximately 25%) in methadone patients' mean pain threshold.

The combined findings (Schall *et al.*, 1996; Dyer *et al.*, 1999) strongly indicate that changing plasma methadone concentrations within an inter-dosing interval are an important factor in determining pain responses in this population. Indeed, it has been observed that the peak analgesic effect and peak serum concentration following methadone administration occur nearly simultaneously (Inturrisi *et al.*, 1987). Interestingly, the findings of Dyer *et al.* (1999) and Schall *et al.* (1996) that, at peak plasma methadone concentrations, methadone patients are more pain tolerant than control subjects contrast with those studies using a cold pressor test: methadone patients appear to be intolerant of this particular method of pain

induction compared with control subjects.

Pain tolerance in opioid addicts (currently opioid abstinent) has also been the subject of further investigation in patients (n=10, all male) during (ie. after at least 6 weeks) treatment with the opioid antagonist naltrexone, and after discontinuation (at least one week post-treatment) of naltrexone (Compton, 1998). The pain tolerance responses of 10 volunteers, who met Diagnostic and Statistical Manual (DSM) III-R criteria for opioid dependence prior to commencing naltrexone treatment, were tested by using a cold pressor test; an ice bath was filled with water maintained at a temperature between 0-2° C. Subjects were asked to place their dominant hand in the bath until the pain became intolerable. Results revealed that the pain responses of subjects during the period of naltrexone treatment were significantly greater (20% longer) compared with the responses after discontinuation of naltrexone treatment (mean $\pm$ s.d, 133 $\pm$ 116.8 seconds vs. 108 $\pm$ 113.7 seconds, respectively). Compton theorised that chronic naltrexone treatment may result in opioid system upregulation ie. increased numbers of opioid receptors, a phenomenon reported by Unterwald *et al.* (1995) in rats exposed to chronic administration of naltrexone, resulting in decreased pain sensitivity. This is an interesting hypothesis that warrants further and more intensive human research.

Compton has continued her investigations of the pain sensitivity of methadone maintenance patients (Compton, *et al.*, 2000). Their study was specifically designed to describe pain tolerance and analgesic response in a sample of opioid addicts (n=60) stabilised in methadone maintenance treatment (no dose changes for at least 2 weeks; mean dose 66 $\pm$ 19.8 mg) in comparison to age and gender matched drug-free control subjects (n=60). Methadone patients began testing approximately 2 hours after receiving their daily maintenance dose. The study used a randomised unblinded placebo-controlled two-way factorial design. Tolerance to cold-pressor pain was examined, both before and after (60 minutes post dose) oral administration of single therapeutic doses of hydromorphone (2mg), the non-steroidal anti-inflammatory ketorolac (10mg), and a placebo. The cold pressor test consisted of subjects placing their dominant arm in a container of cold water (0-2° C) until they could no longer tolerate the pain intensity. The results showed that methadone maintenance patients were significantly less tolerant of the cold-pressor pain than control subjects (43.7 [S.D. = 61] vs. 93.9 [S.D.=103.6] seconds). Furthermore, there were no significant analgesic effects for either medication amongst patients or control subjects. This study did not involve blood collection from any of the participants and hence there could

possibly have been differences between the plasma concentrations of hydromorphone and/or ketorolac in either group (methadone patients or control subjects). It would have strengthened the results if plasma concentrations had been measured for all of drugs (methadone, hydromorphone and ketorolac) in order to determine if there was any relationship between plasma drug concentrations and pain responses. This highlights the need to measure individual plasma drug concentrations in studies determining the analgesic effects of various drugs.

Compton et al. (2001) continued to further investigate pain sensitivity amongst opioid maintained patients. Indeed, their study aimed to investigate possible differences in pain sensitivity between patients (ex-addicts) maintained on stable doses of methadone vs. buprenorphine; they compared pain responses between 18 methadone patients, 18 buprenorphine patients and 18 drug-free controls. The nociceptive stimulus was the cold-pressor test as described in Compton's earlier work. Methadone patients had a mean dose of 62 ± 21 mg (range 12-100 mg), and those maintained on buprenorphine had a mean daily dose of 8.9 ± 1.7 mg (range 8-12 mg). All three groups of subjects were tested on 3 occasions; each one was 48 hours apart. Pain tolerance to the cold pressor test was measured in seconds; methadone patients averaged approximately 55 seconds, buprenorphine patients 67 seconds, and the drug-free controls 138 seconds (standard deviations were graphically illustrated but not defined). Compton and colleagues concluded that patients maintained on opioid drugs are sensitive to nociceptive stimuli regardless of the intrinsic activity of the opioid drug (methadone or buprenorphine) with which they are treated. It would have strengthened the results if plasma concentrations had been measured for all of drugs (methadone and buprenorphine) in order to determine if there was any relationship between plasma drug concentrations and pain responses. Once again, this highlights the need to measure individual plasma drug concentrations in studies determining the analgesic effects of various drugs.

Not all studies investigating pain sensitivity of opioid dependent and formerly opioid dependent individuals find pain intolerance compared with control subjects. Liebmann and co-workers (1994) investigated the pain sensitivity of 40 detoxified opioid addicts undergoing rehabilitation. These subjects (65% male, 19-56 years old) had histories of heroin dependence ranging from 2 to 25 years, but all had been heroin-free for periods of 1-28 months. Forty age-matched, non-dependent volunteers (30% of whom were male, aged 20-5 years old) were used as a control group. Pain sensitivity was measured using a cold

pressor test; subjects immersed their dominant forearm in a warm water bath (37° C) for 2 minutes, and then placed the forearm in a cold water bath (4-6° C). Pain threshold (ie. when pain was first perceived) and pain tolerance (ie. when the subject could no longer tolerate the pain) were measured in seconds. Pain threshold (pain detection) levels of the ex-addicts were significantly higher than the control group. There were no significant differences for pain tolerance. It has even been contended by Liebmann and colleagues that amongst opioid addicts, decreased nociceptive sensitivity precedes opioid addiction. They suggested that the decreased nociceptive sensitivity may be a feature of neurophysiologic dysfunction in these patients (Lehofer *et al*, 1997). Their suggestion and theory is not based on any sound evidence. Interestingly, it has been suggested that opioid dependent patients often present with medical conditions in an advanced state of progression because they have an increased pain threshold, secondary to their chronic use of opioids, which has masked warning symptoms (Hicks, 1989). However, no data were provided to support this suggestion.

In contrast, Bullock (1999) proposed that patients dependent on opioids often present to dental clinics with dental pain that is in excess of the presenting problem. This suggestion is limited by the lack of any references to published evidence. However, it is supported by the empirical experience of Streltzer (1998), who proposed that long-term opioid patients have increased pain sensitivity. Once again, no specific evidence is given to support this claim.

In summary, there are discrepancies in the literature about the pain sensitivity of methadone maintenance patients. It is possible that the contradictions in the literature may be due to differences in pain induction and pain measurement indices; various methods of pain induction (cold pressor test, mechanical pressure, electrical stimulation) have been used to determine pain sensitivity. Further, there has been a lack of consistency in the measurement of pain thresholds ie. onset of pain measured in some studies, with pain tolerance and pain discomfort measured in others. In order to resolve this, it is necessary to use multiple pain induction and pain measurement methods, and to account for fluctuations in plasma methadone concentration. However, in the context of this thesis it is also of vital importance to review the relevant literature with regard to the problem of acute pain management in this patient group.

1.5 Pain management needs of methadone patients

Patients stabilised on methadone maintenance, even those on large doses of methadone, are just as likely to experience acute and chronic pain, as do others in the general population. Portenoy and Payne (1997) proposed that heroin addicts experience traumatic injuries (Cameron, 1964) and a myriad of medical disorders (Sapira, 1968) at a disproportionately higher rate than the general population. They also argued that the management of pain in the addict is not a trivial issue. Chappel (1973) reported that hospitals often refused to admit or treat recognised cases of drug dependence; patients receiving methadone maintenance treatment were turned away from hospitals because “we don’t treat junkies”. Indeed, physicians have been warned that patients with current or past substance abuse are difficult to manage and should probably be excluded from treatment with opioid analgesics (Kennedy & Crowley, 1990).

1.5.1 Factors affecting pain management of methadone patients

Some of the factors possibly affecting effective pain management in this patient population such as inadequate training in pain management, fear of exacerbating addiction through the use of dependence-producing pharmacotherapies, lack of knowledge about addictive behaviours, tolerance, and societal prejudices against addicts factors, opiophobia, have all been discussed in section 1.2. There are of course many other factors that may have an impact on pain management.

Tolerance, which refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect (Jaffe, 1985; Foley, 1991), can have a negative impact on pain management for methadone maintained individuals (St. Marie, 1996; Hicks, 1989). Methadone is a μ -opioid agonist drug and produces cross-tolerance to other commonly used opioid drugs (Foley, 1993), and hence patients tolerant to the analgesic effects of one μ -opioid agonist analgesic are often tolerant to other μ -opioid agonist analgesics (Crews *et al.*, 1993). Tolerance will be discussed in greater detail in sections 1.16 and 1.17. Portenoy (1990) stated, “absolute tolerance to the analgesic effects of opioids does not occur”. Savage (1998) proposed that in general, tolerance to the side effects of morphine develops more rapidly than does tolerance to the drug’s analgesic effects, although no specific evidence was provided to support this suggestion. Savage also added that opioids can therefore be used safely and effectively at even very high doses in individuals who have gradually increased their exposure to opioids over a prolonged period of time, with virtually no limiting side-effects. Savage did,

however, caution that all significant increases in dose should be accompanied by careful monitoring for over-sedation. Others reiterate that in pain management of addicts, doses must be titrated according to patient response, and that there is no pre-defined appropriate dose range (Portenoy & Payne, 1997; Scimeca *et al.*, 2000).

The management of acute and chronic pain in patients with a history of substance abuse is both challenging and stressful. Patients are often reluctant to give accurate histories because physicians may withhold opioid analgesics for the patient with a history of drug abuse (Hicks, 1989). Furthermore, many medical training programs educate physicians not to over prescribe opioid medications (Rapp *et al.*, 1994), and there is the suggestion that stigmatisation, misunderstanding and negative attitudes continue to influence daily practice (Rettig & Yarmolinsky, 1995).

Portenoy and Payne (1997) proposed that some clinicians could interpret pain reports amongst methadone maintenance patients as a manipulative attempt to obtain opioids for purposes other than analgesia. They added further that in these instances the therapeutic relationship will become compromised and the clinician's goals for analgesia will be superseded by the desire to prevent drug abuse. Scenarios such as these are reported to be common occurrences. This, of course, undermines any semblance of a therapeutic alliance and substantially reduces the likelihood of successful treatment.

Patients with a history of drug and/or alcohol abuse are subject to unfortunate biases and negative attitudes when they come into contact with health professionals in relation to pain management needs; examples of such biases (Pankratz *et al.*, 1989) include:

“they are morally culpable for their addiction. It’s their fault.”

“pain is ‘payback’ for their vices and for getting high.”

“they are deceitful and always manipulating to get drugs”

Recently, Scimeca and co-workers (2000) reviewed approximately 100 reports, and outlined common problems in the management of pain in patients on methadone maintenance treatment. Some examples of poor pain management are described as follows:

- Methadone doses were lowered in the hospital, and as a result, patients experienced withdrawal symptoms.
- Pain medication was denied because the clinician believed that the patient's methadone maintenance doses would provide adequate analgesia.

Because of the stigma associated with methadone maintenance treatment, many patients had negative experiences with health professionals when their status became known (NIH Consensus Conference, 1998; Umbricht-Schneitner, 1994). As a result, some methadone patients admitted to hospital concealed their status from staff, with occasional dire consequences (eg. administration of agonist/antagonist drugs which can precipitate sudden withdrawal) (Savage, 1994).

Some 'negative' published articles on this topic have not helped acute pain management of this patient group. Fultz *et al.* (1980) proposed that the hospitalised patient who abuses narcotics is prone to "exaggerating sensitivity to bodily discomfort". Further, they suggested that these patients will try to manipulate nursing staff for additional medication. Fultz and co-workers' assertion, that the addict is prone to exaggerating sensitivity to bodily discomfort, is not an isolated viewpoint. Other prominent clinicians had also suggested that these patients are characterised by being overly concerned with bodily discomfort and having a proneness to over-react (Isbell *et al.*, 1948a, 1948b; Martin *et al.*, 1973). Undertreatment of pain in this patient group was certainly not helped by the suggestion that hospitalisation and treatment of pain with added doses of narcotics may jeopardise the chance to have decremental doses of methadone, eventual detoxification and possible rehabilitation from drugs (Dole *et al.*, 1966). Such viewpoints from influential opinion leaders in the addiction field could only have strengthened a generalist clinician's fear of exacerbating addiction, ultimately adding to the woes of the addict in pain. Therefore, it is not surprising that, given the dearth of available literature on this complex issue, these 'negative' views of the addict in pain have done little but cement negativity and scepticism in the treatment of these patients.

Some have suggested that sub-therapeutic treatment of pain in this patient population may create craving for analgesics, as well as increasing anxiety, frustration, anger and other feelings that tend to feed addiction (McCaffrey & Vourakis, 1992). Coyne (1997) recommended that unless a clinician can rule out all physical causes of pain, the patient should be believed when he/she says that he/she needs pain relief, regardless of his/her drug abuse history. Payte and Zweben (1998) contended that the under-treatment of pain in methadone maintained patients is a serious problem. They added that in cases of acute pain associated with surgery, trauma, or dental work the physicians or dentists assume that the maintenance dose should relieve any pain and that further treatment should not be needed. Payte & Zweben (1998) proposed that some physicians perhaps fear that a methadone

maintained addict might become dangerous if given opioid analgesia, adding that there “may even be physicians who simply don’t care”, although these authors suggested that adequate analgesia will require higher doses of opioid agonists given more frequently than in the non-tolerant patient.

1.5.2 Methadone patients’ responses to analgesics

There is little scientific evidence of the pain management requirements for methadone patients, apart from basic retrospective case reviews. One such early review involved a case study of 25 methadone patients who had been admitted to a hospital in New York for surgical procedures and treatment of trauma (Kantor *et al.*, 1980). The principal purpose of that particular review was to retrospectively determine the effect of any treatment for physical injuries on patients’ methadone doses post-discharge from the hospital. They compared the hospitalised methadone maintenance cohort with a control group (n=25) who were matched with respect to age, sex and length of time in methadone maintenance treatment. The control subjects were not injured in any way, and therefore did not receive any additional opioids other than their prescribed methadone. The main findings of this review were that the hospitalised methadone maintenance patients, despite being on substantial doses of methadone (mean=70mg), required only ‘normal’ doses of additional analgesics to control pain. Furthermore, the ‘hospital treated’ group did not have higher methadone maintenance doses on discharge from the hospital. Whilst one recognises the limitations of interpreting data from a retrospective case review, this final point ostensibly refutes the earlier suggestion by Dole *et al.* (1966) that treatment of pain in these patients, with additional opioids, would result in detrimental outcomes for their methadone maintenance treatment.

Another retrospective analysis of the pain management needs of methadone maintenance patients was conducted by Rubenstein *et al.* (1976). This involved analysing the case notes of 100 methadone patients (average dose of methadone 83mg) who were admitted for emergency and elective surgery in a major New York hospital. They concluded that, although methadone blocks the euphoric effects of other opioids, it did not interfere with the analgesic effects of narcotics such as morphine or meperidine, and that post-operative analgesia was accomplished satisfactorily with 50-100 mg doses of meperidine at 3 hour intervals. Portenoy and Payne (1997) caution that neither of these retrospective case review studies directly assessed pain relief, and consequently neither they nor any other studies have adequately evaluated the role of tolerance in the clinical setting.

Cushman (1972), on the basis of 5 elective surgical cases, recommended that in “more serious” surgical cases where protracted pain or morbidity was anticipated, patients methadone doses should be tapered to approximately 40 mg (10 mg every 6 hours) . He further added, that the methadone should be discontinued on the day of surgery and not resumed until 4 days post-operatively. Cushman reported that “during this interval” (ie. when the methadone had been stopped) patients’ analgesia and opioid maintenance needs were effectively met using conventional doses of analgesics such as pethidine. This rather strange piece of clinical guidance does not seem to be based on any sound knowledge of opioid tolerance and withdrawal, and inevitably would only cause emergence of withdrawal phenomena, which would most definitely complicate pain management. Once again, some apparently misguided early publications have done little but complicate pain management amongst methadone patients.

In contrast with Cushman’s recommendations, one caveat of pain management in methadone maintenance patients which appears to have general consensus, is that their normal maintenance dose must be maintained (Freedman & Senay, 1973; Hoffman *et al.*, 1991; Wesson *et al.*, 1993; Scimeca *et al.*, 2000), because patients receiving sub-therapeutic doses will experience withdrawal and/or craving, and thus will be much more difficult to treat (Scimeca *et al.*, 2000). Importantly, it should also be remembered that methadone used chronically for maintenance does not treat acute pain (Scimeca *et al.*, 2000).

Hicks (1989) postulated that these patients will require larger starting and maintenance doses of opioids than do opioid naive patients. Moreover, he suggested that “the general rule of thumb” is to give about 1.5 times the dose that would apply to opioid-naive patients with similar medical problems. Kreek (1978) also suggested “doses required may be slightly larger and may need to be given more frequently because of narcotic cross-tolerance” (Kreek, 1978). It has been proposed that the individual in pain should be included in the decision-making process regarding medication choices, dosing and scheduling (Savage, 1998). Tucker (1990), on the basis of three retrospective case studies, suggested that whether the patient abuses opioids, barbiturates, stimulants or prescription drugs, higher doses of narcotics are required post-surgery (Tucker, 1990). Others have proposed that when methadone maintained patients need surgery, higher doses of opioids, more frequently administered, will usually be required to achieve analgesia (Woolf, 1983). However, no specific evidence was given to support this proposal.

Portenoy and Payne (1997) suggested that morphine, which has an average duration of analgesia of 3-4 hours, may produce only 1-2 hours of pain relief in a tolerant opioid addict. Others have merely proposed that methadone maintenance patients with acute pain should be treated with 'appropriate dosages of short acting pain medication', and just increasing the dose of methadone will not relieve pain (Schulz, 1997). In contrast, Rogers (1989), on the basis of only one retrospective case study, proposed that methadone maintenance patients, who have pain, respond better to methadone than morphine. This is supported by the findings of Manfredi *et al.* (2001), who also reported that, in 5 case studies of methadone patients with pain management needs, all of the patients responded much better to additional methadone (administered 3 to 4 times per day) as opposed to other opioid analgesics such as hydromorphone, morphine and fentanyl.

It has been contended that methadone maintenance patients should be treated with a different opioid for acute pain rather than increasing the methadone for pain relief (Schulz, 1997; Savage, 1998). Neither Schulz nor Savage provide any evidence to support their respective recommendations. Savage (1998), further added that this is appropriate because using the same drug (methadone) for addiction and acute pain management may complicate the issues of pain treatment and addiction treatment when acute pain resolves and tapering of pain medication to maintenance doses becomes appropriate. Further, because of its relatively slow onset of action and long-half life, methadone may be difficult to titrate rapidly enough to meet acute pain needs (Scimeca *et al.*, 2000).

In Australia, where there are currently over 30,000 methadone maintenance patients, the lack of scientific evidence in the pain management of methadone maintenance patients is highlighted in the National Health and Medical Research Council's (1999) text "*Acute pain management: scientific evidence*"; ironically in this monograph there is no evidence for the treatment of acute pain in this patient group.

Recently, others have concluded that effective pain management in opioid-dependent patients "can be a difficult and challenging task, and may require significant deviation from standardised protocols" (Macintyre & Ready, 2000). They added further that the practical significance of opioid tolerance in acute pain management is that "tolerant patients may require much higher doses of opioid than an opioid-naïve patient after a similar injury or operation". This suggestion is based on empirical evidence not on specific published data.

A substantial retrospective case review study conducted by Rapp et al. (1995) compared the post-operative opioid consumption and pain sensitivity of 202 (non-addict) chronic pain and opioid consuming patients (CPOC), with 180 patients who did not have pain or use opioids pre-operatively. All patients were matched for age, gender, date of surgery, type of surgery and post-operative pain relief modality; the principal findings from that study were that (1) CPOC patients required 3 to 4 times (135.8 ± 68.5 mg) the amount of post-operative morphine of the previously opioid naïve patients (42.8 ± 32 mg), and (2) despite receiving considerably higher doses of opioids, the CPOC patients had higher pain scores than the opioid naïve group indicating they were more pain sensitive.

These findings corroborate those of other investigators (de Leon-Casasola *et al.*, 1993). They evaluated the analgesic requirement of 116 surgical patients who received epidural analgesia. Specifically there were two groups within that cohort: one group of opioid-naïve patients (n=99), and a group of patients who had previously been taking morphine on a daily basis for at least 3 months; the mean pre-operative oral morphine usage for this group was 183mg per day (range, 90-360). de Leon-Casasola and colleagues reported that the group of patients with a history of opioid use required more epidural bupivacaine (137 vs. 44 mg), and higher intravenous doses (48 mg vs. 10 mg) of morphine compared with the previously opioid-naïve patients. Further, it has been observed that the opioid analgesic (sustained release morphine) requirements of AIDS patients with a history of opioid abuse are at least twice those of previously opioid naïve patients (177.4 mg vs. 84.9 mg) (Kaplan *et al.*, 2000).

Rapp and co-workers (1995) stated that there are “no firm guidelines to provide for satisfactory analgesia in opioid tolerant patients”, and “arriving at a treatment regimen is an iterative process”. They concluded by suggesting that patients with a history of opioid use or dependence can be expected to have significantly higher dose requirements for acute pain management, and that more complaints and higher pain scores are likely to be a feature of such a patient population.

Although this thesis is focussed upon the acute pain management for methadone maintained patients, I recognise that with the recent advent of new pharmacotherapies for the treatment of opioid addiction, there may well be differences in pain sensitivity and analgesic responses amongst patients maintained on these other drugs such as buprenorphine, levo-

alpha acetylmethadol (LAAM), and slow release oral morphine. This will need to be investigated in due course. There is little doubt that the medical management of pain in substance abusers is an exceedingly difficult task. Nevertheless, it is an important issue facing pain and addiction specialists, as well as regulators and policy makers (Joranson & Gilson, 1994). Moreover, pain management amongst individuals on methadone maintenance is a complex and challenging issue. Portenoy and Payne (1997) stated, “there is a need to replace anecdotal observations with scientific findings”. This thesis will hopefully begin this process, and start to shed some scientific light and guidance on what is certainly a very complex issue that has until now been relatively neglected.

1.7 Pain: definitions and terminology

Pain is probably the most common symptom leading to medical consultation (Loeser & Melzack, 1999). The enigma of pain dates back to antiquity (Stimmel, 1997). The oldest interpretation ascribes pain as a punishment for offending the gods. The word pain itself derives from the Latin ‘poene’ and the Greek ‘poine’, meaning penalty or punishment (Dallenbach, 1939). The modern definition of pain promulgated by the International Association for the Study of Pain (IASP) is “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey *et al.*, 1979).

Pain is a highly subjective, unique and complex sensation (Pasternak, 1993; Besson, 1999; Millan, 1999). Loeser & Melzack (1999) proposed that the brain contains widely distributed neural networks, which create an image of self through genetic programs and memories of past experience. Afferent inputs (see section 1.8.1) act on this ‘neuromatrix’ and produce output patterns that lead to the report of pain. These authors further suggested that stress could change the interactions between the neuromatrix and peripheral stimuli, with learned experiences and expectations also able to do this. Indeed, one researcher (Beecher, 1946) compared the analgesic requirements of wounded soldiers during World War 2 to civilians undergoing elective surgical procedures. He observed that the soldiers required far less analgesia despite the greater severity of their wounds, implying that they felt less pain. He concluded that situational factors, such as stress of combat, can modify the perception of pain. This example highlights the complexity of the pain experience as noted in Melzack and Loeser’s aforementioned theory.

A common taxonomy to describe pain and pain syndromes has been put forward (see Table 1.1). This taxonomy, developed by the IASP, allows for a more precise description of phenomena surrounding pain while recognising the importance of modifying factors (Merskey *et al*, 1979).

Table 1.1: Pain terminology (adapted from Merskey, 1979)

Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Allodynia	Pain due to a non-noxious stimulus to normal skin
Analgesia	Absence of pain on noxious stimulation.
Anaesthesia dolorosa	Pain in an area or region that is anaesthetic
Causalgia	A syndrome of sustained burning pain after a traumatic nerve lesion combined with vasomotor and sudomotor dysfunction and later trophic changes.
Central pain	Pain associated with a lesion of the central nervous system.
Deafferentation	Loss of sensory input seen frequently in pain of central origin.
Dysaesthesia	An unpleasant normal sensation comparable to pain.
Hyperalgesia	Increased sensitivity to noxious stimulation.
Hyperaesthesia	Increased sensitivity to stimulation, excluding special senses.
Hyperpathia	A painful syndrome characterised by delay, over-reaction and after-sensitisation to a stimulus, especially a repetitive stimulus.
Hypoalgesia	Diminished sensitivity to noxious stimulation.
Hypoaesthesia	Decreased sensitivity to stimulation, excluding special senses.
Neuralgia	Pain in the distribution of a nerve or nerves.
Neuritis	Inflammation of a nerve or nerves.
Neuropathy	A disturbance of function or pathological change in a nerve; in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; symmetrical and bilateral, polyneuropathy.
Nociceptor	A receptor preferentially sensitive to noxious or potentially noxious stimuli.
Noxious	A noxious stimulus is a tissue damaging stimulus.
Pain threshold	The least stimulus intensity at which a subject perceives pain.
Pain tolerance level	The greatest stimulus intensity causing pain that a subject is able to tolerate.

1.8 Physiology and pharmacology of pain

It is essential to have some understanding of what has been scientifically determined in terms of the neurophysiological mechanisms involved in the perception of pain. Nociception is viewed as a protective mechanism that occurs when tissues are being damaged, causing the individual to react to remove the painful stimulus (Stoelting, 1995). Nociception is not pain (Loeser & Cousins, 1990), but describes the neural events and reflex responses produced by noxious stimuli. It can occur in the absence of the perception of pain, just as pain can arise in the absence of nociception (Compton & Gebhart, 1998).

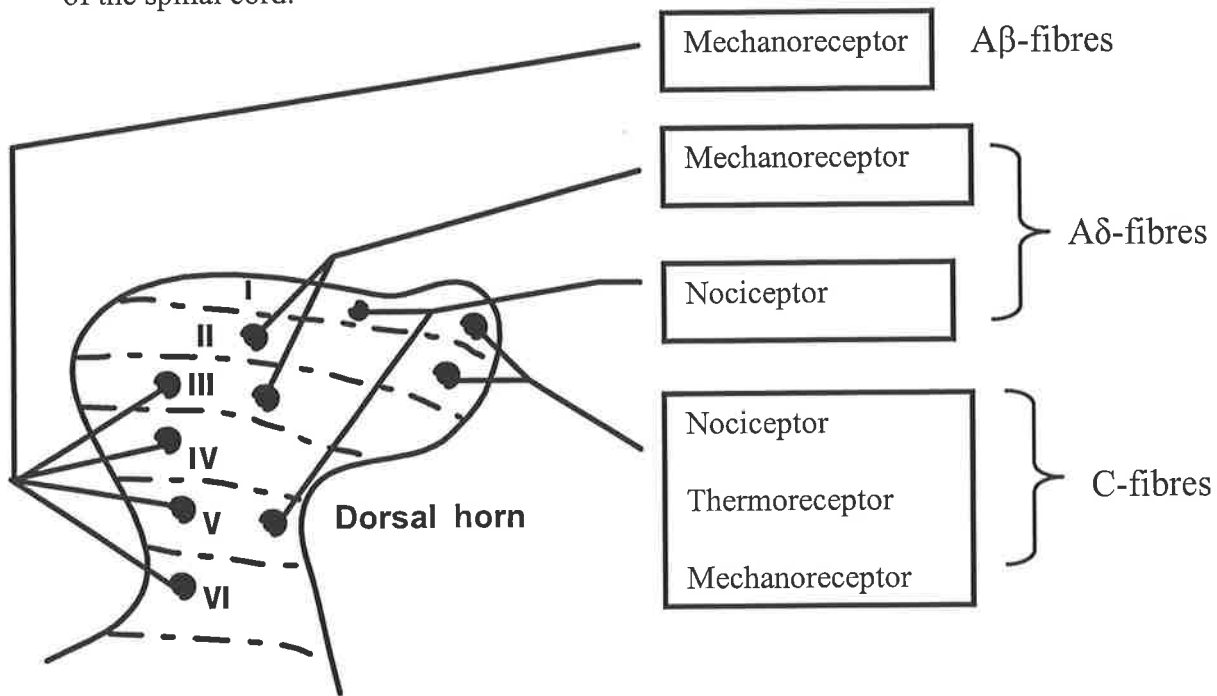
Pain receptors or nociceptors are naked primary afferent nerve endings that signal pain sensation. Pain may be relieved by reducing sensory input from damaged tissue, modulating transmission through the central nervous system, or altering emotional responses to such actual or perceived pain. The neurophysiological mechanisms that underlie the experience of pain may be considered in two classifications: nociceptive pain, ie. pain produced by noxious stimuli, and neuropathic pain, which may result from injury to sensory fibres, or from damage to the CNS itself (Besson, 1999; Millan, 1999). The discussion below will concentrate on nociceptive pain, its transduction and sensitisation.

1.8.1 Ascending pain signal transmission mechanisms

Primary afferent fibres selectively responsive to stimuli that threaten or cause damage are classified as nociceptors (Sherrington, 1906). Nociceptors are located in muscle, fascia, blood vessel walls, tendons, joint capsules, ligaments, fat pads, and periosteum (Stacey, 1969; Willis, 1985; Willis & Coggeshall, 1991).

Afferent nerve fibres are labelled A, B, or C-fibres. A fibres are large, myelinated fibres and respond to light touch, as well as thermal and mechanical nociception. The A fibres are further divided into α , β , γ , and δ fibres. The A δ fibres are thinly myelinated and carry strong noxious stimuli that are potentially or actually damaging to tissues. Other A- and B-fibres do not carry nociceptive impulses (Markenson, 1996). The B fibres are myelinated pre-ganglionic autonomic nerves. C-fibres are non-myelinated, slow conducting fibres, the majority, of which carry afferent noxious stimuli. Their cell bodies are in the dorsal horn of the spinal cord (figure 1.1).

Figure 1.1. The termination of afferent fibres in the six laminae of the dorsal horn of the spinal cord.



These afferent fibres exhibit polymodal responsiveness to tissue damaging stimuli e.g., mechanical, thermal, and chemical. In the skin, these fibres are typically present in proportions of 70, 10 and 20% respectively (Millan, 1999). Each of these classes of primary afferent fibres (nociceptors) are differentially sensitive to noxious and innocuous stimuli. Hence, under normal circumstances only C and Aδ (not Aβ) fibres transmit nociceptive information. The speed of afferent neural transmission is related to the size and myelination of the activated nerve fibres (Markenson, 1996; Millan, 1999). These afferent nerve fibres are classified into three main types on the basis of their diameter, structure and conduction velocity (Millan, 1999), outlined below:

- C - small/thin (0.4 - 1.2 μm in diameter), unmyelinated and slowly conducting (0.5 - 2.0 m sec^{-1}).
- Aδ - medium sized (2-6 μm), thinly myelinated and of intermediate velocity (12-30 m sec^{-1}).
- Aβ - large (> 10 μm), thickly myelinated and fast conducting (30 - 100 m sec^{-1}).

Most nociceptors are polymodal; that is, they respond to multiple modalities of stimulation, ie. thermal, mechanical and chemical, whereas all non-nociceptors are unimodal. The distinguishing feature of nociceptors is their ability to become sensitised when tissue is injured, ie. the threshold intensity for activation is decreased; non-nociceptors do not sensitise when tissue is injured. The subjective qualities of pain, and the protective responses that it initiates, are determined by the way nociceptive signals are integrated and modified in the periphery, in the spinal cord, and in supraspinal structures (Dray, 1997). The neuroanatomy and organisation of ascending pain projection pathways is highly complex (for a review see Millan, 1999; Besson, 1999). There are multiple pain pathways, including the spinothalamic, spinoreticular, spinomesencephalic, spinoparabrachio-hypothalamic, spinoparabrachio-amygdala, and spinocervicothalamic tracts, and post-synaptic dorsal column pathways, which project to the thalamus, reticular formation, mid-brain, periaqueductal gray, amygdala, and the hypothalamus (Besson, 1999; Millan, 1999).

1.8.2 Physiological effects of noxious stimuli

Autonomic reflex responses produced by noxious stimuli include increases in heart rate, blood pressure and respiration. These nociceptive reflexes are protective withdrawal (motor) reflexes that are organised at the level of the spinal cord (Compton & Gebhart, 1998). An example of such action can be seen when a finger is pricked by a needle producing a reflexive withdrawal. This is generally followed by conscious appreciation of pain that requires integration and interpretation of information in several areas of the brain such as the thalamus, cortex and reticular formation (Compton & Gebhart, 1998; Besson, 1999; Millan, 1999).

Generally, upon exposure of the skin to noxious stimuli, A δ myelinated fibres elicit a pain which is 'sharp', 'pricking' or 'stabbing' in nature, whereas the unmyelinated C fibres evoke 'aching', 'throbbing' or 'burning' pain (Ochoa & Torebjork, 1989; Handwerker & Kobal, 1993; Belemonte & Cervero, 1996). A single discharge of an individual primary afferent fibre is generally not perceived as noxious and many nociceptors need to be recruited over a period of time for 'pain' to be experienced (Millan, 1999). Actual pain thresholds are higher, in humans, than the thresholds for activation of individual nociceptors. These observations suggest the existence of central mechanisms for both spatial and temporal summation for pain signalling (Vierck *et al.*, 1997). It is important to note that the threshold for activation of nociceptors is often well below the threshold for pain (Handwerker *et al.*, 1984). Hence, as previously outlined, nociceptors can have a moderate

level of activity before the perception of pain becomes conscious. Perception of pain is increased by numerous substances (some of which are shown in Table 1.2), which are released when tissue is damaged.

1.8.3 Pain mediators

A complementary neurochemical system of primary afferent fibre categorisation may be based upon the nature of the molecules which they contain and release (Millan, 1999). Nociceptors (primary afferent fibres) synthesise a variety of substances potentially involved in the central transmission and modulation of nociceptive information.

Numerous chemical factors produced by tissue damage, inflammation, or nerve injury (see Table 1.2) alter the quality of pain to induce heightened awareness and exaggerated responsiveness to sensory stimuli (hyperalgesia) as well as to sensory stimuli that are normally innocuous (allodynia). Local biochemical changes are produced by liberation of some of these intracellular substances into the extracellular fluid surrounding primary afferent fibres (nerve endings) and induce local pain, tenderness and hyperalgesia (Bonica, 1987).

Table 1.2: Neurotransmitters and neuromodulators implicated in modulating the response to pain. (this not an exhaustive list of all the neurotransmitters and neuromodulators)

Acetylcholine	Histamine
Angiotensin	Hydrogen ions
β endorphins	Indolamines
Bradykinin	Nerve growth factor
Cholecystokinin	Neurotensin
Cytokines	Nitric oxide
Dopamine	Norepinephrine
Epinephrine	Prostaglandins
Glycine	Serotonin
Glutamate	Substance P
Gamma-aminobutyric acid	Thyrotropin releasing hormone
	Vasopressin

The chemical products of tissue damage and inflammation are likely to be responsible for many of the events that occur in sensory fibres during pain (Basbaum & Levine, 1991; Dray, 1994; Rang *et al.*, 1994; Millan, 1999; Besson, 1999). These chemicals can directly activate peripheral fibres to induce pain or, more importantly, to increase their sensitivity and responsiveness to a range of exogenous stimuli.

In essence, injury or tissue damage produces biochemical changes, which are transduced by nociceptors into impulses that are transmitted from the site of tissue damage to the neuraxis via A δ - and C-fibres. Thereafter, these impulses reach the dorsal horn of the spinal cord (see figure 1.1), where they are subjected to peripheral, local, segmental and supraspinal modulating influences which determine their further transmission (Bonica, 1987).

Added to this complex reaction is the fact that primary afferent nociceptors normally have several types of pharmacological receptors on their surface membranes (Willis & Westlund, 1997), including opioid, γ -aminobutyric acid (GABA), bradykinin, histamine, cholecystokinin, acetylcholine, serotonin, and capsaicin receptors (Dray, 1994; Besson, 1999). Furthermore, pain can also result from activation of central (supraspinal) nociceptive pathways without involving peripheral nociceptors, eg., in cases of central pain which may follow damage to the central nervous system (Boivie *et al.*, 1989). For the most part centrally mediated pain appears to be idiosyncratic, and difficult to treat (Bonica, 1991; Boivie, 1994).

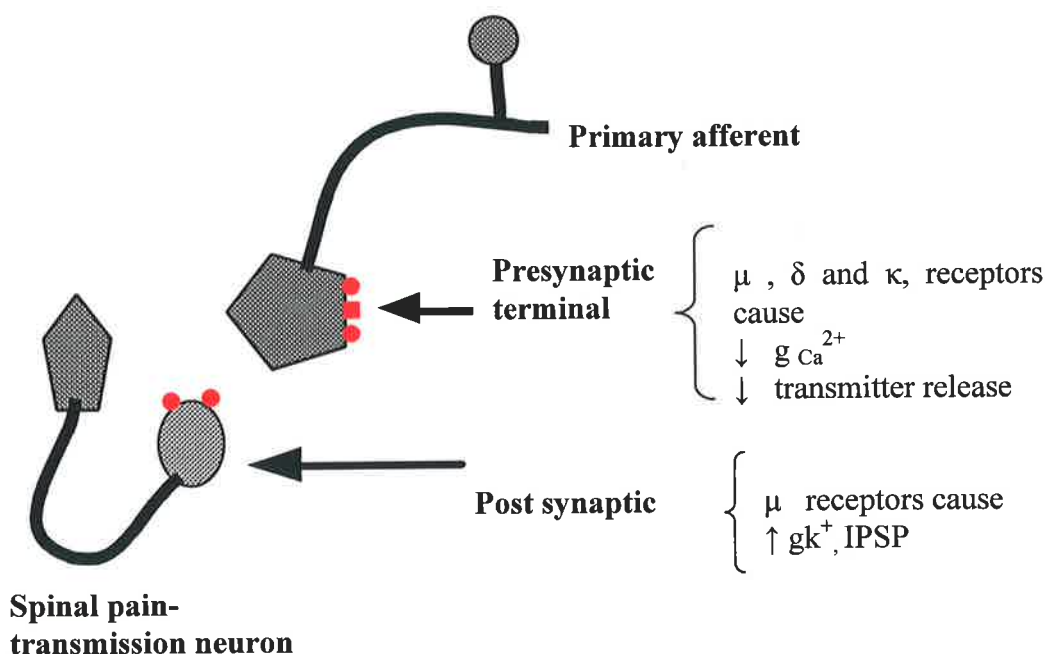
The traditional picture of fixed property nociceptors implanted in damaged tissue passively detecting the chemistry of cell damage no longer holds (Wall, 1995). Advances in modern molecular biology have demonstrated the aforementioned elaborate action and reaction of primary afferent fibres, peripheral receptors and other cells in the region of damage. This supraspinal integration and interpretation of peripheral events are what make pain such a complex and unique experience.

1.8.4 Descending pain modulation

A fundamental component of the descending pain modulatory system was established in the early 1970s. Reynolds (1969) and others (Mayer & Liebeskind, 1974), experimenting on rats, found that electrical stimulation of the periaqueductal grey region of the brain produced analgesia, which was sufficient to enable surgery to occur. These findings were later confirmed in patients with intractable pain who had stimulating electrodes implanted at sites

in the brain similar to those from which the stimulation analgesia was produced in rats (Adams, 1976; Hosobuchi *et al.*, 1977). Hence, the induction of analgesia, separated from any other effect, was of fundamental importance in establishing pain modulation as a distinct physiological function of the central nervous system. Additional discoveries in the field of neuropharmacology revealed that endogenous opioid peptides (enkephalins, dynorphins and endorphins) are present in the central nervous system (this is reviewed in more detail in section 1.16.2), and that the opioid receptor antagonist naloxone attenuated the analgesic effects of stimulation produced analgesia in humans. (Akil *et al.*, 1976). Opioid receptors (reviewed in more detail in section 1.16.2) belong to the superfamily of seven-transmembrane spanning receptors coupled to G-proteins inhibiting adenylyl cyclase (Atcheson & Lambert, 1994; Corbett *et al.*, 1993; Yost, 1993; Nestler & Aghajanian, 1997). At the molecular level, opioid receptors are linked to G-proteins (see section 1.16.2), and are able to affect ion gating, intracellular Ca^{++} disposition, and protein phosphorylation. Opioids inhibit neurotransmitter release (see table 1.2) by a direct effect on Ca^{++} channels on pre-synaptic nerve terminals, and they hyperpolarise, thus they inhibit post-synaptic neurons by opening K^+ channels. Figure 1.2 schematically illustrates the pre- and post-synaptic action at all three receptor types.

Figure 1.2. Spinal sites of opioid action. Mu, kappa, and delta agonists reduce transmitter release from presynaptic terminals of nociceptive primary afferents. Mu agonists also hyperpolarise second-order pain transmission neurons by increasing K^+ conductance, evoking an inhibitory post-synaptic potential (IPSP) (adapted from Way *et al.*, 1998).



Other analgesic systems such as serotonergic and noradrenergic pathways have a role in pain inhibition (Besson, 1999; Fields & Basbaum, 1978, 1989; Millan, 1999). McNally (1999) proposed that pain modulation is a balance between the activity of inhibitory (or antinociceptive) and facilitatory (or pronociceptive) circuits; this is illustrated in figure 1.3. (McNally, 1999 proposes that, whereas antinociceptive circuits inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn producing analgesia, pronociceptive circuits facilitate this transmission thereby inhibiting analgesia or increasing basal pain sensitivity).

It has been shown that pain is not transmitted passively to the central nervous system (CNS), but rather, is shaped and modulated by descending pathways and inhibitory interneurons (Fields & Basbaum, 1994, 1999). Overall, it has been suggested that the study of descending pain pathways is complex, largely due to the functional diversity of neurons and neuronal connections within the dorsal horn (Washington *et al.*, 2000).

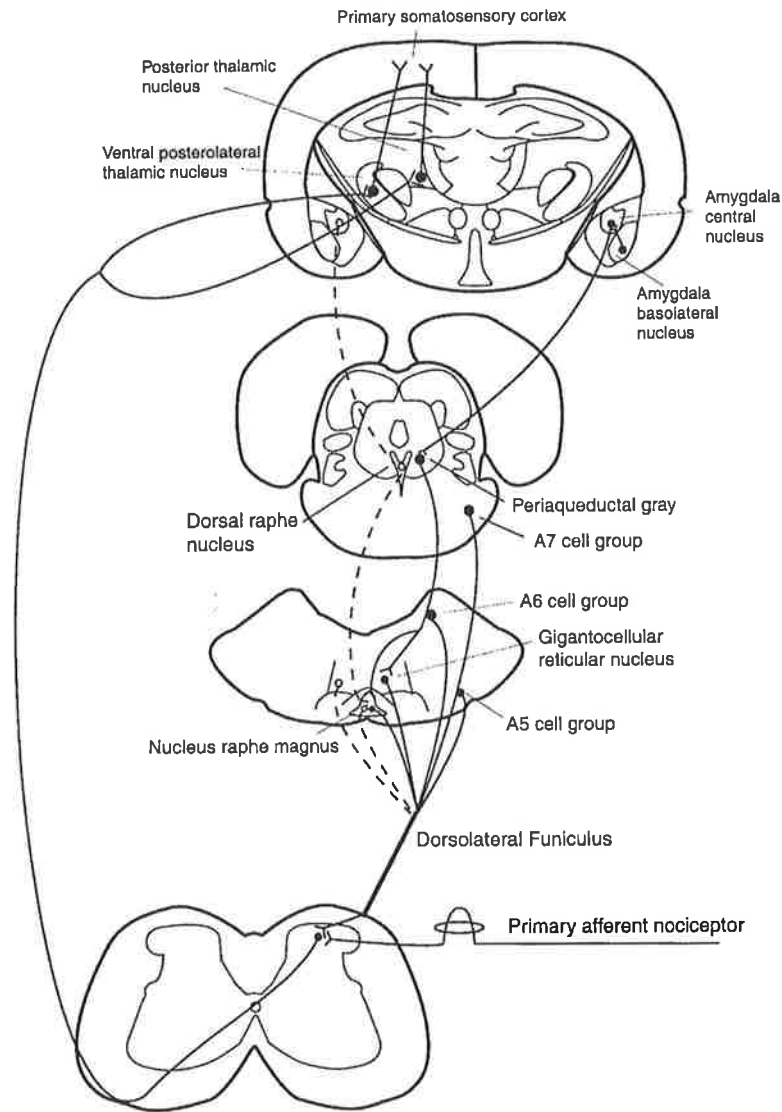


Figure 1.3. Descending mechanisms for pain inhibition and facilitation. Pathways descending from the amygdala via the periaqueductal gray to the rostral ventromedial medulla (including the nucleus raphe magnus and gigantocellular reticular nucleus) and projecting to the dorsal horn of the spinal cord via the dorsolateral funiculus produce analgesia (unbroken lines). This descending pathway is supplemented by descending noradrenergic projections (A5, A6 and A7). At the level of the spinal cord, analgesia is produced by the inhibition of transmitter release from primary afferent nociceptors, the inhibition of dorsal horn nociceptive neurons, as well as the excitation of inhibitory interneurons. Pathways descending from the amygdala via the dorsal raphe nucleus to the rostral ventromedial medulla and projecting to the dorsal horn of the spinal cord via the dorsolateral funiculus produce antianalgesia (broken lines). At the level of the spinal cord, antianalgesia is produced by the inhibition of analgesic mechanisms at both the terminals of primary afferent nociceptors and the post-synaptic nociceptive neuron. Hyperalgesia is mediated by pathways descending from the rostral ventromedial medulla to the spinal cord via the dorsolateral funiculus. The midbrain and forebrain mechanisms for hyperalgesia remain unclear but could involve the periaqueductal gray and amygdala. At the level of the spinal cord hyperalgesia is produced by a sensitisation of spinal nociceptive neurons. (Reproduced from *Neuroscience and Biobehavioral Reviews*, Vol.23, McNally G, pp.1059-1078, (1999) with permission of Elsevier Science, and Dr. Gavan McNally).

1.9 Types of pain

Within the general framework of pain, there are some well recognised sub-types of pain that are commonly experienced.

1.9.1 Transient pain

This is elicited by the activation of nociceptive transducers in skin or other tissues of the body often, but not always, in the absence of any tissue damage. The function of such pain to the individual is related to its speed of onset after stimulation is applied and the speed of offset that indicates that the offending physical disturbance is no longer impinging upon the body (Loeser & Melzack, 1999). Transient pain is ubiquitous in everyday life and does not generally lead to an individual seeking treatment. Simple examples of such pain include instances such as accidentally pricking a finger with a sewing pin, or in the clinical environment, the fleeting pain associated with venepuncture.

1.9.2 Acute pain

This consists of a constellation of unpleasant perceptual and emotional experiences and associated autonomic reflex responses, psychological and behavioural reactions (Bonica, 1987). It is generally elicited by injury of body tissue and activation of nociceptive transducers at the site of local tissue damage. The local injury changes the response characteristics of the nociceptors, their central connections, and the autonomic nervous system in the region (Loeser & Melzack, 1999). Not all acute pain episodes require medical intervention. However, treatment can be beneficial, ie. to reduce or prevent pain and to enhance the healing process by shortening the duration of the injury. Often acute pain, associated with injury, imposes limitation of activity to avoid aggravation of the pathophysiology. Acute pain is commonly associated with trauma and surgery. Acute pain does not persist for months or years.

1.9.3 Chronic pain

This has been defined as a pain that persists a month beyond the usual course of an acute disease or a reasonable time for an injury to heal (Bonica, 1980). Although some clinicians have used the arbitrary time of six months to designate pain as being chronic (Crue, 1985), it is prudent to suggest that this is not appropriate because there are many acute diseases which heal in a matter of 2-4 weeks. Bonica (1987) proposed that in these situations, if pain is still present 4 weeks after it should have subsided, pain must be considered chronic.

However, others have argued that it is not duration of pain that distinguishes acute from chronic pain but, more importantly, the ability of the body to restore its physiological functions to normal homeostatic levels (Loeser & Melzack, 1999). Chronic pain may be caused by chronic pathological processes in somatic structures or viscera, or by prolonged dysfunction of parts of the peripheral and/or central nervous system(s) (Bonica, 1987). Examples of chronic pain are low back pain, post-herpetic neuralgia, and fibromyalgia.

The perception of pain is a common experience. However, there can be no doubt that pain is essentially a unique experience, thus making the induction of experimental pain and its measurement (inter and intra-individual) a difficult issue.

1.10 Experimental pain

The nociceptive stimuli associated with clinical pain are unobservable, and hence no endpoint criterion can be unambiguously established. In contrast, in experimental pain tests, stimulus parameters and measurement criteria can be established which allow for an investigation of pain activation and modulation as well as the factors determining individual differences (Chen *et al.*, 1989).

The objective measurement of pain has been one of the most challenging problems for clinicians and researchers (Walsh *et al.*, 1989). The role of experimentally induced human pain in the evaluation of analgesic drug efficacy has long been a controversial issue in clinical pharmacology (Keats *et al.*, 1950; Hardy *et al.*, 1953; Beecher, 1953; Wolf *et al.*, 1966; Moore *et al.*, 1997). It has been contended, “there is a fundamental and mysterious difference between pain produced in a laboratory and the pain produced by disease or injury” (Beecher, 1962). Beecher’s strong attack on the usefulness of experimental pain in evaluating analgesics, largely reflects the relative absence of anxiety in experimental pain.

Beecher (1962) critically rejected experimental pain in man as a means of evaluating analgesic effectiveness, because of its lack of meaning to the individual. Whereas he posited that clinical pain is of real significance to the patient, others have suggested that this concept exaggerated and oversimplified the difference between experimentally induced and pathological pain (Wolff *et al.*, 1966). Furthermore, it has been contended that Beecher’s pessimism impeded the development of experimental algometry for a long time (Handwerker & Reeh, 1986).

Despite the aforementioned alleged impediment, experimental algometry has somewhat improved since Beecher's day. There are many methods (including electric stimulation, mechanical stimulation, cold pressor test, ischaemic tourniquet, radiant heat) used to induce experimental pain. All of these experimental methods share a common goal of accurately representing the human pain experience. Some of these methods are described below (section 1.10.1).

1.10.1 Experimental pain induction

1.10.1.1 Cold pressor test

The cold pressor test was first used by Hines and Brown (1933) for the measurement of variability in blood pressure. It is an experimental model of tonic pain that has strong affective and autonomic components (Hilgard & Hilgard, 1983). Wolff *et al.* (1940) later gave a detailed description of the pain in response to cold; they reported that intramuscular morphine produced a dose-dependent increase in pain threshold using a cold pressor test. Since then it has been widely used in a variety of experimental settings. Subsequent studies have proved the efficacy of the cold pressor test in experimental pain (Wolff *et al.*, 1966; Wolff *et al.*, 1968) and demonstrated variations in responses between different analgesics and, indeed, between different strengths of analgesics (Posner *et al.*, 1985; Jones *et al.*, 1988). Posner and colleagues tested the analgesic effects of dipipanone (oral doses of 2, 4, and 8 mg) in a double-blind randomised, placebo-controlled, balanced cross-over design. They concluded that the cold pressor test is indeed sensitive to opioid administration with significant reductions in pain scores following administration of doses that were "lower than those commonly used in clinical practice". Further, Jones *et al.* (1988) compared the sensitivity of morphine and ibuprofen using a cold pressor test in a double-blind, double-dummy, placebo-controlled cross-over, balanced for order effects (sample of 12 healthy volunteers). They concluded that the cold pressor test could discriminate between morphine and placebo, but that there was no significant difference between ibuprofen and placebo.

The cold pressor test does not damage tissues, and readily permits quantification of pain responses (Jarvik *et al.*, 1981; Walsh *et al.*, 1989). Furthermore, it has been widely used in the assessment of pain threshold and tolerance levels amongst opioid dependent, and formerly dependent, individuals (Inglis & Martin, 1965; Ho & Dole, 1979; Compton, 1994; Compton *et al.*, 2000). This method, of which there are many variations (particularly in water temperature), generally involves immersion of a limb in a container of very cold water.

1.10.1.2 Mechanical pressure

Mechanical pressure has been used to produce sensations of pain by application of gross pressure to the fingers or mastoid process, and by distension of the oesophagus or bile duct (Beecher, 1959). More recent studies often use pressure to a finger joint (Whipple & Komisaruk, 1985; Schall *et al.*, 1996). Pressure algometers have been used since Victorian times (O'Driscoll & Jayson, 1982). Mechanical methods of pain induction produce a wide range of pain intensities and durations (Gracely, 1994). However, stimulus control is difficult since tissue elasticity, and stimulating area, rate, and degree of compression can influence results (Wolff, 1984). Schall *et al.* (1996) reported that pain induced by mechanical pressure could be attenuated by increases in plasma methadone concentrations from putative trough to peak.

1.10.1.3 Electrical stimulation

Electrical pain is one of the most widely used methods for measuring cutaneous pain threshold. Harris and Blockus (1952) described electrical stimulation with square wave impulses as being perhaps one of the most suitable methods of experimental pain induction because it is very simply applied and is reproducible. Since the early endorsement of this method, others have noted that square wave pulses are widely used as algogenic stimuli (Procacci *et al.*, 1979). The parameters of the stimuli can be programmed and predetermined (Gibson, 1963; Notermans, 1966 & 1967; Wolff *et al.*, 1966).

It has been argued that the effective stimulus delivered to the skin depends, according to Ohm's law, on the resistance offered by the skin itself (Procacci *et al.*, 1979). Thus, the intensity of the stimulus varies widely unless the stimulator is provided with a device (constant current unit) maintaining a constant current throughout every variation of cutaneous resistance. It has been reported that a weak intensity of the electrical current stimulus induces a tactile sensation, a stronger intensity a sensation of tingling and an even stronger intensity a clear sensation of pain (Procacci *et al.*, 1979). Electric stimulation has long been used to determine the analgesic efficacy of opioids (Staucher *et al.*, 1986; Willer, 1985; Wolff *et al.*, 1966;). More recently it has been used, successfully, to determine the analgesic effect of methadone in a sample of methadone maintenance patients (Dyer *et al.*, 1999). The results of that particular study, ie. that increases in plasma methadone concentrations resulted in decreased sensitivity to pain induced by cutaneous electrical stimulation of the ear lobe, illustrated the reproducibility of the method and confirmed its ability to measure the antinociceptive effects of opioid drugs.

1.10.1.4 Ischaemic pain

Ischaemic pain is produced by arresting blood flow in an arm by a tourniquet (or sphygmomanometer cuff) and by exercising the hand by isometric or isotonic contractions (Fox *et al.*, 1979; Sternbach, 1983). This method produces a severe, continuous and increasing pain (Gracely, 1984). It is used relatively extensively as both a pain stimulus and as an experimental stressor (Procacci *et al.*, 1979; Penson *et al.*, 2000). It has been suggested that this method of pain induction reflects “cancer pain” (Smith *et al.*, 1968).

1.10.1.5 Radiant heat-induced pain

Radiant heat of a constant intensity is well established as a method of experimental pain induction (Stacher *et al.*, 1982a, b: 1983, 1986; Cooper *et al.*, 1986; Arendt-Nielsen *et al.*, 1995). This method generally involves heat (from a lamp or a laser) being directed at a limb (usually an arm). Subjects are instructed to indicate when they first perceive pain and/or when they can no longer tolerate the pain intensity. These indices are measured in seconds. Stacher and colleagues used radiant heat to compare the analgesic effects of diclofenac (75 and 150mg) with codeine (60mg) and placebo. They reported that doses of both diclofenac and codeine, but not placebo, resulted in decreased pain sensitivity, thus illustrating the usefulness of this method of pain induction in experiments investigating analgesic response to drug administration.

1.11 Indices of pain assessment

1.11.1 Visual analogue scales

Pain response is inherently subjective and pain measurement relies on the verbal report of patients (Bromm, 1984). Visual analogue scales (VAS) are widely used and provide a very simple approach to pain measurement (Scott & Huskisson, 1976; Nicholson, 1978; Stubbs, 1979). Subjects are told to indicate the intensity of a noxious stimuli (pain) by marking a 10cm line that is labelled ‘no pain’ at one end and ‘the worst pain’ at the other. Variations of this scale include asking subjects/patients to produce a number from 1 to 10 to indicate pain intensity. Despite being easy to use, cheap and simple for the individual to comprehend, the use of rating scales assumes pain to be a unidimensional experience, which varies only in intensity (Chapman *et al.*, 1985). Wide variation in the pain experience amongst individuals leads to a large variability in the pain scale ratings of patients who experience similar stimuli or interventions (Farrar *et al.*, 2000). Further, statistically there is evidence that patients use the beginning, middle, and end of measurement scales preferentially (Huskisson

& Scott, 1976; Serlin *et al.*, 1995). Price and colleagues (1983) concluded that VAS can be used reliably to measure either experimentally induced pain or clinical pain, whereas others suggest that such procedures are liable to response biases (Graceley, 1980). Craig (1989) stated that “people are notoriously unreliable in remembering and reporting on their experiences, even when well motivated to do so”. Critics of VAS contend that measurement and estimation are two different processes (Savage, 1970); for example, asking an individual to estimate his or her body weight, blood pressure, or I.Q. is very different from actually measuring these factors.

1.11.2 Pain thresholds

The desirability of identifying a commonly accepted threshold value, and the difficulties in defining a clinically important difference for symptomatic conditions such as pain have been well recognised (Beecher, 1959; Lasagna, 1960; Houde, 1982; Turk *et al.*, 1993; Moore *et al.*, 1997). Harris and Rollman (1983), following a study investigating the characteristic of various pain measures, found that threshold (when pain is first perceived) and tolerance (the point at when the pain stimulus is no longer tolerable) judgements are dissimilar. They qualified this by stating that “threshold emphasises the discrimination of nociceptive quality”, whereas “tolerance is expression of unwillingness to receive more intense stimulation”. They recommended that both of these response indices should be used in studies involving experimental pain. It could well be that measures of threshold and tolerance may not simply be the extremes of one continuum of painfulness; rather, each may be influenced by some combination of sensory and affective variables (Harris & Rollman, 1983; Rollman & Harris, 1984). The difference between pain threshold and tolerance values has been termed the ‘pain sensitivity range’ (Wolff, 1964).

Refinements have been made to experimental pain methods making them valuable tools in assessing the efficacy of many analgesics. Electrical stimulation and the cold pressor test have both been shown to be responsive to opioids, and offer variety in pain stimulus, and have both been used in studies investigating the issue of pain sensitivity amongst opioid addicts (Inglis & Martin, 1964; Ho & Dole, 1979; Compton, 1994, 1998; Dyer *et al.*, 1999; Compton *et al.*, 2000). Further, both have been used successfully in healthy, previously opioid-naïve volunteers to determine analgesic response (Wolff *et al.*, 1966; Jones *et al.*, 1988; Posner *et al.*, 1985). Hence, these methods of pain induction will be used in all of the nociceptive experiments contained in this thesis.

Compton and Gebhart (1998), suggested that as clinical knowledge of the neurophysiology of pain has increased over the past 30 years, new treatments for pain and new ways of effectively integrating pain treatment approaches have evolved. However, Besson (1999) suggested that whilst there have been many advances in defining pain pathways and the neurobiology of pain, the translation of such information into clinical practice has been considerably slower. Throughout the undoubted advances in the knowledge and treatment of pain, morphine remains the premier agent for the treatment of moderate to severe pain (WHO, 1996). It is essential to understand some of the actions (effects) of morphine and related drugs.

1.12 Opioids

1.12.1 Opioids: a historical perspective

The history of the poppy begins in antiquity. The exact date of the first systematic cultivation of this plant is not known. Somewhere around 2000 BC, the poppy was cultivated by the Sumerians in order to extract opium for its anti-diarrhoeal, pain relieving and sedating properties (Macht, 1915; Anslinger & Tompkins, 1953). Opium is an extract derived from the poppy, *Papaver somniferum*. The milky juice is dried and powdered to make powdered opium, which contains a number of alkaloids; only a few, morphine, codeine, and papaverine, have clinical usefulness (Reisine & Pasternak, 1995). Opium is the oldest medication known. Indeed, its therapeutic use was discussed by Hippocrates circa 420 B.C. (Grier, 1937). Tincture of laudanum, an alcoholic extract of opium, was devised by Thomas Sydenham, and was widely used as an oral preparation (LaWall, 1927).

A German chemist's assistant, Friedrich Sertürner, first isolated the active compound from opium in 1803 (Casey & Parfitt, 1996). He named this compound "morphium", from Morpheus the Greek god of dreams. Morphine and laudanum were widely used for their analgesic and anti-diarrhoea properties, as well as a plethora of other uses, until the end of the 19th century (Churchill & Churchill, 1916). More than 100 years passed, after Sertürner isolated the compound he called morphine, before the actual structure of the compound was proposed (Guilland & Robinson, 1923).

The contemporary term 'opioid' was first coined by Acheson in 1973, who used it to designate drugs whose actions resembled morphine but whose chemical structure could be quite different from opiate analgesics (Martin, 1967). Opioid drugs represent a heterogeneous group of chemical entities with morphine-like properties. They include

natural and synthetic compounds as well as endogenous peptides, including the four distinct peptide families (described in section 1.16.2). The term opioid is now used to describe all of the compounds that interact with stereospecific opioid receptors in the central and peripheral nervous systems (Foley, 1993). It is preferred over the terms 'opiate' and 'narcotic analgesics'. Opiate is a specific term that is used to describe drugs (natural and semi-synthetic) derived from the juice of the opium poppy. For example, morphine is an opiate but methadone, which is a synthetic drug, is not (Jaffe & Martin, 1990). The term narcotic is derived from the Greek word 'narke' meaning numbness or stupor; it is an imprecise and pejorative term that is not useful in a pharmacological context (Cherny, 1996) and is generally used in a legal context. As outlined above, the principal active ingredient of opium is the alkaloid morphine. Despite the aforementioned success in isolating the original compound, little was known about the mechanism of action of opioid drugs until relatively recently. The concept of pharmacologically relevant receptors for opioids, based on the activities of stereoisomers, was first proposed by Beckett and Casey (1954).

1.12.2 Endogenous opioid peptides and opioid receptors

In the early 1970s research scientists from three laboratories simultaneously published biochemical evidence for the existence of stereospecific binding sites for opioids in animal brain (Pert & Snyder, 1973; Simon *et al.*, 1973; Terenius, 1973). Further evidence was published that there were such sites in the human brain (Hiller *et al.*, 1973). This led to the postulate that the receptors must have endogenous functions and, as a corollary that endogenous opioid ligands were likely to exist. In 1975, a team of scientists, working in Kosterlitz's laboratory, were the first to achieve success in purifying and characterising the structure of endogenous molecules with opioid activity (Hughes *et al.*, 1975).

These substances proved to be two closely similar peptides, Tyr-Gly-Gly-Phe-Met and Tyr-Gly-Gly-Phe-Leu, which were named methionine and leucine enkephalin, respectively. Since then other peptides, now known as endorphins and dynorphins, have been identified. It is widely accepted that there are three distinct families of peptides: enkephalins, endorphins and dynorphins (Reisine & Pasternak, 1995). More recently, other endogenous peptides have been discovered which may be important agonists at opioid receptors. Endomorphin 1 and 2 have been found in mammalian tissues and have high affinity and selectivity for μ receptors (Zadina *et al.*, 1997). Nociceptin is a 17-aminoacid peptide found in nervous tissue and is thought to be the endogenous ligand for the orphan opioid receptor (Meunier *et al.*, 1995).

The concept that there were subtypes of the opioid receptor was originally introduced by Martin (1976); based on pharmacological observations and electrophysiological experiments in the chronic spinal dog (Gilbert & Martin 1976; Martin *et al.*, 1976). Their findings appeared to be consistent with the existence of at least three types of opioid receptors, which they subsequently named μ (for morphine), κ (for ketocyclazocine), and σ (for SKF-10047). These drugs exhibited different pharmacological profiles and were unable to replace each other in the suppression of withdrawal symptoms in dogs treated with one of them. Therefore, separate receptors appeared to be the most straightforward explanation.

The discovery of the enkephalins led to the postulate of another receptor type with a preference for these opioid pentapeptides. The first evidence for this came from the pioneering work, conducted in Kosterlitz's laboratory, with isolated organ systems (Lord *et al.*, 1977). Enkephalins were less effective than morphine in inhibiting electrically invoked contractions of the isolated guinea pig ileum, whereas the reverse was true in the isolated mouse vas deferens. The enkephalin preferring receptor which seemed to predominate in the mouse vas deferens was subsequently named δ (after deferens). The σ receptor was later recognised as being non-opioid, although some opioids do have activity at σ receptors, the effect is not reversed by naloxone, ie. an opioid antagonist.

Several additional types of receptors have been proposed, most notably a specific receptor for β -endorphin called ϵ , epsilon, (Schulz *et al.*, 1979), although the epsilon receptor is not widely recognised as an opioid receptor. It is widely accepted that there are three distinct classes of opioid receptors (i.e. delta (Opioid I), kappa (Opioid II) and mu (Opioid III) (Dhawan *et al.*, 1996) which have different roles in the pharmacodynamic actions of opioids (see table 1.3). These opioid receptors 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 the neural plexus in the gastrointestinal tract (Atweh & Kumar, 1977a,b,c; Besse *et al.*, 1990; Dhawan *et al.*, 1996; Jaffe, 1992; Jaffe *et al.*, 1997; Mansour *et al.*, 1988; Kreek, 1992; McLean *et al.*, 1986). Subtypes of receptors have also been suggested (Pasternak *et al.*, 1980; Stefano *et al.*, 1993), but there is no definitive evidence from molecular biology to support these premises (Besson, 1999).

Opioid receptors belong to the superfamily of seven-transmembrane spanning receptors coupled to guanosine diphosphate (GDP) binding proteins known as G-proteins (Atcheson & Lambert, 1994; Corbett *et al.*, 1993; Yost, 1993; Nestler & Aghajanian, 1997). G-proteins consist of 3 subunits (α , β and γ). Under resting conditions, GDP is associated with the

α subunit and guanosine triphosphate (GTP) takes its place. This produces a change that causes the opioid to dissociate from the receptor. The α subunit bound to GTP also dissociates from the β and γ subunits, and interacts with the system within the cell that produces the effect. The intrinsic enzymatic activity of the α subunit causes GTP to be converted back to GDP, and the α subunit re-associates with the β and γ subunits to return the receptor complex to its normal state.

The endogenous ligands for opioid receptors, β -endorphin, dynorphin and enkephalin respectively, are encoded by three different genes and are expressed heterogeneously throughout the CNS and in peripheral tissues (Young *et al.*, 1993). Their distribution is generally in parallel with that of opioid receptors. The enkephalins have a higher affinity for the δ receptors compared to μ and little affinity for κ receptors. The β -endorphins have similar affinities for the μ and δ receptors with much lower affinity for κ receptors, while the dynorphins have high affinity for κ receptors (Corbett *et al.*, 1993). Each family is derived from a distinct precursor polypeptide: proenkephalin for the enkephalins; pro-opiomelanocortin (POMC) for the endorphins; and, prodynorphin for the dynorphins (Jaffe & Martin, 1992; Kreek, 1992a). Some biologically active peptides are derived from these precursors. For 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). Indeed, there is evidence from animal studies that chronic morphine treatment leads to decreases in mRNA coding for POMC, the precursor of β -endorphin (Mocchetti *et al.*, 1989; Bronstein *et al.*, 1990). Interestingly, others have suggested that chronic opioid antagonist treatment may cause up-regulation of endogenous peptides (Tempel *et al.*, 1990; Bronstein *et al.*, 1991). However, the general consensus is that the effect of opioids on the endogenous opioid system remains uncertain (Fishman, 1978; O'Brien, 1993), as no definitive evidence had been produced to support the aforementioned theory proposed by Gold and colleagues (1981), and by Simon and colleagues (1992).

Table 1.3. Summary of the principal locations, associated neurotransmitters and functions of opioid receptors (adapted from Dhawan *et al.*, 1996; Jaffe & Martin, 1990).

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 increased urination ↓ feeding endocrine secretion immune function constipation thermoregulation Does not produce positive 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 Reduced intestinal transit ↓ locomotor activity thermoregulation Produces positive subjective effects and is reinforcing

1.13 Opioid classifications

On the basis of their interactions with the various receptors previously described, opioid compounds can be divided into agonist, partial agonist, agonist-antagonist and antagonist classes (Cherny, 1996), which are outlined below.

1.13.1 Pure agonists

An agonist is a drug that has affinity for and binds to receptors to induce changes in the cell that stimulate physiological activity. Potency of an agonist reflects the dose-response relationship, is influenced by pharmacokinetic factors (ie. how much of the drug gets into the systemic circulation and then reaches the receptors), by the affinity of the drug for the receptor, and by the level of intrinsic activity of the drug at the receptor level. Morphine, methadone, pethidine, hydrocodone, oxycodone and methadone are opioid agonists.

1.13.2 Partial agonists

A partial agonist is a drug that binds to a receptor but does not produce maximum stimulation. Because it occupies the receptor it can prevent a concurrently administered agonist with weaker receptor affinity from producing its full agonist effect. This is most likely to occur when it is administered to a patient receiving high doses of a pure agonist. Buprenorphine is a partial agonist.

1.13.3 Agonist-antagonists

The mixed agonist-antagonist drugs produce agonist effects at one receptor and antagonist effects at another. Pentazocine is the prototypical agonist-antagonist: having agonist effects at κ receptors, and weak μ receptor antagonist actions. Other agonist-antagonists include butorphanol and nalbuphine.

1.13.4 Antagonists

Antagonist drugs have no intrinsic pharmacological action but can block the action of an agonist. Naloxone and naltrexone are opioid receptor antagonists, which can reverse the effects of agonists such as morphine.

1.13.5 Relative potency and equianalgesic doses

Relative potency is the ratio of the dose of two analgesics required to produce the same analgesic effect (Cherny, 1996). Historically the relative potency of each of the commonly used opioids is based upon a comparison with 10mg of intravenous morphine (Houde *et al.*, 1966). Data from single dose and repeated dose studies in patients with acute and chronic pain have been used to develop an equianalgesic dose table that provides guidelines for dose selection when the drug or route of administration is changed (see table 1.4).

Table 1. 4. Equianalgesic intramuscular (IM) and oral (PO) doses of selected opioid analgesics, their elimination half-lives ($t_{1/2\beta}$) and single dose duration of action. (adapted from Cherny, 1996; Portenoy & Payne, 1997).

Drug	Dose ^a			$t_{1/2\beta}$ (hours)	Duration of action (hours)
	IM	PO	IM:PO potency ratio		
Morphine	10	60	1:6 ^b	2-3	3-6
Codeine	130	200	1:1.5	2-3	2-4
Oxycodone	15	30	1:2	3-4	2-4
Hydromorphone	1.5	7.5	1:5	2-3	2-4
Pethidine	75	300	1:4	2-3	2-4
Methadone	10	20	1:2	15-96	4-8
Buprenorphine	0.4	0.8	1:2	2-3	6-9
Levorphanol	2	4	1:2	12-16	3-6
Tramadol	100	120	1:1.2	4-6	4-6

^a Equivalent to IM morphine 10mg.

^b Extensive survey data suggest that the relative potency of IM: PO morphine of 1:6 changes to 1:2-3 with chronic dosing.

1.14 Opioid pharmacokinetics

Most μ receptor agonist opioids in clinical use have similar pharmacodynamic properties (Mather, 1990), with many desirable (eg. pain relief and cough suppression) and undesirable effects (respiratory depression, nausea, vomiting, and constipation) as outlined in section 1.19, but they have substantially different pharmacokinetic properties (Upton *et al.*, 1997). A feature of the clinical use of opioids is the wide variation (8 to 10 fold) in dose requirements for pain management (Macintyre & Jarvis, 1996), which is often due to differences in pharmacokinetics. There are several factors that can influence the pharmacokinetics of opioids, some of which are discussed below (section 1.14.1).

1.14.1 Factors affecting opioid pharmacokinetics

An increased sensitivity to opioids occurs at the extremes of age (Scholz *et al.*, 1996; Scott & Stanski, 1985). Whether this is because of pharmacokinetic or pharmacodynamic mechanisms is uncertain (Scholz *et al.*, 1996). Neonates, especially pre-term infants exhibit reduced clearance rates and therefore, longer elimination half-lives, most likely because of decreased blood flow and metabolising enzyme function (Scholz *et al.*, 1996). Elderly people are also more sensitive to opioids (Scholz *et al.*, 1996). Morphine clearance rates are gradually decreased after 50 years of age (Inturrisi, 1989). Macintyre and Jarvis (1995) concluded that age is the best predictor of postoperative morphine requirements. Reducing the dose and lengthening the time interval between doses are approaches for minimising the development of serious adverse effects in both the young and elderly (Foley, 1993). Burns *et al.* (1989) noted that male patients required more morphine than female patients but other

studies found no difference due to gender (Ginsberg *et al.*, 1989; Monk *et al.*, 1990).

The influence of other drugs can also have an impact on pharmacokinetics. The concurrent administration of drugs that induce hepatic mixed-function systems can alter the distribution of certain opioids (Foley, 1993). For example, the metabolism of pethidine is increased by phenytoin (Pond & Kretschmar, 1981), and that of methadone is increased by phenytoin and rifampicin (Kreek *et al.*, 1976; Tong *et al.*, 1981). More recently, it has been reported that sertraline will increase plasma methadone levels by approximately 25 % (Hamilton *et al.*, 2000). Indeed, there are an increasing number of drugs impact upon methadone's pharmacokinetics (for reviews see Davis & Walsh, 2001; Moolchan *et al.*, 2001).

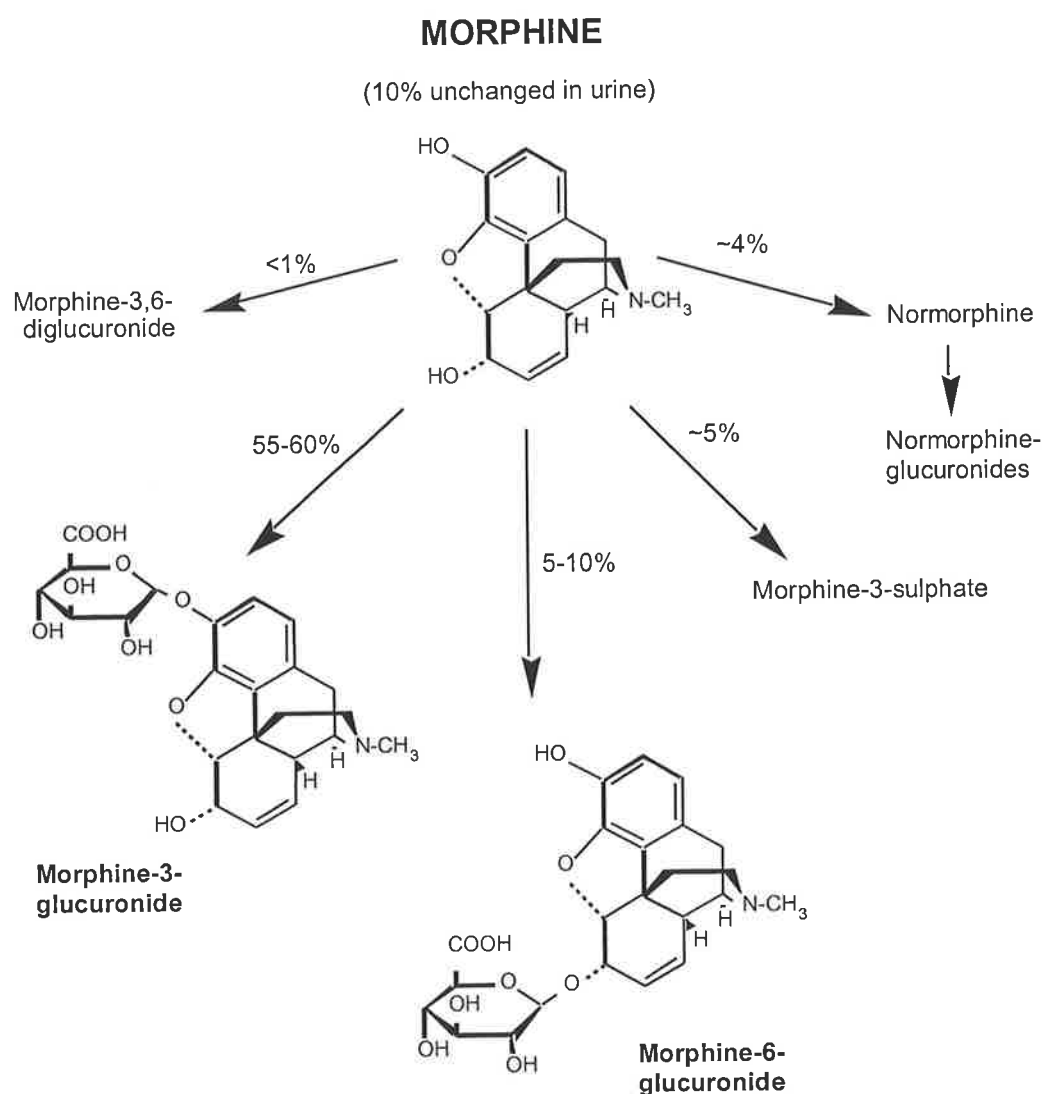
Some but not many opioids are bound to various proteins in the blood, mainly albumin and α_1 -acid glycoprotein (AAG). Patients with reduced plasma protein levels have increased sensitivity to drug effects because of the larger free fraction of the drug (Austrup & Korean, 1999). The rate of diffusion of a drug from the blood to the receptor site is proportional to the concentration of free drug and not the total drug (Bailey, 1994; Scholz *et al.*, 1996). The concentration of AAG is increased following trauma, surgery, malignancy, and chronic inflammatory states (Macfie *et al.*, 1992).

The route of drug administration also has an impact on pharmacokinetics. The intravenous route provides the most rapid and shortest duration of action compared with the intramuscular or oral route (Austrup & Korean, 1999). It bypasses first pass hepatic metabolism, which may occur with oral administration. Intramuscular and subcutaneous routes of administration are commonly used, the onset to peak analgesic effect being longer than that of intravenous administration but shorter than the oral route (Inturrisi, 1989). Epidural and intrathecal administration provide a longer duration of action at lower doses than those required by systemic administration (Inturrisi, 1989). Variability in the blood kinetics of opioids may account for differences in opioid requirements (Upton *et al.*, 1997); generally, studies show 2- to 4-fold variability in systemic kinetic parameters between individuals (Dahlstrom *et al.*, 1982; Hill *et al.*, 1990). The pharmacokinetics of morphine and methadone, the two principal opioid drugs in the context of this thesis, are outlined below.

1.14.2 Morphine

Morphine, which was first synthesised over 40 years ago (Gates & Tschudi, 1952), has low lipid solubility that limits its passage between plasma and tissues (Mather & Cousins, 1986; Glare & Walsh, 1991; Mather, 1994; Christrup, 1997). Morphine (7,8-didehydro-4,5-epoxy-17-methyl-{5 α ,6 α }-morphinan-3,6-diol) has the structure shown in Figure 1.4.

Figure 1.4. Morphine metabolic pathway.



1.14.2.1 Absorption and metabolism

Morphine is absorbed, to some extent, through all mucosae and across the spinal dura, facilitating multiple routes for drug administration (Glare & Walsh, 1991). However, it does not readily penetrate intact skin (Vandenberghe *et al.*, 1982). A number of studies in humans have shown that following complete gastro-intestinal absorption morphine undergoes extensive presystemic or 'first pass' elimination in the liver (Stanski *et al.*, 1978; Sawe *et al.*, 1981; Sawe *et al.*, 1983; Sawe, 1986; Osborne *et al.*, 1990). The predominant

metabolic pathway in humans is glucuronidation (Böerner *et al.*, 1975; Glare & Walsh, 1991; Milne *et al.*, 1996). The liver is the predominant site for biotransformation (Milne *et al.*, 1996), although it has been suggested that it also occurs to a small extent in the kidney and brain (Yue *et al.*, 1988; Wahlström *et al.*, 1988).

In humans, about 90% of the morphine dose is converted into metabolites, principally to the glucuronide conjugates morphine-3-glucuronide (M3G) (approximately 45-55% of the dose) and morphine-6-glucuronide (M6G) (10-15% of the dose), but also to minor metabolites including morphine-3,6-diglucuronide, morphine-3-etheral sulphate (all via conjugation), normorphine, normorphine-6-glucuronide (for a review see Milne *et al.*, 1996; Yeh *et al.*, 1977)).

Both M6G and normorphine bind to the μ opioid receptor with high affinity (Chen *et al.*, 1991) and possess analgesic properties (Sullivan *et al.*, 1989). The major metabolite M3G has a very low affinity for opioid receptors (Chen *et al.*, 1991) and does not possess any analgesic activity (Sullivan *et al.*, 1989). It has been suggested that M3G probably functionally antagonises morphine and M6G produced antinociception (Smith *et al.*, 1990; Faura *et al.*, 1996).

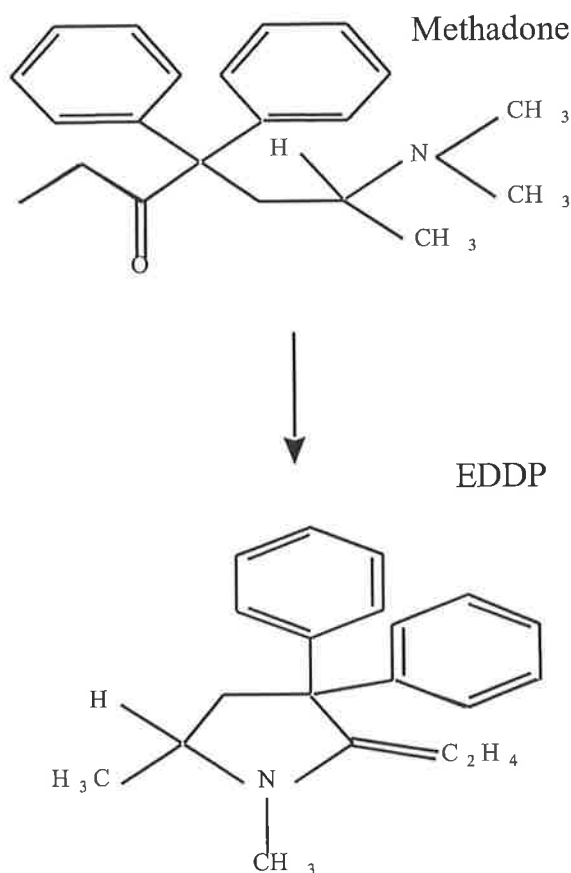
1.14.2.2 Distribution and excretion

In humans, after absorption, morphine leaves the systemic circulation rapidly; the distribution half-life for intravenous morphine is 0.9 - 2.5 minutes (Dahlström *et al.*, 1979; Osborne *et al.*, 1990). Morphine is readily distributed throughout the body to highly perfused tissues, such as lungs, kidneys, liver, spleen and muscles (Brunk & Delle, 1974; Stanski *et al.*, 1978). Mean volume of distribution in humans ranges from 2.1 to 4.0 L/kg (Sawe *et al.*, 1981; Osborne *et al.*, 1990; Westerling *et al.*, 1993). Disposition of morphine is triphasic, with the rapid distribution phase being followed by a biphasic elimination, which has a major early phase and a slow minor terminal phase (Glare & Walsh, 1991). Up to 85% of a morphine dose is excreted in urine as metabolites and parent compound (Vandenberghe *et al.*, 1982).

1.14.3 Methadone

Methadone ([$\pm$ 6]-dimethylamino-4,4-diphenyl-3-hepatone hydrochloride) has a chemical structure (Figure 1.5) that is unrelated to the phenanthrene structures of the opiate derivatives (Ripamonti *et al.*, 1997). Methadone is a μ opioid agonist like morphine. It is administered as a racemate: (-)-(R)- and (+)-(S)-methadone). The μ agonist activity resides almost exclusively with the (-)-(R)- enantiomer as it has a 10-fold higher affinity at opioid receptors (Kristensen *et al.*, 1995) and possesses up to 50 times the analgesic activity of (+)-(S)-methadone in human and animal models of antinociception (Scott *et al.*, 1948).

Figure 1.5. Methadone and its major metabolite 1,5-dimethyl-3,3-diphenyl-2-ethylidene-pyrrolidine (EDDP)



1.14.3.1 Absorption and metabolism

Methadone is rapidly absorbed from the gastro-intestinal tract with measurable concentrations in plasma within 30 minutes of oral administration (Inturrisi & Verebely, 1972; Meresaar *et al.*, 1981). Peak plasma concentrations after an oral dose are generally between 2-4 hours (Meresaar *et al.*, 1981; Wolff *et al.*, 1997; Dyer *et al.*, 1999). Wolff and

colleagues (1997) found that absorption is slower in opioid users compared with healthy volunteers. This could well reflect the pharmacological effect of opioids in slowing gastric emptying (Yuan *et al.*, 1998).

Methadone is almost entirely absorbed across the gastrointestinal tract and its oral bioavailability is about 80%, ranging from 41 to 99% (Nilsson *et al.*, 1982a; Gourlay *et al.*, 1986). These values are three times those of oral morphine (Sawe *et al.*, 1981; Gourlay *et al.*, 1986). Moreover, larger variation in bioavailability has been found for oral morphine (50%) compared to oral methadone (15%) (Gourlay *et al.*, 1986). The metabolism of methadone in humans is a complex process, with nine metabolites identified (Sullivan *et al.*, 1972; Pond *et al.*, 1985). The major pathway involves N-demethylation via CYP3A4 (Foster *et al.*, 1998) to 1,5-dimethyl-3,3-diphenyl-2-ethylidene-pyrrolidine (EDDP) (Figure 1.5) EDDP is subsequently N-demethylated to 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP). EDDP is not known to have any opioid agonist activity.

1.14.3.2 Distribution and excretion

Methadone is widely distributed throughout the body, with a volume of distribution of approximately 3-5 L/kg (Meresaar *et al.*, 1981; Nilsson *et al.*, 1983; Wolff *et al.*, 1997). . Disposition is biphasic, with a relatively rapid 'distribution phase' of 1-2 hours followed by a much slower 'terminal phase'. Methadone has a highly variable elimination half-life (14 to 58 hours) (Inturrisi *et al.*, 1987). In humans, methadone binds to plasma proteins to a high degree (86%) (Inturrisi *et al.*, 1987). Methadone binds predominantly to α_1 -acid glycoprotein (AAG) (Romach *et al.*, 1981; Wilkins *et al.*, 1997), which is an acute phase reactant protein that exhibits variations in its plasma levels, depending upon physiological or pathological conditions (Olsen, 1973). It is generally recognised that, during stress conditions, AAG concentrations show a significant increase (Garrido & Troconiz, 1999). Such an increase was found to be the main factor responsible for lower free fractions in plasma in cancer patients and opioid addicts compared with healthy volunteers (Abramson, 1982; Calvo *et al.*, 1996).

Urinary elimination of methadone and EDDP accounts for about 40% of the dose, with faecal excretion accounting for the greater part of the dose, with at most, approximately 60% being recovered as methadone and EDDP (Verebely *et al.*, 1975). Renal excretion is influenced by the pH of the urine with increased renal clearance observed when the pH of urine is below 6 (Nilsson *et al.*, 1982b).

1.15 Pharmacodynamic effects of opioids

The major use of opioids is to provide analgesia ie. pain relief. The mechanism of action of morphine and other opioids in eliciting analgesia and other effects has been the subject of numerous reviews and monographs (Crain & Shen, 1990; Lipp, 1991; Di Chiara & North, 1992; Stein, 1993; Yaksh, 1993; McNally, 1999). Opioids have also been used as anti-tussives (cough suppressants) and to treat diarrhoea. Their effects can be classified as either desirable or undesirable. This desirability may change depending upon the clinical indications for the use of the drug. A sense of well being, analgesia, and suppression of cough and diarrhoea are desirable effects, whereas sedation, dysphoria, respiratory depression, nausea and vomiting, constipation, pruritis and confusion are considered undesirable effects (Foley, 1993).

1.15.1 Analgesia

Analgesic effects of opioids are mediated through supraspinal, spinal and peripheral mechanisms of action. Mu receptors play a major role in the supraspinal and spinal mechanisms, with δ and κ receptors playing a role in the spinal cord mechanisms of analgesia (Fields, 1993; Yaksh, 1993). The analgesic effects are dose-dependent, with increasing doses of opioid drugs associated with increasing analgesia to the point of anaesthesia (Foley, 1993).

The transmission of sensory information from nociceptors to motor neurones is depressed by opioids, as is nociceptive stimulation of neurones projecting into the supraspinal region, as previously outlined in section 1.8.4. A significant component of this depression is mediated via μ receptors in the dorsal horn of the spinal cord. Opioids produce analgesia by binding to μ receptors in the peripheral and central nervous systems, both spinally and supraspinally, and inhibit nociceptive activity (Burks, 1989; Codd *et al.*, 1995; Fields, 1993; McNally, 1999). Similar direct actions by opioids may also inhibit supraspinal nociceptive transmission neurones at the thalamic and cortical levels (Fields, 1993; Melzack, 1990). Furthermore, there is some evidence to suggest that morphine, the prototypic μ receptor agonist, elicits peripheral antinociceptive effects via interaction with opioid receptors located in inflamed tissues (Stein *et al.*, 1991; Millan, 1999).

Indirect mechanisms for opioid analgesia involve the actions of opioids upon the modulatory network incorporating the periaqueductal gray and the rostral ventromedial medulla, which in turn controls nociceptive transmission neurones (Fields, 1989; 1993;

Liebmann *et al.*, 1994; Millan 1993). Hence, 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.

1.15.2 Respiration

Opioid analgesics interact with respiratory modulator processes principally by decreasing the responsiveness of the respiratory centre to carbon dioxide (CO₂), and may have some selectivity in depressing neuronal modulation of the respiratory centre (Gen *et al.*, 1967; Martin, 1984). Opioid analgesics alter respiratory rate, rhythm and pattern (Breckenridge & Hoff, 1952). There are high concentrations of opioid receptors, as well as endogenous peptides, found in the medullary areas considered to be important in respiratory control (Reisine & Pasternak, 1995). Respiratory depression is the most serious adverse effect of opioid use, and death from an opioid overdose is almost always due to respiratory arrest (Sjögren & Erikson, 1994). Therapeutic doses of opioids may induce a dose-dependent respiratory depression in opioid naïve individuals, which may in turn lead to apnoea. Morphine induces a dose-dependent depression in the ventilatory response to an increase in the partial pressure of carbon dioxide in arterial blood (pCO₂). Interestingly, it has been shown that experimental pain stimulates respiration by an increase in CO₂-response threshold during morphine-induced respiratory depression (Borgberg *et al.*, 1994).

Opioid-induced respiratory depression results, in part, from depression of brain stem respiratory responses to CO₂. Hurlé *et al.* (1983) concluded that the medullary and pontine structures related to respiration are differentially affected by opioids. They found that pontine nuclei are more sensitive to opioid depression and account for changes in frequency of breaths, whereas medullary depression results in reduction of tidal volume and CO₂ sensitivity. Although CO₂ response decreases in a dose-dependent fashion with the administration of μ agonist opioids, clinically significant respiratory depression does not usually occur in the course of treatment of healthy patients with standard doses of opioids.

In general, μ 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. Increasing doses of opioids reduce the frequency of breathing as well as tidal volume (Jaffe & Martin, 1992; Florez & Hurlé, 1993; Santiago & Edelman, 1985; White & Irvine, 1999). Natural sleep may also produce a decrease in the sensitivity of the medullary centre to carbon dioxide, and the effects of μ agonists and

sleep might be additive (Jaffe & Martin, 1992).

Changes 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 observed in patients stabilised on methadone for several months (Gritz *et al.*, 1975; Dyer *et al.*, 1999). Martin *et al.* (1967) also suggested that this effect persists during chronic opioid administration, and is the only vital sign that falls below the customary clinical limits of normal in an addicted individual. It has been suggested that there is no compensatory increase in the depth of respiration, alveolar ventilation decreases during early addiction and arterial oxygen tension (pO₂) and oxygen saturation decrease slightly (Sapira, 1968; MacDonald *et al.*, 1967).

1.15.3 Sedation

Sedation is one of the first signs of respiratory depression (Foley, 1993; Macintyre & Ready, 2000). Sedation is a dose-dependent effect of opioids. It is a central phenomenon, which most commonly occurs at the beginning of treatment, and when doses are increased, but this usually resolves once a stable therapeutic dose is achieved and sustained for a period of time (Zacny, 1995). Sedation may often prevent dose increases necessary to control pain (Sjögren & Erikson, 1994; National Health and Medical Research Council, 1999; Macintyre & Ready, 2000).

1.15.4 Cough suppression

Opioids suppress the cough reflex, which is mediated in the medulla. The dose required to suppress coughing is much lower than the dose needed for analgesia (Foley, 1993; Reisine & Pasternak, 1995). The specific mechanism for this is unknown.

1.15.5 Nausea and Vomiting

Nausea and vomiting are common in the early stages of methadone maintenance treatment (Byrne, 1995; Thompson & Dilts, 1991). Nausea and vomiting are likely to result from direct stimulation of the chemoreceptor trigger zone for emesis, located in the medullary reticular formation (Jaffe & Martin, 1992). These symptoms are dose dependent, and tolerance is thought to develop fairly rapidly (Florez & Hurlé, 1993). The incidence of nausea and vomiting is increased in ambulatory patients, not so much in recumbent patients (Comroe & Dripps, 1948). This suggests that opioid drugs possibly alter vestibular sensitivity (Foley, 1993; Reisine & Pasternak, 1995).

1.15.6 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 tractus solitarius and intermediolateral nucleus (Fadden, 1993). There is some disparity in the literature with respect to the direct effect of opioids on a patient's blood pressure. For example some have reported that opioids may depress central vasomotor control resulting in decreased blood pressure (Gritz *et al.*, 1975; Platt, 1988; Rogers & Spector, 1980), whereas it has also been suggested that stimulation of mu receptors may be associated with increased blood pressure (Fadden, 1993), and that mu agonists have no major effect on blood pressure (Jaffe & Martin, 1992). Some opioids seem to have opposing effects on vasomotor control that are mediated by opioid receptors within the central nervous system. This can result in a small decrease in peripheral arteriolar and venous resistance, and a decrease in heart rate (Martin, 1984). However, it has been reported that subjects made dependent on morphine (240 mg per day) for a period of 29 weeks exhibited an elevation of systolic and diastolic blood pressure and heart rate (Jasinski, 1981). The implications of this finding in relation to people chronically maintained on opioids are not clear.

However, therapeutic doses of opioids have been reported to produce peripheral vasodilatation and inhibit baroreceptor reflexes. Therefore, abnormally low blood pressure may occur when a supine individual assumes an erect position (Jaffe & Martin, 1992; Thompson & Dilts, 1991). Decreased and irregular heart rates are rarely reported effects of methadone that may occur at peak plasma methadone concentrations (Gritz *et al.*, 1975). The mechanism for these effects is not known (Olsen, 1996; Preston, 1986).

1.15.7 Constipation

This is one of the most common adverse effects of opioid analgesics, often undesirable but certainly a positive effect when used to treat diarrhoea. Opioids are thought to act at multiple sites along the gastrointestinal tract (Krömer, 1993), producing a general decrease in secretions and peristalsis, resulting in constipation. The major factors responsible for constipation include delay of gastric emptying and changes in the motility and transit of the gut, although the precise mechanism of the constipating action of opioids is not fully understood (Collett, 1998; Yuan *et al.*, 1998). A recent study investigating gut motility in methadone maintenance patients found a significant delay of the oral-cecal transit time amongst these patients compared with healthy volunteers (Yuan *et al.*, 1998). Specifically,

oral-cecal transit time was assessed by measuring pulmonary hydrogen concentrations. This method is based on the measurement of the hydrogen that is produced in exhaled air when unabsorbable disaccharide (lactulose) is fermented by colonic bacteria (Yuan *et al.*, 1998). Yuan and colleagues reported that the mean oral-cecal transit time of methadone maintenance patients (159 ± 49.2 minutes) was significantly longer ($p < 0.01$) than that of healthy volunteers (105 ± 31 minutes) reported in a previous study (Yuan *et al.*, 1996).

1.15.8 Pruritis

Of the μ agonist opioids, morphine is recognised to release histamine from mast cells, which is often associated with pruritis (Duthie & Nimmo, 1987; Ballantyne *et al.*, 1988).

1.15.9 Miosis

Miosis (contraction of the pupil) is frequently used as an objective index of opioid effect (Inturrisi & Verebey, 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; Reisine & Pasternak, 1995). 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 taking methadone as part of a methadone program (Jaffe & Martin, 1992; McCaul *et al.*, 1982; Platt, 1988; Dyer *et al.*, 1999). Miosis remains a common sign in opioid intoxication (Foley, 1993).

1.15.10 Mood

Opioid drugs have been demonstrated to possess mood altering and reinforcing properties, but the mechanism by which such reinforcement occurs is not well understood. It is thought that opioids increase activity in dopaminergic neurons in the ventral tegmental area, which ascend to the nucleus accumbens and frontal cortex. (Foley, 1993). This increase in dopamine is considered to produce euphoria (Foley, 1993).

1.15.11 Micturition

Difficulty with micturition (urine elimination) is mediated through central as well as peripheral opioid receptors situated in the spinal cord and in the bladder, respectively (Sjögren & Eriksen, 1994).

1.16 Tolerance

Tolerance refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect (Jaffe, 1985; Foley, 1991). The term tachyphylaxis refers to a similar phenomenon in a shorter time frame, typically minutes (Portenoy, 1994). Tolerance to opioids is characterised by shortened duration and decreased intensity of the analgesic, euphoric, sedative and other effects caused by depression of the central nervous system (Collett, 1998), as well as by marked elevation in the average lethal dose (Jaffe, 1985). Tolerance may occur both to a drug's analgesic effects and to its unwanted effects, such as respiratory depression, sedation or nausea but not constipation. There are various types of tolerance (O'Brien, 1996), which are briefly outlined below.

1.16.1 Innate tolerance

This refers to the genetically determined sensitivity to a drug that is observed the first time that the drug is administered. It contrasts with acquired tolerance, which can be divided into three types: pharmacokinetic, pharmacodynamic and learned tolerance.

1.16.2 Pharmacokinetic tolerance

This refers to changes in the metabolism (clearance) of the drug after repeated drug administration that result in reduced concentrations in the blood and subsequently at the site(s) of action. The most common mechanism is an increase in the rate of metabolism.

1.16.3 Pharmacodynamic tolerance

This refers to adaptive changes that have taken place within systems affected by the drug, such as drug-induced changes in receptor density, so that the response to a given concentration of the drug is reduced.

1.16.4 Learned tolerance

This refers to a reduction in the effects of a drug as a result of compensatory mechanisms that are learned. One type of learned tolerance is behavioural tolerance. This describes the skills that can be developed through repeated attempts to function when in a state of mild to moderate intoxication, eg. learning to walk a straight line in spite of motor impairment resulting from alcohol intoxication. Another behavioural tolerance is referred to as 'conditioned tolerance', which is a learning mechanism that develops when environmental

cues are consistently paired with the administration of the drug. If the drug is always preceded by the same cues, an adaptive response to the drug will be learned and this can prevent full manifestation of the drug's effect (tolerance). However, if the drug is taken in novel circumstances, tolerance can be reduced and the drug's effects enhanced.

1.16.5 Tolerance variability

There is no specific time period in which tolerance occurs. It varies from individual to individual, and it may develop within a few days or weeks depending on the drug, dose and mode of administration (Jaffe & Martin, 1990; Vaught, 1991; Yaksh, 1991). Furthermore, tolerance also develops at different rates to the various effects of opioid drugs (Ling *et al.*, 1989). This has been termed 'selective tolerance' (Taub, 1982). Tolerance to nausea and vomiting, sedation, euphoria and respiratory depression occur rapidly, while tolerance to constipation and miosis is minimal (Light & Torrance, 1929; Kreek, 1973; Bruera *et al.*, 1989; O'Brien, 1996). Some investigators have proposed that tolerance to the various non-analgesic effects of opioids is characterised by large intra-individual and inter-individual variability (Jasinski, 1977; Martin, 1977).

1.16.6 Cross-tolerance

Repeated doses of a drug confer tolerance not only to the drug being used but also to other drugs in the same pharmacological class (O'Brien, 1996). This effect is known as cross-tolerance and is a key component in the problem of managing pain in opioid maintained individuals (Wilson & Yaksh, 1980).

Animal studies have shown cross-tolerance to opioids to be incomplete (Ivarsson & Neil, 1989; Moulin *et al.*, 1988; Neil, 1982). Neil demonstrated that mice pre-treated with morphine were tolerant to morphine only, while methadone-treated mice were tolerant to methadone, morphine, codeine, and D-propoxyphene and more so to morphine than methadone itself (Neil, 1982). Further studies by Ivarsson and Neil (1989) indicated that the efficacy of methadone was higher than morphine in guinea-pig ileum. This may possibly explain asymmetries in cross-tolerance between these drugs. In essence, intrinsic efficacy may predict both the pattern of tolerance to antinociceptive effects and the degree of cross-tolerance conferred by different opioid drugs (Ivarsson & Neil, 1989; Stevens & Yaksh, 1989; Paronis & Holtzman, 1992). Moreover, it has been shown that pharmacodynamic tolerance is receptor selective; a μ selective drug will induce only minimal tolerance at kappa or delta receptors (Stevens & Yaksh, 1991).

There is disparity in the literature about the influence of pain on tolerance development.

Lyness *et al.* (1989) stated that the presence of pain may have an influence on the development of tolerance to opioids. They demonstrated that rats with adjuvant-induced arthritis self-injected less morphine than pain-free rats. Further, the morphine dose of the arthritic rats remained stable over 29 days, whereas the pain-free rats showed dose escalation in the same time period. There is also the “system theory” which states that chronic nociceptive stimulation acts to antagonise the apparent tolerance to analgesic effects otherwise associated with prolonged opioid administration (Colpaert, 1996). Moreover, Colpaert proposed that chronic opioid administration causes hyperalgesia, and suggested that the opioid maintains its effectiveness, but the hyperalgesia creates the impression that the opioid has become less effective. Indeed, it has been argued that pain inhibits the development of tolerance (Colpaert *et al.*, 1978; Colpaert, 1979; Vaccarino *et al.*, 1993), although the precise mechanism of this proposed inhibition has not been thoroughly defined or indeed been proven.

Several studies investigating the use of opioids in the management of cancer pain indicate that opioid dose requirements increase only during the progression of the underlying disease process and that, with stable disease or treatment of painful tissue pathology, the need for medication remains the same or actually decreases (Foley, 1991; Twycross, 1974). Conversely, there is evidence of the development of progressive tolerance to the analgesic effects of opioids when they are administered on a continuous basis over a period of several days (Hill *et al.*, 1990, 1992). Other studies have indicated that pain accelerates the development of opioid analgesic tolerance (Ferguson & Mitchell, 1969; Kayser & Guilband, 1985; Gutstein *et al.*, 1995). However, Collett (1998) suggested that the pre-eminent question, ‘whether the very presence of pain has some modulatory effect on the development of tolerance’, has yet to be answered. In terms of pain management, Portenoy (1994) concluded that the need for dose escalation could be attributed to tolerance only in the absence of other reasons for increasing pain, such as progression of lesion or psychological distress.

1.17 Mechanisms of opioid tolerance

Tolerance has also been termed 'neuroadaptation', reflecting the long-held idea that this phenomenon represents adaptive changes in neural systems to chronic exposure (Trujillo & Akil, 1991). Opioid receptor agonists bind to cellular membrane receptor proteins, which are functionally coupled with cellular G-protein-regulated mechanisms (second messengers, ion channels) involved in the signal transduction pathways that activate various final effector mechanisms (Crews *et al.*, 1993; Nestler & Aghajanian, 1997). Some have suggested that in opioid tolerance, a functional de-coupling of opioid receptors from the G-protein-regulated cellular mechanisms occurs, in addition to down-regulation of endogenous opioids and/or opioid receptors and adaptive behavioural changes (Neil, 1990; Trujillo & Akil, 1991; Nestler & Aghajanian, 1997). Other studies have demonstrated that changes in receptor number are not necessary for tolerance to occur (Cox, 1991).

Desensitisation or un-coupling of the receptor from the guanosine triphosphate (GTP)-binding decreases agonist binding affinity (Chavkin & Goldstein, 1982, 1984; Rogers & El-Fakahany, 1986). Loss of receptors from the cell surface may also result in fewer binding sites and decreased action (Chavkin & Goldstein, 1982, 1984; Rogers & El-Fakahany, 1986). Hence, the desensitisation to agonist binding and the loss in the number of opioid receptors result in higher dose requirements to produce the same cellular response (de Leon-Casasola, 1996). It is also thought that chronic opioid treatment may result in up-regulation of cyclic AMP pathways (Avidor-Reiss *et al.*, 1996; Sharma *et al.*, 1997), which has been interpreted to represent uncoupling of the opioid receptor from the G-protein (Cox, 1991).

Endogenous opioid-mediated pain control systems may be specifically altered by the analgesic and tolerance-producing characteristics of opioids (Compton, 1994). Although unproven, the presence of exogenous opioids may result in the development of cross-tolerance to endogenous opioid activity, thereby decreasing pain tolerance (Compton, 1994). Several scientists investigating this issue have failed to demonstrate change in receptor numbers or sensitivity in opioid addicts (Koob & Bloom, 1988; Jaffe, 1990; Zukin & Tempel, 1986), nor in the endogenous opioid concentrations in the cerebrospinal fluid and blood of patients maintained on methadone or buprenorphine (Facchinetti *et al.*, 1984; Holmstrand *et al.*, 1981; Kosten *et al.*, 1992; Kreek *et al.*, 1983; O'Brien *et al.*, 1982).

Others have implicated the N-methyl-D-aspartate (NMDA) receptor in the development of acute tolerance (Trujillo & Akil, 1991b; Elliot *et al.*, 1994). NMDA antagonists including

MK-801, LY274614, dextromethorphan and ketamine can attenuate or reverse the development of tolerance to morphine's antinociceptive effects in animals (Marek *et al.*, 1991; Trujillo & Akil, 1991; Tiseo & Inturrisi, 1993; Elliot *et al.*, 1994a,b; 1995; Tiseo *et al.*, 1994; Mao *et al.*, 1996; Shimoyama *et al.*, 1996). Interestingly, animals tested one week after the discontinuation of drug treatments (LY274614 plus morphine) retained their analgesic sensitivity to morphine whereas control animals (morphine only) remained tolerant (Tiseo & Inturrisi, 1993; Tiseo *et al.*, 1994).

It has been suggested that chronic opioid treatment results in increased translocation of protein kinase C (PKC) (Mayer *et al.*, 1995) and opioid receptors or their associated G-proteins are phosphorylated by this PKC. There is direct evidence to support PKC phosphorylation of μ -opioid receptors (Chen & Yu, 1994). The NMDA receptor-associated Ca^{++} channel is probably also phosphorylated, although it seems likely that this results from acute as well as chronic treatment with μ -opioids (Mayer & Mao, 1999). PKC translocation is greatly increased by chronic as compared to acute morphine administration (Mayer *et al.*, 1995). Further, it has been postulated that type 1 metabotropic glutamate receptors (mGluRs), via an increase in 1,4,5-triphosphate (IP_3), are also involved in the upregulation of PKC (Fundytus & Coderre, 1999a, b), although others suggest that this remains to be demonstrated (Mayer & Mao, 1999).

Mayer and colleagues (Mayer & Mao, 1999; Mayer *et al.*, 1999) postulated the following model of opioid tolerance: [1] Activation of μ -opioid receptor initiates a second messenger PKC translocation to the membrane (Chen & Huang, 1991); [2] this PKC translocation activates the NMDA receptor by removal of the Mg^{++} blockade (Chen & Huang, 1992); [3] the removal of the Mg^{++} blockade from the NMDA receptor allows for an increased influx of Ca^{++} despite membrane hyperpolarisation by μ -opioids and low levels of presynaptic glutamate release; [4] the influx of Ca^{++} has two principal effects (Mayer *et al.*, 1995): it activates either a separate pool of PKC (PKC2) or much greater amounts of the original pool of PKC (PKC1); [5] this second pool of PKC may be translocated directly to the membrane, modifying various excitatory amino acid (EAA) and/or other receptors, and it may modify nuclear transcription, the products of which result in delayed and persistent changes in cellular function that cannot be reversed by acute administration of NMDA antagonists; [6] a second effect of the influx of Ca^{++} is to activate nitric oxide synthase (NOS), which increases the production of nitric oxide (NO) and superoxide (Pou *et al.*, 1992). [7] The simultaneous generation of these two molecules favours the production of peroxynitrite, a

potent initiator of DNA strand breakage. It is further proposed that peroxynitrite initiates the production of the nuclear repair enzyme poly (ADP ribose) synthetase (PARS); [8] pronounced activation of PARS can result in cell dysfunction and eventually cell death because of inhibition of mitochondrial respiration and depletion of cellular energy stores; [9] this then leads to the formation of dark neurons possibly by the way of programmed cell death (apoptosis). They concluded that, overall, such an excitotoxic cascade may underlie some aspects of opioid tolerance (for a review see Mayer & Mao, 1999). Mayer and colleagues have also previously suggested that cAMP, Ca^{++} /calmodulin and other second and third messengers, non-NMDA receptors, and cholecystokinin (CKK) and other non-glutamate receptors also participate in the development of opioid tolerance and dependence (Mayer *et al.*, 1995). The two major components of this hypothetical mechanism are a positive feedback loop wherein the NMDA receptor becomes progressively sensitised, and a negative feedback loop wherein activation of PKC reduces the sensitivity of the mu receptor (Price *et al.*, 2000).

Chen and Huang (1991) observed that within a single neuron, expressing both NMDA and μ opioid receptors, the magnitude of NMDA receptor-mediated inward membrane current is enhanced by μ opioid agonists. They also showed that μ receptor activation results in PKC translocation/activation (Chen & Huang, 1992). PKC can facilitate NMDA channel activation, and may also be involved in additional down-stream events including the modulation of G-protein coupled potassium channels and the uncoupling of the μ receptor (Mao *et al.*, 1995). In support of this sequence is the observation that during morphine tolerance spinal cord concentrations of membrane-bound PKC increase, and GM1 ganglioside, an intracellular inhibitor of PKC translocation and activation, and H-7, a PKC inhibitor, both attenuate morphine tolerance *in vivo* (Mao *et al.*, 1994; Mao *et al.*, 1995; Mayer *et al.*, 1995). Mao and colleagues have proposed that morphine tolerance is a consequence of opioid receptor-mediated hyperalgesia (Mao *et al.*, 1995), and that they share common pathophysiological mechanisms (Mao, 1999; Mayer *et al.*, 1999). The pathophysiology of tolerance is still incompletely understood (Watanabe & Bruera, 1994; Vanderah *et al.*, 2001).

The same intracellular processes linked to NMDA receptor activation (eg. synthesis of nitric oxide, increased levels of protein kinases and Ca^{++}) are critical for the production of hyperalgesia and have been implicated in the development of opioid analgesic tolerance (Price *et al.*, 2000). McNally (1999) proposed, that in general, this is consistent with a role

for spinal mechanisms for hyperalgesia in tolerance development. However, the extent to which hyperalgesic states contribute to morphine tolerance seen after systemic administration remains to be determined (Inturrisi, 1999). Nevertheless, the implications are that NMDA receptor antagonists can be expected to produce synergistic interactions with μ opioids such as morphine. Therefore, a major indication for opioid-NMDA receptor antagonist combinations should be pain states in which opioid potency has been reduced as a result of hyperalgesia, allodynia, and/or opioid tolerance (Dickenson *et al.*, 1997; Inturrisi, 1997; Kauppila *et al.*, 1998).

1.18 NMDA receptor

The molecular mechanisms underlying the effects of drugs like ketamine, phencyclidine, and dextromethorphan have been identified. These drugs interfere with the action of excitatory amino acid (EAA) neurotransmitters, including glutamate and aspartate (Krystal *et al.*, 1994). The EAAs are the most prevalent excitatory neurotransmitters in the brain and are particularly important in cortico-cortical and cortical-subcortical interactions (Cotman & Monaghan, 1987). The EAAs act via four main types of receptors. Three EAA receptor subtypes contain ion channels: the N-methyl-D-aspartate (NMDA), kainate, and 3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (Cotman & Monaghan, 1987; Moriyoshi *et al.*, 1991; Dingledine, 1991). The fourth principal EAA subtype is a metabotropic glutamate receptor coupled by G-proteins to the inositol phosphate signal transduction pathway (Schoepp *et al.*, 1990; Masu *et al.*, 1991). In the human brain, the NMDA receptor is most densely localised in the cerebral and hippocampal cortices (Kornhuber *et al.*, 1989), where EAA binding activates neurons by opening a voltage-dependent cation channel that is permeable principally to Ca^{++} (Cotman & Monaghan, 1987; Javitt & Zukin, 1991) and to a lesser extent Na^+ and K^+ (Bergman, 1999).

Ketamine is member of a chemically diverse group of compounds that are collectively known as non-competitive NMDA receptor antagonists (Bergman, 1999). All of these compounds bind to proteins, which make up the ion channel of the NMDA receptor. This prevents the influx of Ca^{++} ions following EAA binding (Thompson *et al.*, 1985; Cotman & Monaghan, 1987), thereby preventing depolarisation (Bergman, 1999). Ketamine has been shown to bind to the NMDA receptor complex at the same site as phencyclidine, with an affinity of approximately 35 $\mu\text{mol/L}$ (Hampton *et al.*, 1982). However, it has a shorter half-life than phencyclidine (Kammerer & Cho, 1981; Wieber *et al.*, 1975) reducing the likelihood of lingering behavioural effects (Krystal *et al.*, 1994).

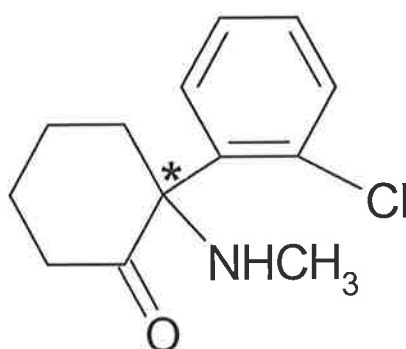
1.19 Ketamine

Ketamine is a non-competitive NMDA ion channel-blocking drug (Church & Lodge, 1990) that is used clinically, predominantly as an anaesthetic (White, 1988). Ketamine was first synthesised in the early 1960s as a further development of phencyclidine and its congener cyclohexamine. The first clinical trials with ketamine were reported by Corssen and Domino in 1966. The term 'dissociative anaesthesia' was coined to describe the anaesthetic state produced by ketamine, based on the observation of dissociation of electroencephalographic activity between the thalamoneocortical and limbic areas of the cat brain (Corssen *et al.*, 1966). Evidence of the psychotogenic properties of ketamine emerged initially from general anaesthetic use where clinicians documented post-anaesthetic reactions, which were characterised by confusional states, vivid dreaming and hallucinations (Siegel, 1978). These 'emergence' phenomena limited the clinical use of ketamine in the 1970s and 1980s.

1.19.1 Pharmacology

Ketamine's molecular structure (see figure 1.6) (2-(O-chlorophenyl)-2-methylamino cyclohexanone) contains a chiral centre at the C-2 carbon of the cyclohexanone ring so that two enantiomers of the ketamine molecule exist: (+)-(S)-ketamine and (-)-(R)-ketamine. In both animals and humans (+)-(S)-ketamine is approximately 3-4 times more potent than (-)-(R)-ketamine for pain relief (Marietta *et al.*, 1977; Ryder *et al.*, 1978; White *et al.*, 1985; Oye *et al.*, 1992; Geisslinger *et al.*, 1993; Mathison *et al.*, 1995; Joó *et al.*, 2000). Under physiologic conditions the uncharged form of ketamine is highly lipid soluble (10 times that of thiopentone) and can rapidly cross the blood brain barrier (Reich & Silvay, 1989).

Figure 1.6 Chemical structure of ketamine (* denotes chiral carbon).



Extensive first-pass metabolism and lower absorption necessitate higher doses when ketamine is given orally or rectally (Reich & Silvay, 1989), and it has been reported that only 16.6% of an oral dose is readily available in systemic circulation (Clements *et al.*, 1981). It is metabolised extensively by hepatic drug-metabolising enzyme systems (White *et al.*, 1982). A major pathway involves N-demethylation of ketamine via cytochrome P-450 3A to form norketamine, which may undergo dehydrogenation to dehydronorketamine (White *et al.*, 1982; Schmidt, 1999; Gill & Stajic, 2000; Yoshitsugu *et al.*, 2001). Norketamine has one third of the activity of ketamine (Reich & Silvay, 1989). Very little attention has been paid to the possible pharmacological effects of the different metabolites of ketamine (White *et al.*, 1982). Norketamine may contribute to the analgesic effects of ketamine (Shimoyama *et al.*, 1999) because higher plasma concentrations are achieved.

Ketamine pharmacokinetics follow a three-term exponential decline (Reich & Silvay, 1989). In one study involving un-premedicated patients following intravenous administration, redistribution half-life ($t_{1/2\alpha}$) was 4.68 minutes, and elimination half-life ($t_{1/2\beta}$) was 2.17 hours (Clements & Nimmo, 1981). Other pharmacokinetic studies of ketamine in humans, have reported that the $t_{1/2\alpha}$ phase of intravenous ketamine from plasma to peripheral tissue is approximately 7–13 minutes (Wieber *et al.*, 1985; Zsigmond & Domino, 1980; White *et al.*, 1985). White *et al.* (1985) also reported that (+)-(S)-ketamine has a distribution half-life of 22.8 ± 14.7 minutes respectively. The elimination half-life of racemic ketamine is approximately 2-3 hours (Wieber *et al.*, 1975; Clements *et al.*, 1981; White *et al.*, 1985), and that of (+)-(S)-ketamine has been reported as being approximately 2.5 hours (White *et al.*, 1985). White *et al.* (1985) also reported that the volume of distribution for racemic ketamine and (+)-(S)-ketamine was 2.9 ± 0.5 (L/kg) and 4.7 ± 1.1 (L/kg), respectively. Following intravenous administration, less than 4 per cent of a dose is recovered from urine (only small amounts in faeces) as either unchanged drug or norketamine, and approximately 16 per cent appears as hydroxylated derivatives (Chang *et al.*, 1970; Adams *et al.*, 1981; White *et al.*, 1982; Reich & Silvay, 1989). White *et al.* (1985) reported clearance ($\text{ml kg}^{-1} \text{min}^{-1}$) values of $16 (\pm 4.6)$ for racemic ketamine, $21.3 (\pm 1.6)$ for (+)-(S)-ketamine, and $17.4 (\pm 2.5)$ for (-)-(R)-ketamine.

1.19.2 Clinical use of ketamine

Ketamine was first approved for clinical use as an anaesthetic in 1970 (Schmid *et al.*, 1999). The enantiomers differ in their pharmacokinetics and pharmacodynamic effects (Kharasch & Labroo, 1992). In both animals and humans (+)-(S)-ketamine is approximately 3-4 times more potent than (-)-(R)-ketamine for pain relief (Marietta *et al.*, 1977; Ryder *et al.*, 1978; White *et al.*, 1985; Oye *et al.*, 1992; Geisslinger *et al.*, 1993; Mathison *et al.*, 1995; Joó *et al.*, 2000). In equianalgesic doses (+)-(S)-ketamine produces fewer psychotomimetic disturbances and less agitation than (-)-(R)-ketamine or the racemate (White *et al.*, 1980; Calvey, 1995).

An early study compared the effects of (+)-(S)-ketamine, (-)-(R)-ketamine and the racemate amongst surgical patients (White *et al.*, 1980). They assessed the intra-operative and postoperative effects of the enantiomers compared to the racemic mixture as sole anaesthetic; equianalgesic doses of racemic-ketamine (2mg/kg), (+)-(S)-ketamine (1mg/kg) and (-)-(R)-ketamine (3mg/kg) were administered intravenously in a randomised, double-blind design to 60 healthy patients undergoing elective outpatient procedures. (+)-(S)-ketamine was judged to produce more effective anaesthesia than either racemic-ketamine or (-)-(R)-ketamine (95 vs. 75 vs 68 percent, respectively). Further, they reported that quantification of verbal responses in the post-anaesthetic period suggested that more psychic emergence reactions occurred after administration of (-)-(R)-ketamine, then of racemic-ketamine and (+)-(S)-ketamine (occurrence of 53 vs. 15 vs. 5 percent, respectively). (+)-(S)-ketamine possesses far superior efficacy with fewer side effects, and faster elimination and anaesthetic recovery compared to the racemate (White *et al.*, 1980; White *et al.*, 1982; Schuttler *et al.*, 1987). These differences strongly suggest that (+)-(S)-ketamine be used rather than the racemic form of the drug (Kharasch & Labroo, 1992). Others have also concluded, that in the clinical environment, it is more rational to use (+)-(S)-ketamine rather than the racemic compound (Geisslinger *et al.*, 1993; Arendt-Nielsen *et al.*, 1995; Shimoyama *et al.*, 1996). Racemic ketamine is now widely used in the clinical setting as anaesthetic and analgesic (Maurset *et al.*, 1989; Stannard & Porter, 1993; Eide *et al.*, 1995; Mathisen *et al.*, 1995; Kawamata *et al.*, 2000). There was early evidence in the literature that at sub-anaesthetic doses, ketamine effectively attenuated acute nociceptive pain in humans (Domino *et al.*, 1965). Early observations suggested that analgesia following ketamine administration outlasted the period of anaesthesia (Bjarnesen & Corssen, 1967).

1.19.3 Mechanisms of action

Ketamine acts on a wide variety of receptors including nicotinic (Scheller *et al.*, 1996) and muscarinic (Hustvit *et al.*, 1995) receptors. It also interacts with mu, delta and kappa opioid receptors (Smith *et al.*, 1980; Finck & Ngai, 1982) as well as interacting with monoaminergic and voltage sensitive Ca^{++} channels (Hirota & Lambert, 1996). It is mostly known as a non-competitive NMDA antagonist (Church & Lodge, 1990) binding at the phencyclidine (PCP) site, by blocking the ion channel coupled to the NMDA receptor (Anis *et al.*, 1983; Willets *et al.*, 1990; Yanagihara *et al.*, 1990). Ketamine inhibits the excitatory effect of glutamate at these receptors (Lodge & Johnson, 1990). The PCP site is located in the NR1 subunit, which is common to all NMDA receptors (Domino *et al.*, 1965).

Although ketamine acts on several receptor systems, NMDA ion channel blockade is probably the predominant analgesic mechanism relevant to small doses (up to 1 mg/kg) of ketamine (Eide *et al.*, 1997). Øye *et al.* (1992) investigated the effects of (+)-(S)-ketamine (0.05, 0.10, 0.15, 0.2 mg/kg) and (-)-(R)-ketamine (0.2, 0.4, 0.6, 0.8 mg/kg) in a sample of 6 healthy volunteers. They also compared the relative affinities for (+)-(S)-ketamine and (-)-(R)-ketamine for the PCP sites in guinea pig and human brain homogenate. They reported that (+)-(S)-ketamine has 4 times higher affinity than (-)-(R)-ketamine (1.2 vs 5 μM). Furthermore, they also reported that (+)-(S)-ketamine was 4 times more potent as analgesic than (-)-(R)-ketamine as measured by reduced perception of ischaemic-induced pain.

1.19.4 Analgesic effects and mechanisms

Ketamine is a potent analgesic at sub-anaesthetic plasma concentrations (<500ng/mL), and its analgesic and/or anaesthetic effects may be mediated by different mechanisms (Reich & Silvay, 1989). It was initially thought that the analgesia may be due to an interaction between ketamine and central or spinal opioid receptors (Collins, 1986). Numerous studies performed at the level of the spinal cord have shown that NMDA receptor activation plays a role in the transmission of nociceptive information (Dickenson, 1995; Ren *et al.*, 1992; Yamamoto *et al.*, 1993; Kohrs & Duireux, 1999).

An important technique employed to decrease side-effects in pharmacology is the use of combinations of low doses of several drugs that produce the same therapeutic effects (Joó *et al.*, 2000). Joó *et al.* (2000) reported that intrathecal co-administration of ketamine, and (+)-(S)-ketamine (100mcg, but not 30mcg) significantly enhanced and prolonged the antinociceptive effect of morphine in rats. It has been suggested that powerful synergism arises from the combination of low-dose morphine with low doses of NMDA antagonists

(Chapman and Dickenson, 1992; Dickenson, 1997; Wiesenfeld-Hallin, 1998; Wong *et al.*, 1996; Joó *et al.*, 2000). However, other studies have failed to observe any potentiation of NMDA receptor antagonists on morphine-induced antinociception in animal models involving acute pain tests (Ossipov *et al.*, 1995; Srivastava *et al.*, 1995; Nishizawa *et al.*, 1998). Interestingly, at lower concentrations the effect of ketamine on pain perception is not inhibited by naloxone, indicating that opioid receptors are not involved (Maurset *et al.*, 1989). It has been suggested that other pharmacological mechanisms may contribute to the effects of ketamine at high anaesthetic concentrations (Meller, 1996). Ketamine has been shown to act as both a noradrenergic (Kress, 1994) and serotonergic uptake inhibitor (Tao & Auerbach, 1994). Both of these actions involve descending antinociceptive systems, and both of these actions can produce profound analgesia when selective agents are used (Meller, 1996).

There is disparity in the literature regarding the mechanisms underlying the antinociception of ketamine. Ketamine, but not selective NMDA receptor antagonists such as MK-801 and D,L-2-amino-5-phosphonovaleric acid, also has an analgesic effect for acute nociception, in which NMDA receptors were thought not to be activated (Tung & Yaksh, 1981; Pekoe & Smith, 1982; Smith *et al.*, 1989; Sonoda & Omote, 1996). Several behavioural and electrophysiological studies have suggested that ketamine produced antinociceptive effects because of an activation of a descending inhibitory system (Okuda, 1986; Pekoe & Smith, 1982; Smith *et al.*, 1989; Sonoda & Omote, 1996; Tonemori *et al.*, 1981). Others have proposed that spinal mechanisms are central to ketamine's antinociceptive effects (Tung & Yaksh, 1981; Okuda, 1986; Hao *et al.*, 1998). In particular, involvement of the spinal monoaminergic system has been put forward as a key factor (Tung & Yaksh, 1981; Crisp *et al.*, 1991). The precise mechanisms underlying the interaction of ketamine with the monoaminergic descending inhibitory pathway are unclear. Although it has been reported that ketamine activates the monoaminergic descending inhibitory system through opioid receptors (Smith *et al.*, 1989), others have suggested that agonist actions of ketamine on opioid receptors play a minor role in its analgesic effects (Hustveit *et al.*, 1995). No definitive mechanism has been proffered; hence ketamine's antinociceptive mechanism remains controversial. Inturrisi (1998) suggested that it would be of interest to learn whether ketamine may improve pain management in opioid-tolerant patients by virtue of its NMDA receptor-mediated effects on opioid tolerance and its direct analgesic effects.

1.19.5 Other pharmacodynamic effects

Unlike many other general anaesthetics, ketamine has cardiovascular stimulatory properties; it increases heart rate, blood pressure and cardiac output (Pagel *et al.*, 1992). Studies examining cardiovascular response to low-dose ketamine report minimal changes in heart rate and blood pressure (Sadove *et al.*, 1971; Owen *et al.*, 1987; Dich-Nielsen *et al.*, 1992; Edwards *et al.*, 1993; Jahangir *et al.*, 1993). Two studies found a decrease in heart rate and blood pressure, however these were principally attributed to a decrease in pain (Joachimsson *et al.*, 1986; Royblat *et al.*, 1993), whereas others have reported that in an experimental situation ketamine produces small but dose-related increases in systolic but not diastolic pressure (Krystal *et al.*, 1994).

Ketamine also differs from most anaesthetics in not producing significant respiratory depression (White & Ryan, 1996). An exception to this occurs when the increase in plasma ketamine concentrations is very rapid (Zsigmond *et al.*, 1976). There is some evidence that low-dose ketamine may cause mild sedation (Sadove *et al.*, 1971) that is less than sedation seen with opioids (Bristow & Orlikowski, 1989; Bhattacharya *et al.*, 1994). Others, however, reported that when administered in combination with opioids, low-dose ketamine does not appear to enhance or add to opioid-induced sedation (Javery *et al.*, 1996; Stubhaug *et al.*, 1997).

1.20 Summary

Pain is a very complex process and presents great challenges for modern medicine and pharmacology. There seems to be a general consensus that in the treatment of pain, patients with a prior history of substance abuse (particularly opioid dependent individuals) appear to be at increased risk for mismanagement problems. There have been many reasons postulated as to why this population is more likely to receive sub-optimal treatment, with further ad hoc suggestions as to their opioid analgesic needs. There are discrepancies in the literature about the pain sensitivity of methadone maintenance patients. It is possible that the contradictions in the literature may be due to differences in pain induction and pain measurement indices; various single methods of pain induction have been used to determine pain sensitivity. Further, there has been a lack of consistency in the measurement of pain thresholds ie. onset of pain measured in some studies, and pain tolerance measured in others. In order to resolve this, it is necessary to use more than one method of experimental pain induction, and to measure pain detection and tolerance levels. Furthermore, there are very few data on methadone patients' responses to additionally administered analgesic drugs. Hence, there is an urgent need to investigate the antinociceptive effects of additionally administered morphine amongst these patients.

In summary, we are now in an era where we are guided by the paradigm of evidence-based-medicine. The guidelines that currently exist for the prescribing of opioid drugs for relief of pain in methadone maintenance patients have generally been based on experience and consensus rather than sound research data. There are major clinical gaps in the treatment of acute and chronic pain in this patient population (Portenoy *et al.*, 1997; Donohoe, 1998). Pain management of methadone maintenance patients must be guided by a greater understanding of their basal sensitivity to pain, as well as their response to additionally administered opioids. If, as expected, tolerance, or more specifically, cross-tolerance does reduce the analgesic efficacy of additional opioids, then other pharmacological approaches, such as the use of an NMDA receptor antagonist e.g., (+)-(S)-ketamine in combination with an opioid need to be investigated. There is an undoubted and urgent need for a scientific approach to this issue in order to effect optimal care of these patients. The basis of my Ph.D program was designed to produce data that will eventually help in the formulation of prescribing guidelines, improved policies, and more importantly help direct optimal pain management in this group of patients.

1.21 The present research

The following is a very brief outline of the experimental plan of this thesis, with aims and hypotheses related to each relevant chapter.

Chapter 2; Aim: To compare pain threshold and pain tolerance in methadone maintenance patients and healthy volunteers. **Hypotheses:** 1. Methadone maintenance patients are more sensitive and less tolerant to pain than matched drug free control subjects. 2. Methadone maintenance patients are differentially sensitive to pain induced by cutaneous electrical stimulation and a cold pressor test.

Chapter 3; Aim: To compare the antinociceptive effects of conventional doses of morphine on pain sensitivity in methadone maintained patients. **Hypothesis:** Methadone maintenance patients will be tolerant to the antinociceptive effects morphine at plasma concentrations known to produce analgesia in opioid-naïve patients with acute pain.

Chapter 4; Aim: To compare the physiological and subjective effects of additionally administered morphine in methadone maintenance patients. **Hypothesis:** Plasma morphine concentrations known to result in effective antinociception in opioid-naïve patients will have minimal physiological or subjective effects in methadone maintenance patients.

Chapter 5; Aim: To compare the antinociceptive, physiological and subjective effects of (+)-(S)-ketamine alone, and in combination with morphine, in methadone maintenance patients. **Hypotheses:** 1. (+)-(S)-ketamine alone will induce antinociception in methadone maintenance patients but not in control subjects. 2. (+)-(S)-ketamine in combination with morphine will have greater antinociceptive effects than (+)-(S)-ketamine alone in methadone maintenance patients. 3. (+)-(S)-ketamine alone, or in combination with morphine will not have significant physiological or subjective effects amongst methadone patients.

CHAPTER 2

AN INVESTIGATION OF PAIN SENSITIVITY IN METHADONE MAINTENANCE PATIENTS

2.1 Introduction

There are increasing numbers of people who are receiving opioids as substitution treatment for dependence (Kreek & Reisinger, 1997). Acute pain management in this population is difficult and challenging for a number of reasons, including: opiophobia amongst prescribers (Morgan & Puder, 1989), fears of exacerbating addiction (Cleeland, 1987), legislative barriers in the United States (Joranson & Gilson, 1994), lack of knowledge about addictive behaviours, societal prejudices against addicts (Savage, 1998), and patients being reluctant to give accurate histories because physicians tend to withhold opioid analgesics for the patient with a history of drug abuse (Hicks, 1989). Furthermore, the development of opioid tolerance and dependence may result in altered pain sensitivity, and subsequent response to additional opioids.

2.2 Pain sensitivity of methadone maintenance patients

To date, the results of studies investigating pain sensitivity of patients on methadone maintenance treatment have been inconsistent (see section 1.4 for a review). Inglis and Martin (1964) investigated the pain tolerance responses of 24 former opioid addicts compared with 24 matched control subjects. They induced pain using a cold pressor test; they found the former opioid addicts were markedly less pain tolerant compared with the control subjects. Ho and Dole (1979) also using a cold pressor test, found that pain threshold (i.e. when pain was first perceived) was significantly lower in groups of drug-free ex-addicts and methadone maintained patients compared with drug free controls. No significant difference in pain tolerance (i.e. when the stimulus was no longer tolerated) was found between the groups. More recently Compton (1994), also using a cold pressor method, measured pain tolerance in people seeking treatment for abuse of opioids and/or cocaine, and found that methadone maintenance patients were pain intolerant compared with those currently abusing, or abstinent from, cocaine.

Other methods of pain induction have been used to measure pain sensitivity in methadone patients. For example, Schall *et al.*, (1996), using mechanical pressure-induced pain, found that pain threshold and tolerance values of methadone patients were similar to drug-free controls at the time of trough plasma methadone concentrations. However, at the time of

peak plasma concentration, methadone patients had significantly higher threshold and tolerance values than controls. Similar results were reported by Dyer *et al.*, (1999), who compared pain threshold levels, using cutaneous electrical stimulation of the ear lobe, between methadone patients and drug-free controls.

Complicating matters further is the fact that Liebmann and co-workers suggested that opioid addicts have higher pain thresholds than other patients (Liebmann *et al.*, 1994). They investigated pain threshold (ie. pain detection) and pain tolerance responses of former opioid addicts and matched control subjects; pain was induced using a cold pressor test (see section 1.6). They found that the pain detection levels of the former addicts were significantly higher than those of control subjects; there were no significant differences for pain tolerance levels. Indeed, it has even been suggested that opioid dependent patients often present with medical conditions in an advanced state of progression because they have an increased pain threshold, secondary to their chronic use of opioids, which has masked warning symptoms (Hicks, 1989). Hicks did not support this suggestion with any documented evidence.

It is possible that the contradictions in the literature may be due to differences in pain induction and pain measurement indices. In order to resolve this, it is necessary to use multiple pain induction and pain measurement methods, and to account for fluctuations in plasma methadone concentration. I decided to use two distinct methods of pain induction: (1) electrical stimulation, and (2) a cold pressor test; both have been shown to be reproducible and responsive to opioids, offer variety in pain stimulus (phasic pain vs. tonic pain), and both have been used in studies investigating the issue of pain sensitivity amongst opioid addicts (Inglis & Martin, 1964; Ho & Dole, 1979; Compton, 1994, 1998; Dyer *et al.*, 1999; Compton *et al.*, 2000).

2.3 Aims of the study

The aims of the study were to (i) compare the nociceptive responses (pain detection and tolerance) within and between methadone maintenance patients and matched controls; (ii) determine whether the method of pain induction results in different responses; and in methadone maintenance patients, (iii) determine if nociceptive responses are different at trough and peak plasma methadone concentrations.

Hypotheses:

1. Methadone maintenance patients are more sensitive and less tolerant to pain than matched drug free control subjects
2. Methadone maintenance patients are differentially sensitive to pain induced by cutaneous electrical stimulation and a cold pressor test.

2.4 Methods

2.4.1 Patients and control subjects

Approval for this study was given by the Research Ethics Committee, Royal Adelaide Hospital, Adelaide, South Australia. Sixteen patients (11 male and 5 female), age range 21 – 43 (mean=32) years, who had been enrolled in the South Australian Public Methadone Maintenance Program for at least 4 months (range 4 months to 10 years) with no dose changes in the previous month were recruited. The average dose of methadone was $62\text{mg} \pm 5.8$ (mean $\pm$ SEM) (range 30-120 mg; 0.66 – 2.37 mg/kg).

Exclusion criteria included pregnancy, positive HIV serology, major psychiatric illness, benzodiazepine and/or alcohol abuse, chronic pain conditions and neurological disorders. A urine sample was collected from each patient for the detection of opioids (other than methadone), benzodiazepines, sympathomimetic amines, cannabinoids and barbiturates. Sixteen age and sex matched control subjects were also recruited. None of the control subjects had taken any known psychoactive substance, other than caffeine, alcohol and/or nicotine, in the month before commencement of the study. All subjects were paid for their participation in this study and were free to withdraw at any time.

Eight of the 16 methadone patients regularly smoked cannabis; 4 smoked it daily, with the other 4 smoking cannabis less than 3 days per week. Two methadone patients tested positive for three different unprescribed benzodiazepines (oxazepam, diazepam, and temazepam). Four of the methadone patients tested positive for opioids other than methadone. Fifteen out of the 16 methadone patients smoked cigarettes every day. None of the control subjects tested positive for any substances other than nicotine. Three of the 16 control subjects smoked cigarettes every day.

2.4.2 Procedures and measures

This study was conducted in a temperature-controlled room (24 °C) under constant illumination (65 lux). Between 0800 and 1300 hours each patient and control subject was tested in a single day session, but no session included more than one patient or subject. For methadone patients the first test took place 30 minutes prior to their scheduled dose (0 hours), and the second test 3 hours after the first test (3 hours). Controls were also tested twice in a single session, with 3 hours separating the testing. I collected a 6 mL blood sample by venipuncture from each methadone patient at 0 and 3 hours. I centrifuged the blood samples and stored the plasma at -20° C until assay. Fifty percent of subjects in each group received one method of pain induction (eg. cold pressor test) first followed by the other method (electrical stimulation); with the other 50% the order was reversed.

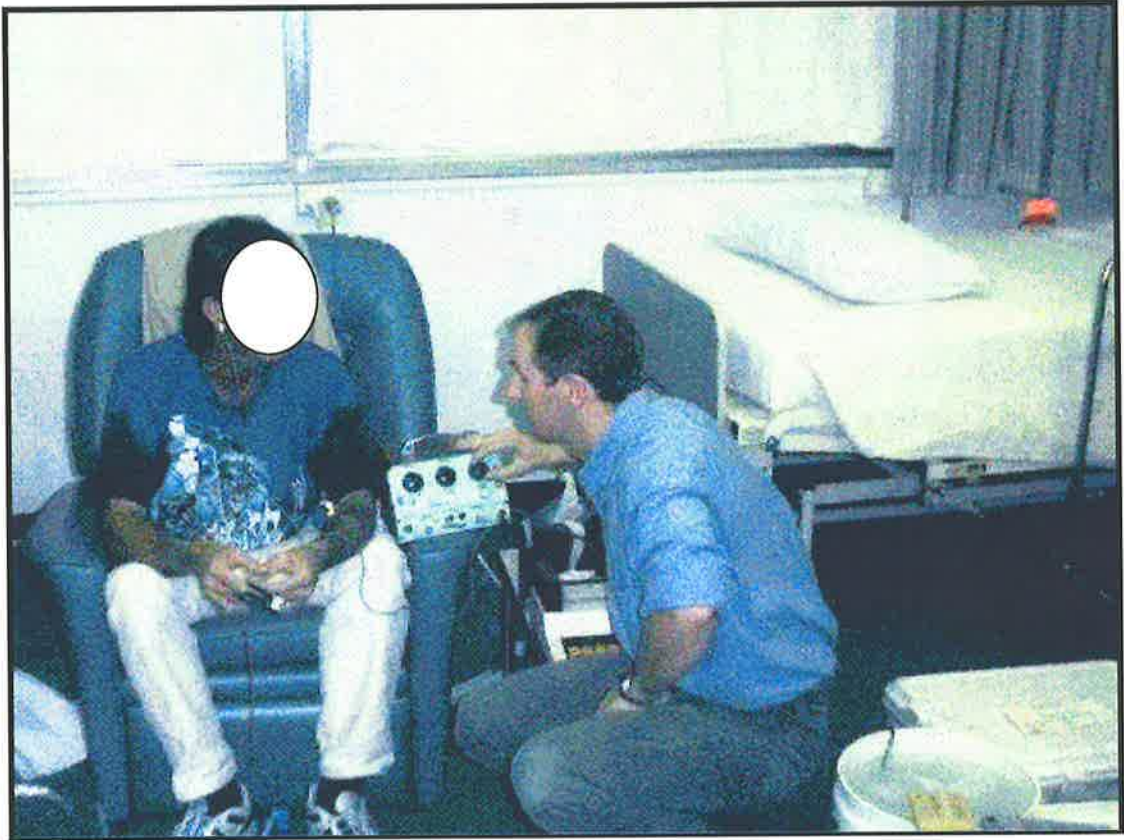
2.5 Pain induction

Two methods of pain induction were used to determine nociceptive responses at each of the two time points: electrical stimulation and the cold pressor test.

2.5.1 Electrical stimulation

This was delivered via cutaneous electrodes attached to one earlobe. The electrical stimulator (Grass model S6C, Grass Instruments, Quincy, MA, USA) delivered square wave pulses of 14-millisecond duration (0.7 pulses per second). Electrode gel (Spectra 360, Parker Laboratories, Orange, NJ, USA) was used to provide conductance between the ear clip and the skin. Voltage, set to zero at baseline, was increased at a constant rate of 2 volts every 1.4 seconds (range 0 to 100 volts). Each subject sat in a comfortable chair for the duration of this method (see Figure 2.1). As the voltage increased, the subjects verbally indicated when they first perceived pain (detection), and when they could no longer tolerate the stimulus intensity (tolerance). The stimulus was terminated immediately upon indication of the latter. Both indices were quantified in volts.

Figure 2.1. Electrical stimulation. Picture illustrating the manner in which pain was induced by cutaneous electrical stimulation of an ear lobe.



2.5.2 Cold pressor test

I adapted this method from the procedures of Eckhardt *et al.* (1998). Two cylindrical plastic containers (380 cm in depth, 300 cm in diameter) were used (see Figure 2.2). One contained warm water (34.5 – 35.5 °C), which was controlled by a thermo-regulator (Unistat 110, Thermoline Scientific, Sydney, Australia). The other container was filled with crushed ice and cold water (temperature 0.5 – 1 °C). Ice was added as required to ensure the temperature remained between 0.5 and 1 °C. An aquatic pump (Brolga MV 1500, Brolga Australia Pty. Ltd., Haberfield, NSW, Australia) was used to circulate the cold water in order to prevent laminar warming around the subject's limb (see Figure 2.3 and 2.4).

Figure 2.2. Cold pressor test apparatus. Picture showing the two plastic cylindrical containers used for the cold pressor test. The container on the left hand side is filled with ice-cold water (0.5°C), whilst the container on the right hand side (with a thermoregulator resting on a wooden bridge) is filled with warm water (35°C).



Prior to testing, each subject was instructed to verbally indicate when they first felt pain (detection) and when they could no longer tolerate the stimulus (tolerance) to remove their arm from the container. Each subject was then instructed to kneel on cushions in front of the two water containers and eye patches were placed over both eyes to exclude visual distractions including temporal cues (see Figure 2.3). Subjects then placed the non-dominant hand and forearm, with fingers wide apart, in the warm water container for 2 minutes. A blood pressure cuff was placed on the non-dominant upper arm. One minute 45 seconds after immersion the cuff was inflated to 20mmHg below diastolic pressure to minimise the role of vascular flow in determining reaction to the cold water. Fifteen seconds later (at exactly the 2 minute mark) subjects were instructed/assisted to transfer their arm from the warm water container into the cold water with fingers wide apart and not touching the container.

Detection was recorded as the time from full immersion of the limb to verbal indication of pain; tolerance was recorded as the time from full immersion until withdrawal of the arm from the cold water container. Both indices were quantified in seconds. The blood pressure cuff was then deflated, eye patches removed, and each subject was given a towel to dry their forearm.

Figure 2.3. Limb immersed in warm water. Subject is kneeling on cushions placed on the floor in front of the water containers. Eyes are covered with eye patches, the blood pressure cuff (on the non-dominant arm) is inflated to 20mmHg below diastolic pressure to minimise the role of vascular flow in determining reaction to the cold water.



Figure 2.4. Limb immersed in cold water. Picture of a subjects arm in the cold water container; water pump is circulating the water to prevent laminar warming around the limb.



2.6 Plasma methadone concentrations

(-)-(R) and (+)-(S)- methadone were quantified in plasma using high-performance liquid chromatography (HPLC) as described by Foster *et al.* (2000). The method has a limit of quantification of 15ng/ml for each enantiomer. Inter- and intra-day precision and accuracy data, of low, medium and high quality control concentrations, as assessed by the coefficients of variation, were less than 12%. I collected all blood samples from the indwelling venous catheter. I centrifuged each sample; the plasma was then stored at -20° C in pre-labelled plastic containers in preparation for later HPLC analysis by Mr. Andrew Menelaou (Research Assistant, Department of Clinical and Experimental Pharmacology, Adelaide University). Mr. Menelaou gave me a list of the actual plasma concentrations for every sample. I then used these data for subsequent analysis and interpretation.

2.7 Data analysis and statistics

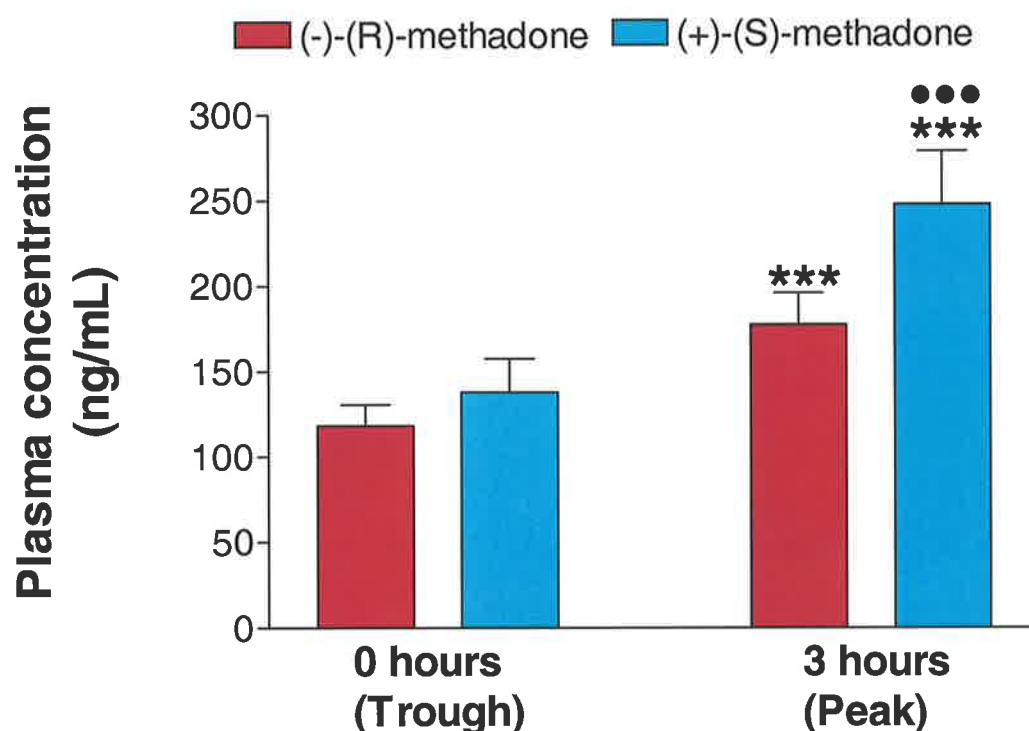
Data are presented as mean $\pm$ SEM (with 95% confidence intervals, CI). Between-group comparisons (methadone vs. control) were made using Student's *t* tests (independent), and within-group comparisons were made using Student's *t* tests (paired). The alpha level was set at $p < 0.05$. Pain tolerance to detection ratios were also calculated as a means of discriminating pain responses. I analysed all data using SPSS™ for Windows (version 10, SPSS Inc., Chicago, Illinois, USA), which carried out tests for homogeneity of variance and adjusted the *p* value accordingly.

2.8 Results

2.8.1 Plasma methadone concentrations

Plasma concentrations of (-)-(R)- and (+)-(S)- methadone were 118 ($\pm$ 12; range, 35-186) and 138 ($\pm$ 20; range, 30-297) ng/mL, respectively at 0 hours, and at 3 hours 185 ($\pm$ 18; range, 58-284) and 259 ($\pm$ 31; range, 73-496) ng/mL (see Figure 2.5). For each of the two enantiomers, the difference in plasma concentration between the two time points was statistically significant ($p < 0.0001$). Comparisons between (-)-(R)- and (+)-(S)- enantiomers at both time points showed no statistical difference at 0 hours ($p = 0.096$, [95% CI, -43.2, 3.97; whereas at 3 hours there was a highly significant difference ($p < 0.0001$, [95% CI, -102.3, -38.72])). The peak to trough plasma concentration ratio of (-)-(R)-methadone was 80% of that obtained for (+)-(S)-methadone.

Figure 2.5. Mean ($\pm$ SEM) plasma (-)-(R) and (+)-(S) methadone concentrations at 0 hour (trough) and 3 hours (peak). 0 vs. 3 hours: *** $p < 0.0005$; R(-)- methadone vs. S(+)-methadone: ●●● $p < 0.0005$.

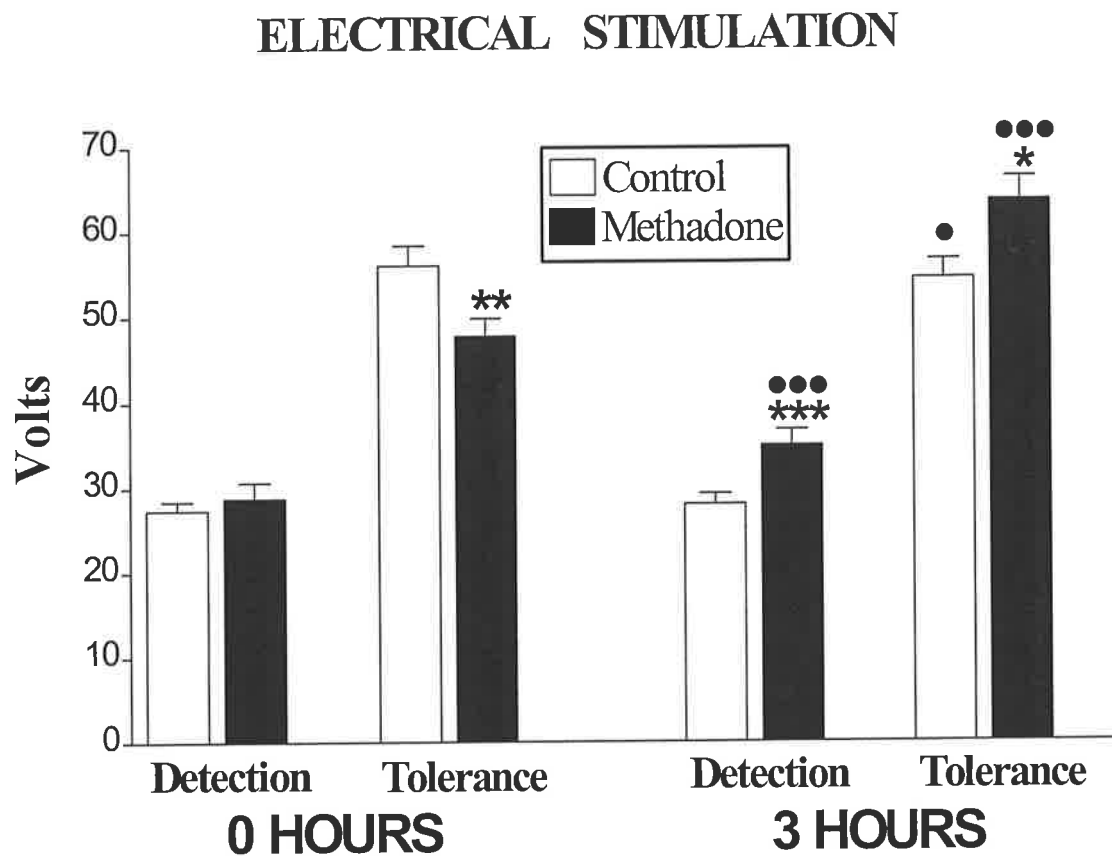


2.8.2 Electrical stimulation

Results from methadone patients and controls are shown in Fig.2.6. At 0 hours there was no significant difference between the groups for pain detection ($p = 0.744$, [95%CI, -3.89, 5.39]). However, pain tolerance values at 0 hours in methadone patients were significantly less than in controls ($p = 0.013$, [95%CI, -14.59, -1.9]). At 3 hours, methadone patients' pain detection and pain tolerance values were significantly higher than for controls ($p = 0.002$, [95%CI, 3.11, 11.89] and $p = 0.015$, [95%CI, 1.88, 16.37], respectively).

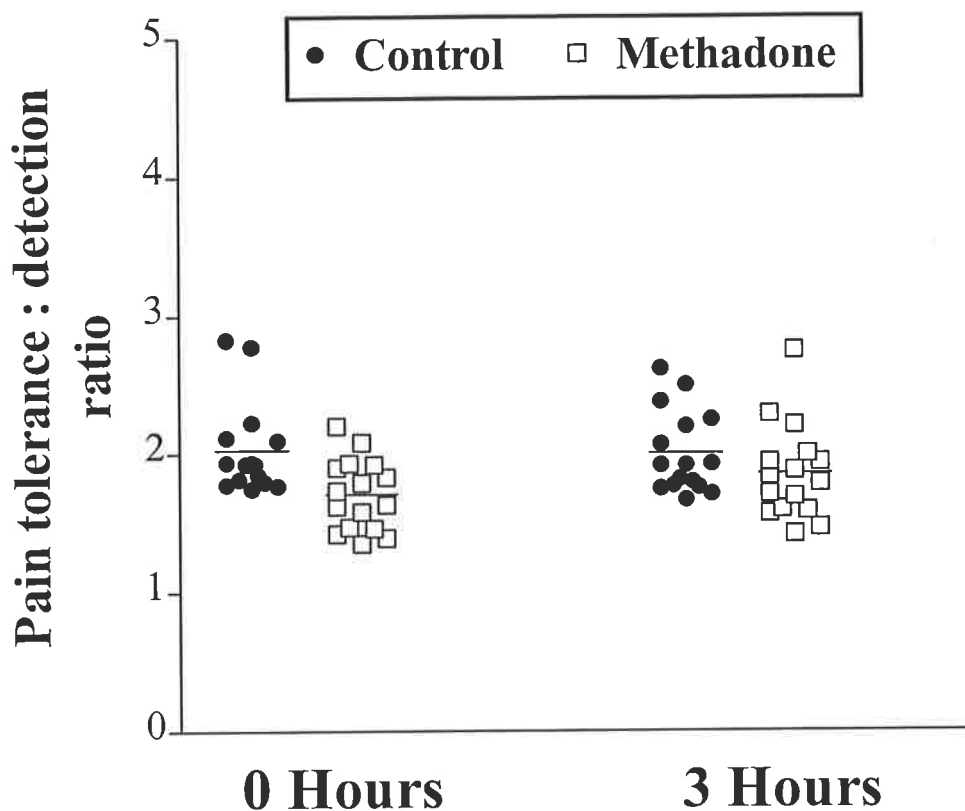
Comparisons were made between values obtained at 0 and 3 hours for each subject group. In methadone patients, mean pain detection and pain tolerance values were significantly higher at 3 hours compared to 0 hours ($p < 0.0001$, [95%CI, -8.89, -3.36] and $p < 0.0001$, [95%CI, -21.34, -10.15], respectively). For controls, pain detection values at 3 hours were not significantly different to those at 0 hours ($p = 0.096$, [95%CI, -0.12, 1.37]), whereas for pain tolerance, the control subjects' values at 3 hours were significantly lower than at 0 hours ($p = 0.018$, [95%CI, 0.32, 2.93]), although the magnitude of the difference was small. As outlined in the methods section Fifty percent of subjects in each group received one method of pain induction (eg. cold pressor test) first followed by the other method (electrical stimulation); with the other 50% the order was reversed. There were no significant order effects of pain induction within each group; pain detection at 0 and 3 hours ($p = 0.153$ and $p = 0.475$, respectively), pain tolerance at 0 and 3 hours ($p = 0.234$ and $p = 0.931$, respectively).

Figure 2.6. Electrical stimulation. Comparison of mean ($\pm$ SEM) pain detection and pain tolerance values at 0 and 3 hours in 16 methadone maintenance patients and 16 matched controls. **Methadone vs. controls:** 0 hours: Detection $p=0.744$, Tolerance $**p=0.013$. 3 hours: Detection $***p=0.002$, Tolerance $*p=0.015$. **0 vs. 3 hours:** Methadone: Detection $***p<0.0001$, Tolerance $***p<0.0001$; controls: Detection $p=0.096$, Tolerance, $\bullet p=0.018$.



Pain tolerance/pain detection ratios (Fig.2.7) for methadone patients were significantly lower than in controls at 0 hours ($p = 0.005$, [95%CI, -0.54, -0.11]); whereas at 3 hours there was no significant difference between the groups ($p = 0.204$, [95%CI, -0.38, 0.08]). Within the methadone group, there was a small but significant increase in the ratio from 0 to 3 hours ($p = 0.022$, [95%CI, 0.03, 0.28]). There was no significant difference in the ratio within the control group between 0 and 3 hours ($p = 0.444$, [95%CI, -0.09, 0.4]).

Figure 2.7. Electrical stimulation: pain tolerance to detection ratios at 0 and 3 hours. Methadone vs. controls: mean ratios at 0 hours are 1.7 vs.2.0 ($p=0.005$); 3 hours, 1.9 vs.2.0 ($p=0.204$.) 0 vs. 3 hours: Methadone, $p=0.022$; controls, $p=0.444$.

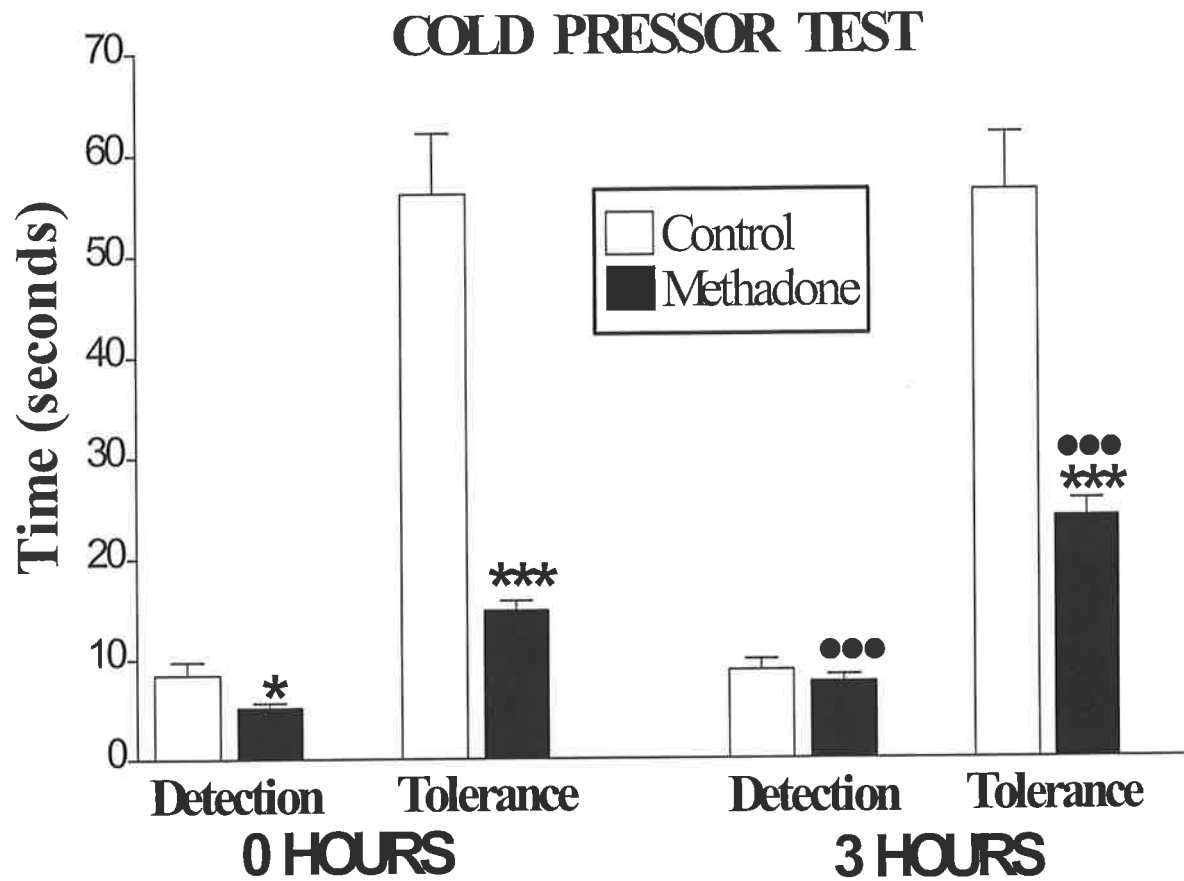


2.8.3 Cold pressor test

Results for the cold pressor test are presented in Fig.2.8. At 0 hours, pain detection values for methadone patients were significantly lower than for controls ($p = 0.023$, [95%CI, -6.23, -0.52]). Similarly, pain tolerance values for methadone patients were significantly lower than for controls ($p < 0.0001$, [95%CI, -54.17, -28.33]). At 3 hours, pain detection values were not significantly different between the groups ($p = 0.369$, [95%CI, -3.84, 1.47]), whereas pain tolerance values in methadone patients were significantly lower than for controls ($p < 0.0001$, [95%CI, -44.81, -19.93]).

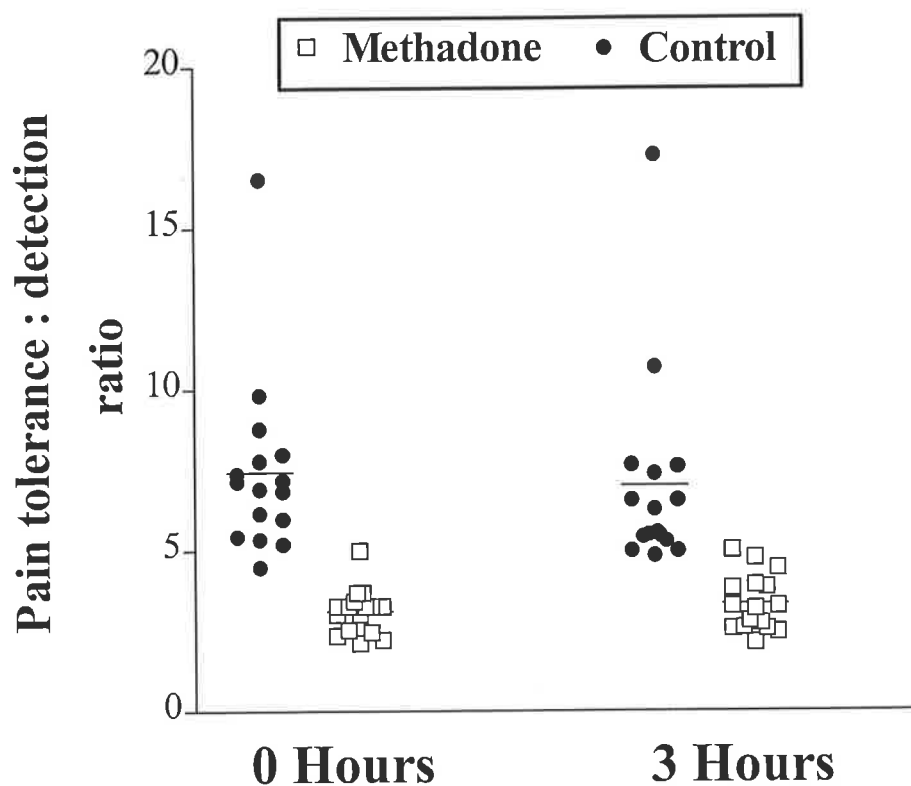
Comparisons were made between values obtained at 0 and 3 hours for each group. In methadone patients, mean pain detection and pain tolerance values at 3 hours were significantly higher than at 0 hours ($p < 0.0001$, [95%CI, 3.34, 1.78] and $p < 0.0001$, [95%CI, 11.9, 7.02] respectively). For controls, mean pain detection and pain tolerance values at 3 hours were not significantly different to those at 0 hours ($p = 0.211$, [95%CI, -0.99, 0.24] and $p = 0.857$, [95%CI, -3.17, 2.67], respectively). There were no significant order effects within each group: for pain detection at 0 and 3 hours ($p=0.471$ and $p=0.386$, respectively), and for pain tolerance at 0 and 3 hours ($p=0.654$ and $p=0.607$, respectively).

Figure 2.8. Cold pressor test. Comparison of mean ($\pm$ SEM) pain detection and pain tolerance values at 0 and 3 hours in 16 methadone maintenance patients and 16 matched controls. **Methadone vs. controls.** 0 hours: Detection * $p=0.023$, Tolerance *** $p<0.0001$. 3 hours: Detection $p=0.369$, Tolerance *** $p<0.0001$. **0 vs. 3hours:** Methadone: Detection *** $p<0.0001$, Tolerance *** $p<0.0001$; Controls: Detection $p=0.211$, Tolerance $p=0.857$.



Pain tolerance/pain detection ratios are shown in Fig 2.9. For methadone patients, the ratios were significantly lower than controls at 0 hours and 3 hours ($p < 0.0001$, [95%CI, -5.87, -2.83] and $p < 0.0001$, [95%CI, -5.34, -2.04] respectively). There was no significant difference in the ratio within each group between 0 and 3 hours ($p=0.220$, [95%CI, -0.15, 0.58] for methadone patients and ($p = 0.071$, [95% CI, -0.92, 0.04]) for control subjects.

Figure 2.9. Cold pressor test: pain tolerance to detection ratios at 0 and 3 hours. Methadone vs. controls: mean ratios at 0 hours are 3.1 vs.7.4 ($p<0.0001$); 3 hours, 3.3 vs.7.0 ($p<0.0001$.) 0 vs. 3 hours: Methadone, $p=0.220$; controls, $p=0.071$.



2.9 Discussion

This study sought to compare pain detection and pain tolerance responses between methadone maintenance patients and controls using different methods of pain induction. Furthermore, in methadone maintenance patients, I sought to determine if there were differences in nociceptive responses at trough and peak plasma methadone concentrations. There were marked differences in pain tolerance responses between methadone maintenance patients and controls using the cold pressor test, with methadone patients exhibiting a hyperalgesic response. Using electrical stimulation, differences for pain tolerance between methadone patients and controls were less marked, with methadone patients more pain tolerant than controls when their plasma methadone concentration was at the putative peak. Nociceptive responses of methadone maintenance patients were attenuated by the increase in plasma methadone concentration irrespective of the method of pain induction.

2.9.1 Nociceptive responses

These results help to reconcile the apparent discrepancies in the literature. They partly support the findings of Ho and Dole (1979) who found that pain threshold (detection) values of methadone maintained patients were significantly lower than those of controls. However, with regard to pain tolerance values, these results are very different in that methadone maintained patients were substantially intolerant of cold pressor induced pain compared with control subjects, whereas Ho and Dole found no significant difference. The present finding of pain intolerance in methadone patients is similar to that reported by Compton (1994), who found in a cold pressor model that methadone patients were pain intolerant compared with cocaine abusers. Further, these results are very different to those reported by Liebmann *et al.* (1994), who suggested, but provided no evidence, that opioid addicts have higher pain thresholds than drug-free control subjects. Using electrical stimulation, these results concur with those of Dyer *et al.* (1999) who reported that at the time of trough plasma methadone concentrations, patients had similar threshold (pain detection) values to controls, whereas at time of peak plasma methadone concentrations patients were less pain sensitive than controls. Furthermore, the magnitude of the increase in pain threshold in relation to the increases in plasma methadone concentrations (trough to peak) in the present study is also very similar to those reported by Dyer and colleagues, ie. an approximate increase of 25%.

Important differences in study procedures (e.g., phasic vs. tonic stimulation, and measuring thresholds for pain detection versus pain tolerance) may have contributed to the apparent discrepant results in the literature. Pain sensations produced by phasic stimuli, such as electrical stimulation, differ qualitatively, neurologically, and functionally from deep, prolonged sensations (eg., tonic pain induced by the cold pressor test) which are characteristic of many clinical pain syndromes (Beecher, 1966; Price, 1976; Chen *et al.*, 1989). Chen and colleagues (1989) postulated that phasic pain and tonic pain may well be subserved by different neurophysiological pathways as well as being differentially affected by opioids. This may explain the findings in the present study that methadone maintenance patients are considerably more intolerant of pain induced by the cold pressor test compared to electrical stimulation.

There is evidence that C-fibres mediate cold hyperalgesia, a process involving adaptive changes integrated at the level of the thalamus (Craig, 1995). Nociceptive information concerning cutaneous cold stimuli (originating in lamina I of the dorsal horn) is transmitted to the thalamus via the dorsal spinothalamic tract (Dostrovsky & Craig, 1996; Millan, 1999). Interestingly, cold hyperalgesia is a phenomenon that is present after chronic nerve injury (Fruhstorfer & Lindblom, 1984; Frost *et al.*, 1998; Ochoa & Yarnitsky, 1994), and is frequently encountered in central pain syndromes that follow thalamic infarction (Craig *et al.*, 1994; Vestergaard *et al.*, 1995). The implications of the cold hyperalgesia observed in methadone patients in the present study are unclear at present. Perhaps central plasticity that occurs with chronic opioid treatment, such as those changes involved in opioid tolerance, may be responsible for methadone patients' hyperalgesic responses to pain induced by a cold pressor test. Further and more detailed animal research is necessary to shed scientific light on this theory.

With regard to the indices of pain measurement, my results support the assertion of Harris and Rollman (1983) that threshold (detection) and tolerance judgments are dissimilar. This indicates that when determining the response to experimental pain it is essential to measure both of these indices. I am unaware of the use of the pain tolerance to detection ratio as a means of discriminating pain responses between methadone maintenance patients and controls. This ratio was devised as a means of incorporating both ends of the pain continuum ie. when pain is first felt (detection) and the point when it becomes intolerable (tolerance); both indices are important factors in determining pain sensitivity. Hence, I believed that an index of pain sensitivity should ideally include both ends of the pain

continuum. Interestingly, the magnitude of differences between methadone patients and controls was significant only with the cold pressor test, and this could possibly be a marker of hyperalgesia in methadone patients. Further research is required to determine whether the difference in ratio occurs with other opioid exposed populations such as opioid dependent patients treated with LAAM or buprenorphine, or morphine pain patients.

There is animal evidence of altered pain sensitivity related to chronic opioid exposure (Mao *et al.*, 1994, 1995a, 1995b; Laulin *et al.*, 1999). Mao and co-workers demonstrated that molecular changes in spinal cord dorsal horn neurons associated with the development of opioid tolerance are the same as those associated with the development of central hyperalgesia following tissue injury and inflammation; in particular, the same intracellular processes linked to NMDA receptor activation (eg. synthesis of nitric oxide, increases in the levels of protein kinases, increased levels of Ca^{++}). Interestingly, the development of both morphine tolerance and thermal hyperalgesia were prevented by intrathecal co-administration of the NMDA receptor non-competitive antagonist MK-801. Whilst methadone itself is a weak non-competitive NMDA receptor antagonist (Gorman *et al.*, 1997; Ebert *et al.*, 1998), the clinical implications of this for humans chronically administered methadone are unknown. In particular, the magnitude of NMDA antagonist activity achieved at normal therapeutic concentrations is unknown.

It is possible that the hyperalgesia observed in relation to the cold pressor test could have been due to “a proneness to overreact” or exaggerate bodily discomfort that has been described as a salient feature of the addict (Isbell *et al.*, 1948a, b; Martin *et al.*, 1973; Fultz *et al.*, 1980). However, these results show that methadone maintained patients at the time of peak plasma concentrations, in response to electrical stimulation, are more pain tolerant than healthy drug-free controls.

These results of increased sensitivity to cold pressor pain amongst patients chronically maintained on methadone support those of Rapp *et al.*, (1995) who conducted a review of acute pain management (post-surgical) in patients with prior opioid consumption. Their retrospective case-controlled study found that patients with a history of current opioid use had significantly higher post-surgical pain scores and post-surgical opioid requirements compared with previously opioid naïve patients. Indeed, there is further evidence that patients with a history of opioid consumption prior to surgery, need at least three times the post-surgical opioid requirements of previously opioid naïve patients (de Leon-Casasola *et al.*, 1993).

2.9.2 Inter-dosing plasma methadone concentrations

The magnitude of increases in the plasma concentrations of the pharmacologically active (-)-(R)-methadone from trough to peak plasma methadone concentrations in the methadone patients of the present study is consistent with previous studies which have also investigated the changes in plasma methadone concentrations during the inter-dosing interval in methadone maintenance patients (Dyer *et al.*, 1999; Foster *et al.*, 2000). Furthermore, in the present study, the peak to trough plasma concentration ratio of (-)-(R)-methadone was 80% of that obtained for (+)-(S)-methadone. This is very similar to that reported by Foster *et al.* (2000). It is of interest to note that the concentrations of the individual enantiomers were significantly different at 3 hours (ie. peak concentration) but not at 0 hour (trough concentration); this is probably due to the fact that the enantiomers significantly differ in their disposition (Kristensen *et al.*, 1996), with (-)-(R)-methadone having a larger volume of distribution, longer terminal elimination half-life and higher total body clearance.

2.9.2 Conclusions

The relative pain sensitivity of methadone maintenance patients is determined by the nature of the nociceptive stimulus (eg. cold pressor test vs. electrical stimulation), the concentration of methadone (trough vs. peak plasma concentration), and whether thresholds are determined for detection of pain or pain tolerance. Methadone maintenance patients are hyperalgesic to pain induced by the cold pressor test but not electrical stimulation. This hyperalgesia is particularly pronounced at times of putative trough plasma methadone concentrations. A low pain tolerance to detection ratio may be a marker of this hyperalgesia in methadone maintained patients.

CHAPTER 3

ANTINOCICEPTIVE EFFECTS OF INTRAVENOUS MORPHINE IN METHADONE MAINTENANCE PATIENTS

3.1 Introduction

As discussed in the preceding chapter increasing numbers of people are receiving opioids as substitution treatment for dependence. These people are likely to experience acute and chronic pain to the same degree and frequency as the general population. However, Portenoy and Payne, (1997) suggested that heroin addicts experience traumatic injuries (Cameron, 1964) and a myriad of medical disorders (Sapira, 1968) at a rate disproportionately higher than people in the general population. It has been advocated that the management of pain in the addict is not a trivial issue (Portenoy & Payne, 1997). Chappel (1973) reported that hospitals often refused to admit or treat recognised cases of drug dependence; patients receiving methadone maintenance treatment were turned away from hospitals because “we don’t treat junkies”. Further, it has been suggested that patients with current or past substance abuse are difficult to manage and should probably be excluded from treatment with opioid analgesics (Kennedy & Crowley, 1990). Undertreatment of pain in this patient group was certainly not helped by the suggestion that hospitalisation and treatment of pain with added doses of narcotics may jeopardise the chance to have decremental doses of methadone, eventual detoxification and possible rehabilitation from drugs (Dole *et al.*, 1966). Unfortunately, there are few and conflicting data on the antinociceptive effects of additional opioids in these patients.

3.1.2 Analgesic needs of methadone maintenance patients

In a retrospective case study review, Rubenstein *et al.* (1976) suggested, that although methadone blocks the euphoric effects of opiates, it does not interfere with the analgesic effects of morphine or pethidine. Others have also suggested that the pain management needs of methadone maintained patients can be met using standard doses of opioids, such as morphine or pethidine, in addition to their methadone maintenance dose (Fultz & Senay, 1975; Fultz *et al.*, 1980; Kantor *et al.*, 1980). However, Fultz and Senay (1975) added that because of cross-tolerance to other opioids, most methadone maintained patients would require more frequent administration of an analgesic than opioid naïve patients. Some clinicians have suggested that tolerance to other opioids has a negative impact on pain management for methadone maintained individuals (St. Marie, 1996; Hicks, 1989).

The literature is littered with anecdote and suggestion. Hick (1989) suggested that methadone maintenance patients require about one and a half times the dose of opioids that would normally be given to an opioid naïve patient with a similar medical problem. Others have merely proposed that methadone maintenance patients with acute pain should be treated with ‘appropriate dosages of short acting pain medication’, and just increasing the dose of methadone will not relieve pain (Schulz, 1997). Another anecdotal example is highlighted in Kreek’s suggestion that “doses required may be slightly larger and may need to be given more frequently because of narcotic cross-tolerance” (Kreek, 1978). Others also suggest that when methadone maintained patients need surgery, higher doses of opioids, more frequently administered will usually be required to achieve analgesia (Woolf, 1983).

None of these suggestions are based on controlled scientific evidence. Indeed, the only study of such a nature was recently conducted by Compton *et al.* (2000). They investigated the analgesic effects of small oral doses of (1) hydromorphone, and (2) ketorolac, in 60 methadone maintained patients and 60 matched controls, using a cold pressor test. They did not find any significant analgesic effects of either drug amongst methadone patients or control subjects (see section 1.6). However, that study did not involve blood collection from any of the participants; there could possibly have been differences between the plasma concentrations of hydromorphone and/or ketorolac in either group (methadone patients or control subjects). Further, it would have strengthened these results somewhat if plasma concentrations had been measured for all of drugs (methadone, hydromorphone and ketorolac). This highlights the need to determine individual drug plasma concentrations in studies determining the analgesic effects of various drugs.

As outlined in the previous chapter, methadone maintenance patients are hyperalgesic to pain induced by a cold pressor test. This finding of hyperalgesia may have clinical implications with regard to pain management in this patient population. Potentially, methadone patients may require substantially higher doses of opioid analgesics because of, firstly, cross-tolerance to the effects of opioid agonists and secondly, their baseline hyperalgesia. I am unaware of any controlled studies that have investigated the antinociceptive effects of morphine amongst methadone maintenance patients.

3.1.3 Aims of the present study

The aims of the study were to compare the intensity and duration of antinociceptive effects at two pseudo steady-state plasma morphine concentrations in methadone maintenance patients and matched controls; and to determine, in methadone patients, if the antinociceptive effects of morphine are affected by changes in plasma methadone concentration that occur during an inter-dosing interval; specifically, at the two extremes of methadone concentration: (i) at trough (approximately 23.5 hours after the previous dose), and (ii) at peak (2 hours after the dose).

Hypothesis: Methadone maintenance patients will be tolerant to the antinociceptive effects at plasma morphine concentrations known to produce analgesia in opioid-naïve patients with acute pain.

3.2 Methods

3.2.1 Patients and control subjects

Approval for this open label study was given by the Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia. Four patients (3 male and 1 female), age range 20 – 40 (mean=32.5) years and weight range 54.5 – 110.5 (mean=77.5) kilograms, who had been enrolled in the South Australian Public Methadone Maintenance Program for at least 9 months (range 9 months to 8 years), with no dose changes in the previous month, were recruited. The average dose of methadone was $81\text{mg} \pm 25$ (mean $\pm$ SEM) (range 50-155 mg; 0.59–1.40 mg/kg).

Patients who self-reported intravenous heroin use at a frequency of more than once per month but less than once per week, were recruited, as it was deemed more ethical to administer morphine to individuals who continued to use illicit heroin, rather than giving morphine to patients who were abstaining from using opioids other than their prescribed dose of methadone. Four age, sex and weight matched healthy control subjects were recruited. Exclusion criteria for both groups included those currently receiving therapy for pain, those with a history of cardiac, pulmonary (particularly asthma), hepatic or renal disease, neurological disorders (eg. epilepsy), HIV positive serology, a major psychiatric condition that would prevent giving informed consent, pregnancy and/or lactation. A urine sample was collected from each participant for the detection of opioids (other than methadone), benzodiazepines, sympathomimetic amines, cannabinoids and barbiturates.

Three of the 4 methadone patients (in the trough session) had low plasma morphine concentrations in their baseline blood sample; the actual plasma concentrations were 1.0, 3.8 and 7.3 ng/mL (see section 3.2.4 for assay); this resulted in a group mean baseline plasma morphine concentration of 3.0 ± 1.6 ng/mL. Further, in the peak session, 2 of the 4 methadone patients had low plasma morphine concentrations in their baseline blood sample; the actual plasma concentrations were 4.1 and 2.4 ng/mL, resulting in a group mean baseline (0 hour) plasma concentration of 1.6 ± 1.0 ng/mL. Two of the methadone patients admitted to smoking cannabis at least 3 times per week. One of the methadone patients tested positive (on both testing sessions) for two different benzodiazepines (oxazepam and diazepam). None of the other methadone patients blood samples contained any evidence of benzodiazepine use. All 4 methadone patients smoked cigarettes daily. None of the control subjects' baseline plasma samples contained morphine. One of the 4 control subjects smoked cigarettes.

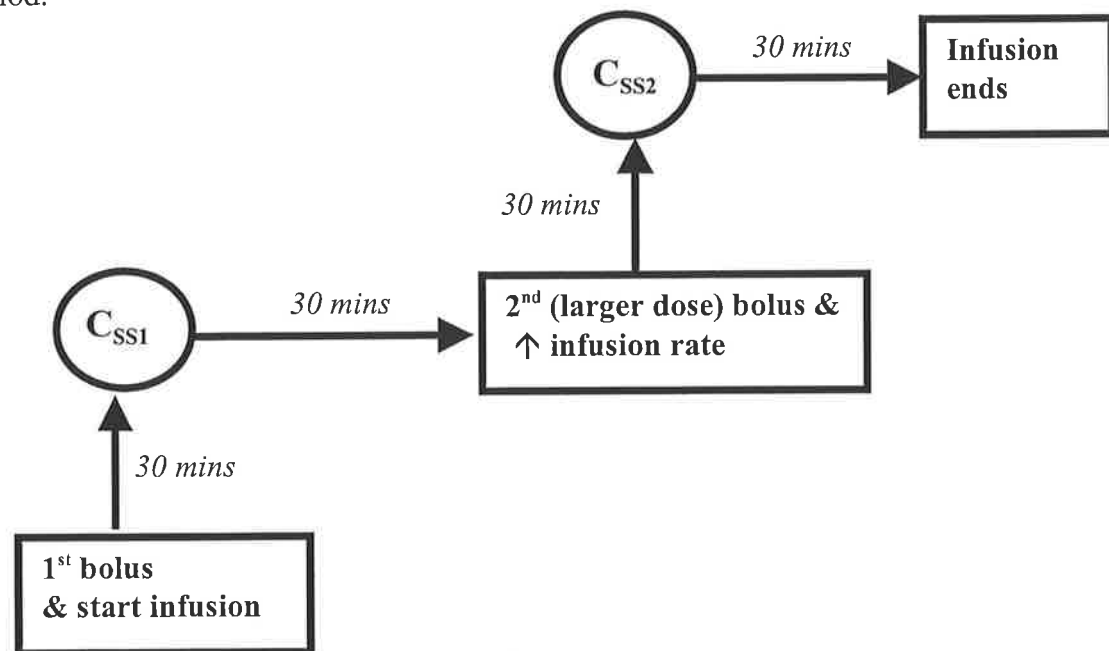
3.2.2 Study design

Methadone patients were tested on two occasions, separated by 7 days. They were randomly allocated into two subgroups: two patients were tested first when their methadone was at the putative trough plasma concentrations (23.5 hours after the previous dose), and the other two patients tested first when at putative peak plasma methadone concentrations (2 hours after the dose). The order was reversed for the second session. Patients in the trough session were given their scheduled daily dose of oral methadone 15 minutes after cessation of the morphine infusion (see below). All control subjects were tested on one occasion only, and did not receive any methadone.

3.2.2.1 Morphine administration

Morphine sulfate was administered intravenously as a 2 step, controlled infusion designed to produce consecutive target plasma concentrations (Hill *et al.*, 1990), using a syringe driver infusion pump (Terumo® model STC-521, Terumo Corporation, Tokyo, Japan). The details of the design are as follows: methadone patients and control subjects were given an initial bolus dose of morphine sulfate (2.2mg), followed by a constant infusion of 1.2 mg/hour for one hour to achieve a target pseudo steady-state plasma morphine concentration (C_{ss1}) of 20ng/mL. At 60 minutes, methadone patients were given an additional bolus dose of morphine sulfate (6.6 mg) and the infusion rate increased to 4.8 mg/hour for one hour to achieve a target pseudo steady-state plasma morphine concentration of 80ng/mL; at 60 minutes, control subjects had an additional bolus dose of morphine sulfate (4.95mg) followed by an increase in the infusion rate to 3.6mg/hour for one hour to achieve a second target pseudo steady-state plasma morphine concentration (C_{ss2}) of 60ng/mL. In the second infusion control subjects were given less morphine than methadone patients in order to minimise anticipated side effects. The total period of morphine administration was 2 hours, and is illustrated schematically in Figure 3.1 below.

Figure 3.1. Schematic representation of the 2 step controlled bolus and infusion designed to produce consecutive pseudo steady-state plasma morphine concentrations (C_{ss}) in a 2 hour period.



3.2.3 Procedures and measures

The study was conducted in a temperature-controlled room (24 °C) under constant illumination (75 lux) in a general hospital setting. Each testing session occurred over a 12 hour period, approximately 0800-2000. Only one subject was tested per session. Two indwelling venous catheters were inserted into the two best available, but opposite, peripheral arm veins; one (22 gauge catheter, Insyte™, Becton Dickinson, Franklin Lakes, NJ, USA) on the dominant arm for drug administration and the other (18 gauge catheter, Optiva™, Critikon, Rome, Italy) on the non-dominant arm for blood sampling. I collected venous blood samples (6mL) at 0 hour (pre-morphine administration), 0.5, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 4.0, and 5 hours after the beginning of the morphine infusion. The blood samples were centrifuged, and the plasma stored at -20° C until assay.

3.2.3.1 Pain induction

Two methods of pain induction were used to determine nociceptive responses, electrical stimulation via an ear lobe, and a cold pressor test as previously described in detail (section 2.5). Two indices for measuring responses were used: (1) when subjects first perceived pain (detection), and (2) when they could no longer tolerate the stimulus intensity (tolerance). Nociceptive responses were recorded at 0 hour (pre-morphine administration), and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 7.0 hours after beginning the morphine infusion.

3.2.4 Plasma morphine concentrations

Plasma morphine concentrations were quantified by Mr. Andrew Menelaou (Research Assistant, Department of Clinical and Experimental Pharmacology, Adelaide University) using a modification of a high-performance liquid chromatographic (HPLC) – electrochemical detection method previously described (van Crugten *et al.*, 1997). High (20ng/ml) and low (2ng/ml) quality control samples were assayed with each subject's set of plasma samples, and were within 10 and 15% respectively of the nominal concentrations. The limit of quantification was 0.5ng/mL. Methadone did not interfere with the method. I collected all blood samples from the indwelling venous catheter. I centrifuged each sample. The plasma was then stored at -20° C in pre-labelled plastic containers in preparation for later analysis. I then used the data for subsequent analysis and interpretation. Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) concentrations were quantified using a HPLC-electrospray mass spectrometry method by a researcher at the Dr. Margarte Fisher-Bosch-Institute for Clinical Pharmacology, Stuttgart, Germany. This method has

been described previously (Schänzle *et al.*, 1999), with limits of quantification for both glucuronides being 0.1ng/mL.

3.2.5 Plasma methadone concentrations

(-)-(R) and (+)-(S)- methadone were quantified in plasma by Mr. Andrew Menelaou using high-performance liquid chromatography (HPLC) as described by Foster *et al.* (2000). The method has a limit of quantification of 15ng/ml for each enantiomer. Inter- and intra-day precision and accuracy data, of low, medium and high quality control concentration, as assessed by the coefficients of variation, were less than 12%. Morphine did not interfere with the method. I collected all blood samples from the indwelling venous catheter. I centrifuged each sample. The plasma was then stored at -20° C in pre-labelled plastic containers in preparation for later HPLC analysis. I then used the data for subsequent analysis and interpretation.

3.2.6 Data analysis and statistics

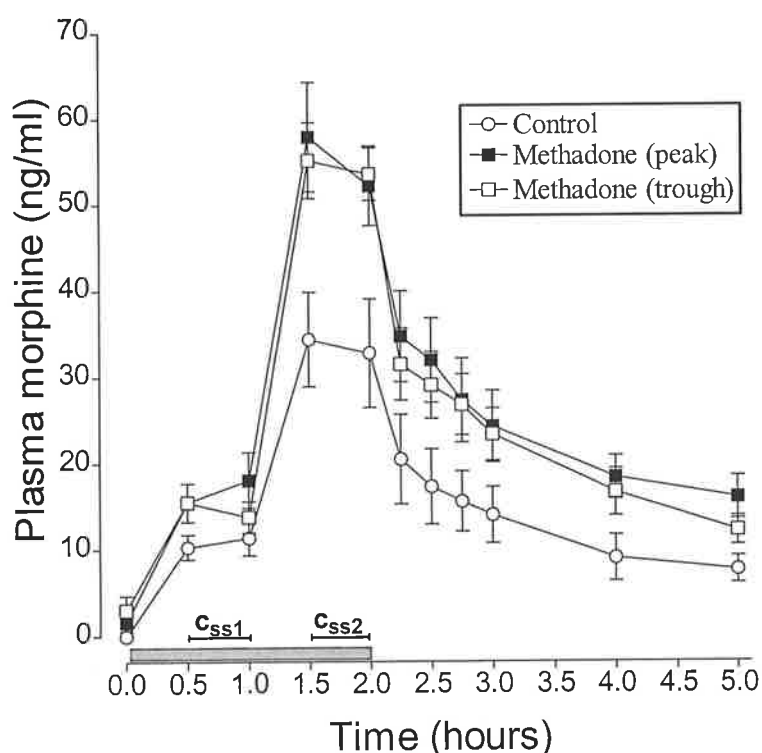
The mean of the two plasma morphine concentrations at 30 minutes and 60 minutes was designated as steady-state one (C_{ss1}), and similarly the mean of the two plasma morphine concentrations at 90 and 120 minutes was designated as steady-state two (C_{ss2}). Data are presented as mean $\pm$ SEM (with 95% confidence intervals, CI). Two-way repeated measures analyses of variance (ANOVA) were used to determine differences in pharmacodynamic responses among methadone patients and control subjects. To account for sphericity, the Greenhouse-Geisser conservative F-test was used to interpret the ANOVA. As there are only two groups (methadone patients and control subjects), the statistical software used in this analysis did not conduct *post hoc* tests; hence specific between-group comparisons (methadone vs. control) were made using Student's *t* tests (independent) with an alpha level of $p < 0.0045$, and within-group comparisons were made using Student's *t* tests (paired) with an alpha level of $p < 0.005$. All such *t* tests involved multiple comparisons; hence I adjusted the alpha accordingly using a Bonferroni adjustment ($p < 0.05/\text{number of comparisons}$). The alpha level is outlined in each part of the results section. Pain tolerance to detection ratios were also calculated. All data were analysed using SPSS™ for Windows (version 10, SPSS Inc., Chicago, Illinois, USA), which carried out tests for homogeneity of variance and adjusted the *p* value accordingly.

3.3 Results

3.3.1 Plasma morphine concentrations (Figure 3.2)

Methadone patients achieved a mean first pseudo steady-state plasma concentration (C_{ss1}) of 16ng/mL (± 2.0 ; range, 12.5 to 21.3 ng/mL) and control subjects 11 ng/mL (± 2 ; absolute range, 7.5 to 14.3 ng/mL). Methadone patients achieved a mean second pseudo steady-state plasma concentration (C_{ss2}) of 55 ng/mL (± 5 ; absolute range, 46.5 to 65.2 ng/mL), whereas the mean C_{ss2} of the control group was 33 ng/mL (± 6 ; absolute range, 23.2 to 50.3 ng/mL). There were no significant differences ($p < 0.295$) between the plasma morphine concentrations at 30 and 60 minutes (C_{ss1}), and between 90 and 120 minutes (C_{ss2}) in either group (methadone patients or control subjects). Comparisons of plasma morphine concentrations reached during trough and peak methadone sessions did not yield any significant differences ($p = 0.22$ to 0.93) in plasma concentrations at any time point during or post-morphine infusion.

Figure 3.2. Mean ($\pm$ SEM) plasma morphine concentrations (0 to 5 hours) in trough session methadone patients (open squares), peak session methadone patients (filled squares) and matched controls (open circles). Grey shaded rectangle illustrates the period of the morphine infusion; C_{ss1} and C_{ss2} periods are also highlighted.



3.3.1.1 Plasma morphine glucuronide concentrations

Plasma morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) concentrations are illustrated in figure 3.3. Mean plasma M3G concentrations for methadone patients (trough session) ranged from 85.58 to 237.1 ng/mL (absolute range, 42.58 to 320.45), whereas during the peak session they ranged from 61.38 to 222.47 ng/mL (absolute range, 29.98 to 311.85). For control subjects mean M3G concentrations ranged from 32.4 to 112.8 ng/mL (absolute range, 26.3 to 135.4). Mean M6G concentrations for methadone patients (trough session) ranged from 15.4 to 51.6 ng/mL (absolute range, 7.7 to 62.5), whereas during the peak session the mean ranged from 10.6 to 44.3 ng/mL (absolute range, 4.85 to 57.3). For control subjects mean M6G concentrations ranged from 7.5 to 32.4 ng/mL (absolute range, 6.65 to 38.4).

M3G: M6G ratios were calculated at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 and 5.0 hours. Mean ($\pm$ SEM) M3G: M6G ratios are summarised in Table 3.1, and are also graphically illustrated in figure 3.4. The alpha level for comparisons of these ratios was set as $p < 0.0071$. Within-group comparisons (trough versus peak methadone session) of M3G and M6G plasma concentrations, did not yield any significant differences for M3G ($p > 0.047$) or M6G concentrations ($p > 0.037$) at any time point.

The M3G: M6G ratios of methadone (trough session) patients were higher, but not significantly ($p > 0.009$) higher than those of control subjects at any time point. The ratios of methadone (peak session) patients were significantly higher than those of control subjects at 2.0 h ($p = 0.003$, [95%CI, 0.71, 2.22]) only.

Within-group comparisons (trough versus peak session) of the ratio did not reveal significant differences at any time point ($p > 0.071$, range 0.072 to 0.986).

Figure 3.3. Mean ($\pm$ SEM) plasma morphine 3- and 6-glucuronide concentrations (0.5 to 5 hours) in trough session methadone patients (open squares), peak session methadone patients (filled squares) and matched controls (open circles). Panel A: M3G concentrations. Panel B: M6G concentrations. Grey shaded rectangles illustrate C_{ss1} and C_{ss2} periods.

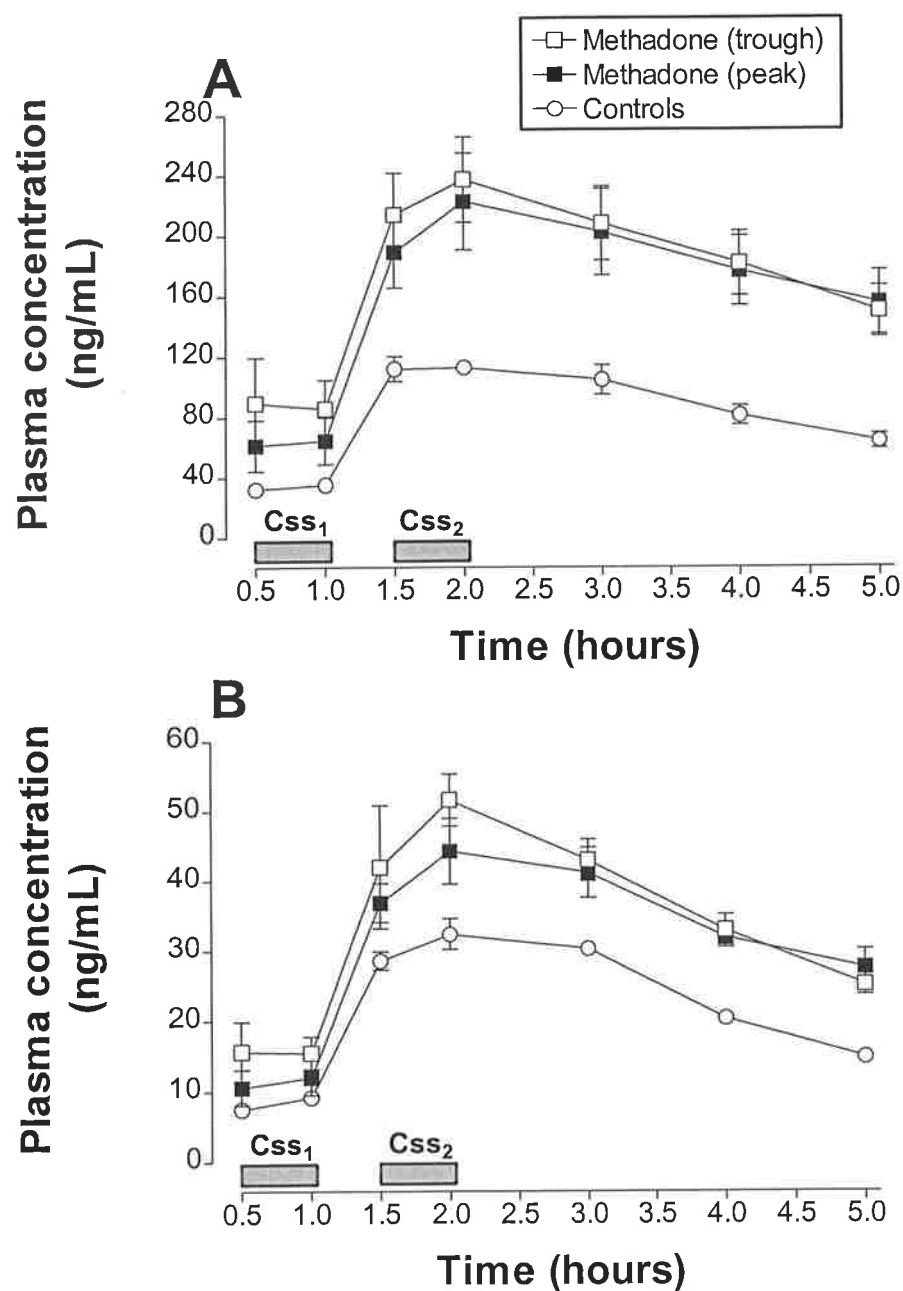
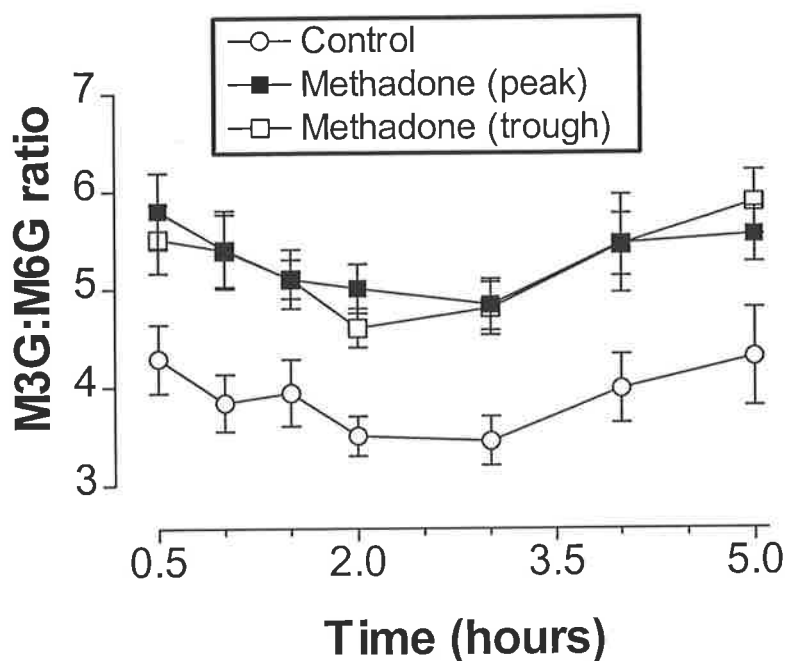


Table 3.1 Mean ($\pm$ SEM) plasma M3G: M6G concentration ratios (0.5 to 5 hours) in trough session methadone patients, peak session methadone patients and matched controls.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0.5 h	5.5 (0.4)	5.8 (0.4)	4.3 (0.4)	*p=0.050, #p=0.030,+p=0.365
1.0 h	5.4 (0.4)	5.4 (0.4)	3.8 (0.3)	*p=0.017, #p=0.020,+p=0.986
1.5 h	5.1 (0.2)	5.1 (0.3)	3.9 (0.3)	*p=0.030, #p=0.046,+p=0.977
2.0 h	4.6 (0.2)	5 (0.2)	3.5 (0.2)	*p=0.009, #p= 0.003 ,+p=0.072
3.0 h	4.8 (0.3)	4.8 (0.3)	3.4 (0.2)	*p=0.010, #p=0.008,+p=0.870
4.0 h	5.5 (0.3)	5.5 (0.5)	4 (0.3)	*p=0.020, #p=0.055,+p=0.976
5.0 h	5.9 (0.3)	5.5 (0.5)	4.3 (0.5)	*p=0.038, #p=0.071, +p=0.125

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0071$) this is highlighted in bold text.

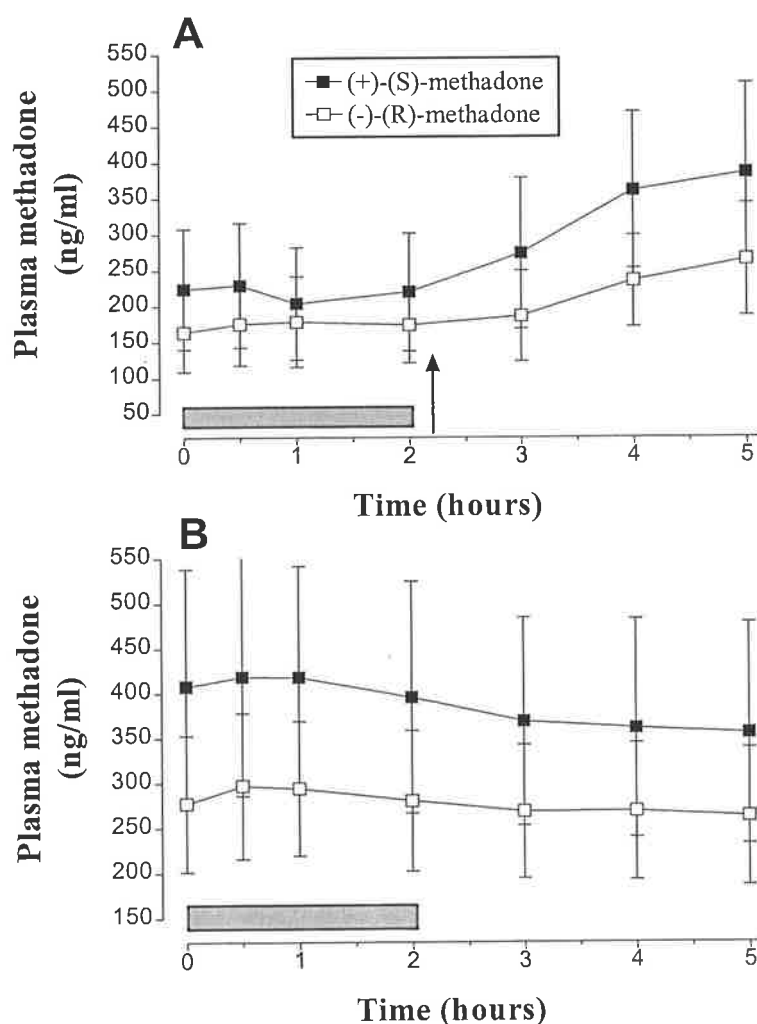
Figure 3.4. Mean ($\pm$ SEM) plasma M3G: M6G concentration ratios from 0.5 to 5.0 hours in trough session methadone patients (open squares), peak session methadone patients (filled squares) and matched controls (open circles).



3.3.2 Plasma methadone concentrations

Mean ($\pm$ SEM) plasma (-)-(R)- and (+)-(S)- methadone concentrations (0-5 hours) are shown in Figure 3.5. The range of mean ($\pm$ SEM) plasma (-)-(R)- and (+)-(S)- methadone concentrations during the 2 hour period of morphine administration in the trough methadone session was 164 ($\pm$ 55) to 178 ($\pm$ 63) ng/mL (absolute range 64 to 303 ng/mL) for the (-)-(R)- enantiomer, and 204 ($\pm$ 78) to 229 ($\pm$ 86) ng/mL (absolute range 60 to 390 ng/mL) for the (+)-(S)- enantiomer. In the peak methadone session, mean plasma concentrations ranged from 277 ($\pm$ 76) to 297 ($\pm$ 81) ng/mL (absolute range 134 to 492 ng/mL) for the (-)-(R)- enantiomer, and from 396 ($\pm$ 129) to 419 ($\pm$ 132) ng/mL (absolute range 163 to 706 ng/mL) for the (+)-(S)- enantiomer.

Figure 3.5. Mean ($\pm$ SEM) plasma (-)-(R)-methadone (open squares) and (+)-(S)-methadone (filled squares) concentrations (0-5 hours). Panel A: trough methadone session; arrow indicates when due dose of methadone was administered. Panel B: peak methadone session (methadone was administered 2 hours before 0 hour). Grey shaded area represents the period when morphine was administered.



3.3.3 Cold Pressor Test

3.3.3.1 Pain detection

Mean ($\pm$ SEM) pain detection responses (0 to 7 h) are summarised in Table 3.2, and are also graphically illustrated in Figure 3.6. Comparing the pain detection values of methadone (trough session) patients with controls', there was a main effect of group ($F(1,6)=15.24$; $p=0.008$); specifically, methadone patients' pain detection values were significantly lower at 0.5, 1.5 and 3.0 hours. There was also a main effect of time ($F(2.3,13.6)=12.6$; $p=0.001$), and significant interaction between group and time ($F(2.3,13.6)=p=0.027$), with control subjects pain detection values significantly changing across time. Compared with baseline values, control subjects' pain detection values were significantly higher ($p=0.001$, [95%CI, 2.6,4.4]) at 3 hours only.

There were no significant differences in pain detection values between methadone (peak session) patients and control subjects ($F(1,6)=5.6$; $p=0.055$). However, there was a main effect of time for pain detection values ($F(2.6,15.8)=17.25$; $p<0.0005$), and a significant interaction between group and time ($F(2.6,33.8)=6.6$; $p=0.005$), with control subjects pain detection values significantly changing across time as outlined above.

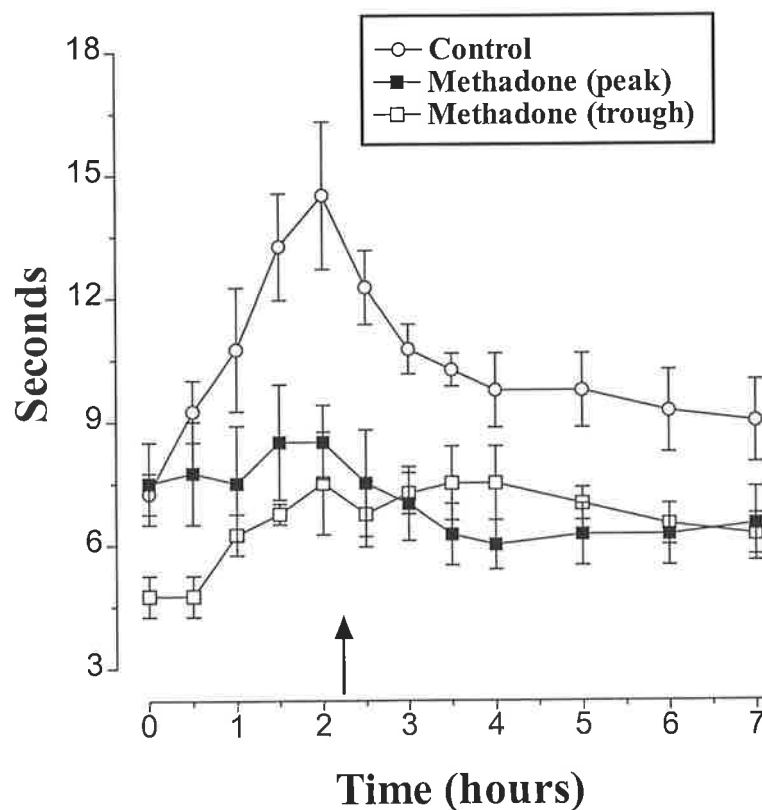
Within-group (trough vs. peak methadone) comparisons revealed that at trough plasma methadone concentrations, patients' pain detection values were not significantly different from those at peak plasma methadone concentrations at any time point ($p>0.021$).

Table 3.2. Comparison of mean ($\pm$ SEM) pain detection values (seconds) for the cold pressor test amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	4.75 (0.5)	7.5 (1.0)	7.25 (0.5)	*p=0.010, #p=0.834, +p=0.022
0.5 h	4.75 (0.5)	7.75 (1.3)	9.25 (0.8)	* p=0.002 , #p=0.343, +p=0.035
1.0 h	6.25 (0.5)	7.5 (1.4)	10.75 (1.5)	*p=0.028, #p=0.169, +p=0.431
1.5 h	6.75 (0.3)	8.5 (1.4)	13.25 (1.3)	* p=0.003 , #p=0.051, +p=0.310
2.0 h	7.5 (1.3)	8.5 (1.0)	14.5 (1.8)	*p=0.020, #p=0.028, +p=0.530
2.5 h	6.75 (0.9)	7.5 (1.3)	12.25 (0.9)	*p=0.005, #p=0.027, +p=0.650
3.0 h	7.25 (0.5)	7.0 (0.9)	10.75 (0.6)	* p=0.004 , #p=0.015, +p=0.718
4.0 h	7.5 (1.0)	6.0 (0.6)	9.75 (0.9)	*p=0.130, #p=0.011, +p=0.058
5.0 h	7.0 (0.4)	6.25 (0.8)	9.75 (0.9)	*p=0.027, #p=0.022, +p=0.215
6.0 h	6.5 (0.5)	6.25 (0.8)	9.25 (1.0)	*p=0.053, #p=0.057, +p=0.718
7.0 h	6.25 (0.5)	6.5 (1.0)	9.0 (1.1)	*p=0.059, #p=0.134, +p=0.789

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 3.6. Mean ($\pm$ SEM) pain detection responses (measured in seconds) from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.



Mean ($\pm$ SEM) pain tolerance values (0 to 7 h) are outlined in Table 3.3, and are also graphically illustrated in Figure 3.7. Comparing pain tolerance values of methadone (trough session) patients with controls', there was a main effect of group ($F(1,6)=46.2$; $p<0.0005$); specifically, methadone patients' pain tolerance values were significantly lower than those of control subjects at every time point except 6.0 and 7.0 hours. There was a main effect of time ($F(1.8,10.8)=31.2$; $p<0.0005$), and significant interaction between group and time ($F(1.8,10.8)=22.4$; $p<0.0005$), with control subjects pain tolerance values significantly changing across time. Compared with baseline values, control subjects' pain tolerance values were significantly higher at 1.5 ($p=0.005$, [95%CI, 30.1,74.4]) and 2.0 hours ($p=0.004$, [95%CI,36,82]).

Similarly, comparing pain tolerance values of methadone (peak session) patients with controls', there was a main effect of group $F(1,6)=55.22$; $p<0.0005$): specifically, methadone patients' pain tolerance values were significantly lower than those of controls at every time point. There was also a main effect of time ($F(2,12.1)=37.82$; $p<0.0005$), and significant interaction between group and time ($F(2,12.1)=17.28$; $p<0.0005$), with control subjects pain tolerance values significantly changing across time as outlined above.

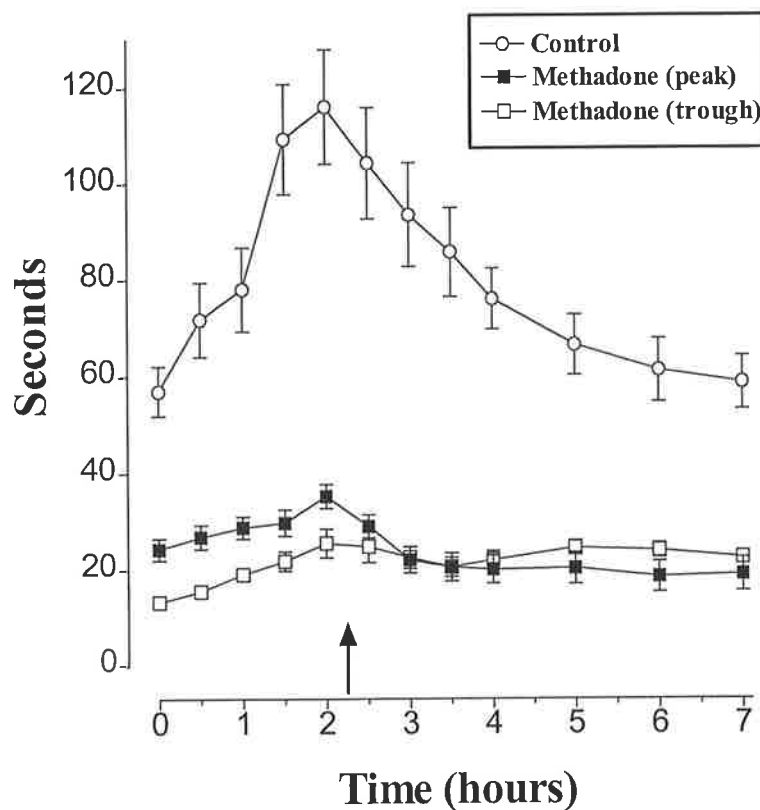
Within-group comparisons (trough versus peak methadone) revealed that trough pain tolerance values were not significantly different from those during the peak session at any time point ($p>0.006$).

Table 3.3. Comparison of mean ($\pm$ SEM) pain tolerance values (seconds) for the cold pressor test amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	13.3 (1.1)	24.3 (2.3)	57 (5.1)	*p<0.0005 , #p=0.001,+p=0.009
0.5 h	15.5 (1.2)	26.8 (2.5)	71.8 (7.7)	*p<0.0005 , #p=0.001,+p=0.012
1.0 h	19 (1.1)	28.8 (2.3)	78 (8.7)	*p=0.001 , #p=0.002,+p=0.014
1.5 h	21.8 (2.0)	29.8 (2.8)	109 (11)	*p<0.0005 , #p=0.001,+p=0.007
2.0 h	25.5 (3.0)	35.3 (2.5)	116 (12)	*p<0.0005 , #p=0.001,+p=0.045
2.5 h	24.8 (3.3)	29 (2.5)	104 (11.5)	*p=0.001 , #p=0.001,+p=0.424
3.0 h	22.5 (2.3)	22 (2.7)	93.5 (11)	*p=0.001 , #p=0.001, +p=0.495
4.0 h	22 (1.8)	20 (2.9)	76 (6.5)	*p<0.0005 , #p<0.0005, +p=0.182
5.0 h	24.5 (1.5)	20.3 (3.4)	66.5 (6.3)	*p=0.001 , #p=0.001, +p=0.260
6.0 h	24 (1.5)	18.5 (3.2)	61.3 (6.5)	*p=0.006 , #p=0.001,+p=0.099
7.0 h	22.3 (1.3)	19 (3.5)	58.8 (5.5)	*p=0.009 , #p=0.001,+p=0.309

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p<0.0045$) this is highlighted in bold text.

Figure 3.7. Mean ($\pm$ SEM) pain tolerance responses (measured in seconds) from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.



Mean ($\pm$ SEM) pain detection responses at baseline, C_{SS1} , and C_{SS2} are outlined in Table 3.4, and are also graphically illustrated in Figure 3.8a. The alpha level was set as $p < 0.05$. For methadone (trough session) patients, there were small but significant increases in pain detection values from baseline to C_{SS1} ($p = 0.014$, [95%CI, 0.3, 1.2]), and from baseline to C_{SS2} ($p = 0.028$, [95%CI, 0.5, 4.2]). For methadone (peak session) patients, there were small but significant increases in pain detection values from baseline to C_{SS2} ($p = 0.016$, [95%CI, 0.4, 1.7]) only. For control subjects, there were significant increases in pain detection values from baseline to C_{SS1} ($p = 0.035$, [95%CI, 0.4, 5.1]), baseline to C_{SS2} ($p = 0.016$, [95%CI, 2.4, 10.9]), and also from C_{SS1} to C_{SS2} ($p = 0.008$, [95%CI, 1.9, 5.9]).

Mean ($\pm$ SEM) pain tolerance responses at baseline, C_{SS1} , and C_{SS2} are outlined in Table 3.5, and are also graphically illustrated in Figure 3.8b. For methadone (trough session) patients, there were small but significant increases in pain tolerance values from baseline to C_{SS1} ($p = 0.001$, [95%CI, 2.9, 4.5]), and from baseline to C_{SS2} ($p = 0.016$, [95%CI, 3.7, 17]). Similarly, for methadone (peak session) patients, pain tolerance values increased significantly from baseline to C_{SS1} ($p < 0.0005$, [95%CI, 2.9, 4.2]), and from baseline to C_{SS2} ($p = 0.010$, [95%CI, 3.7, 12.8]). For control subjects, there were marked and significant increases in pain tolerance values from baseline to C_{SS1} ($p = 0.012$, [95%CI, 7.4, 28.3]), baseline to C_{SS2} ($p = 0.004$, [95%CI, 33.2, 78.1]), and C_{SS1} to C_{SS2} ($p = 0.003$, [95%CI, 23.7, 51.8]).

Table 3.4 Comparison of mean ($\pm$ SEM) pain detection responses (seconds) for the cold pressor test at baseline, C_{SS1} , and C_{SS2} amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

	0 h	C_{SS1}	C_{SS2}	
Methadone (trough)	4.75 (0.5)	5.5 (0.5)	7.1 (0.6)	* $p=0.014$,# $p=0.028$
Methadone (peak)	7.5 (1.0)	7.6 (1.3)	8.5 (1.2)	,# $p=0.016$
Controls	7.25 (0.5)	10 (1.1)	13.9 (1.6)	* $p=0.035$,# $p=0.016$,+ $p=0.008$

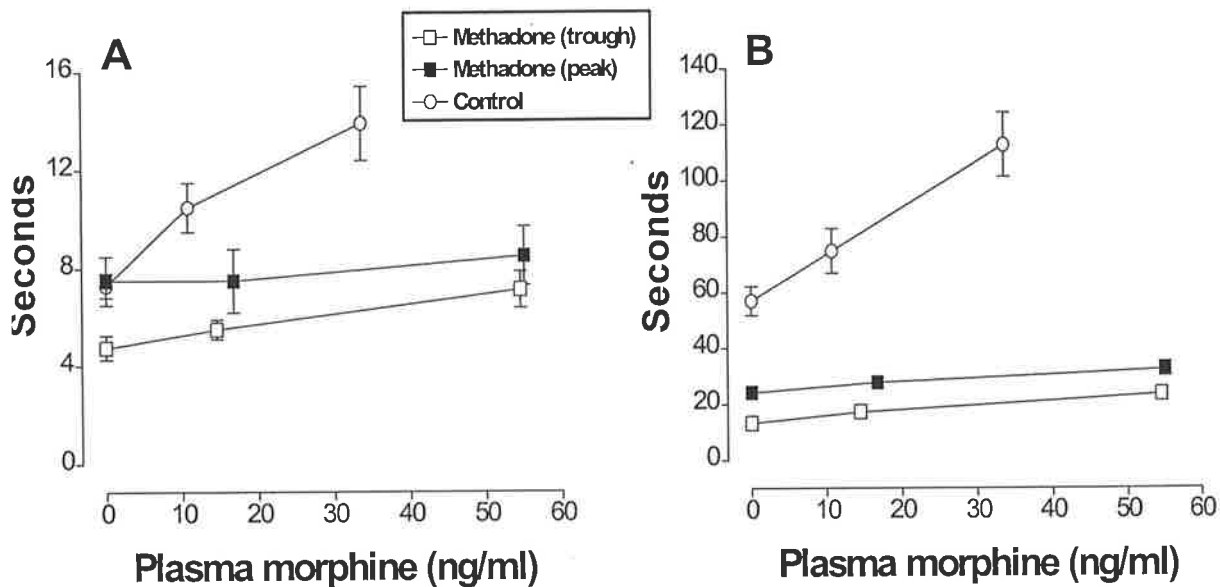
* denotes 0 h vs. C_{SS1} , # denotes 0 h vs. C_{SS2} , + denotes C_{SS1} vs. C_{SS2}

Table 3.5 Comparison of mean ($\pm$ SEM) pain tolerance responses (seconds) for the cold pressor test at baseline, C_{SS1} , and C_{SS2} amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

	0 h	C_{SS1}	C_{SS2}	
Methadone (trough)	13.25 (1.1)	17 (1.0)	23.6 (2.5)	* $p=0.001$,# $p=0.016$
Methadone (peak)	24.25 (2.3)	27.75 (2.4)	32.5 (2.6)	* $p<0.0005$ # $p=0.010$
Controls	57 (5.1)	74.9 (8.2)	112.6 (11.8)	* $p=0.012$,# $p=0.004$, + $p=0.003$

* denotes 0 h vs. C_{SS1} , # denotes 0 h vs. C_{SS2} , + denotes C_{SS1} vs. C_{SS2}

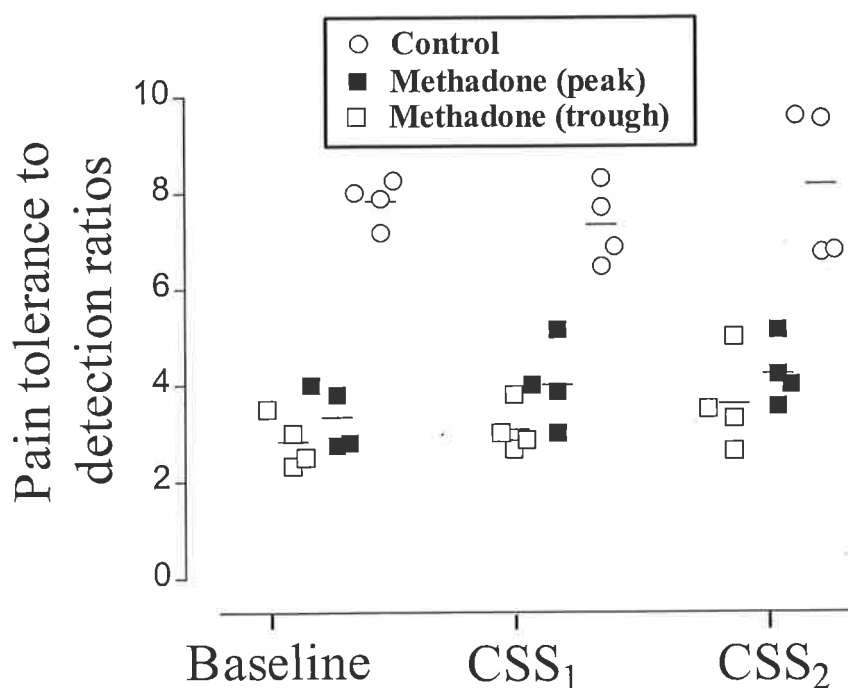
Figure 3.8. Mean ($\pm$ SEM) pain responses (measured in seconds) relative to steady-state plasma morphine concentrations of methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Panel A: pain detection. Panel B: pain tolerance.



3.3.3.4 Pain tolerance to detection ratios

Pain tolerance to detection ratios (methadone patients versus controls) were calculated from data collected prior to morphine administration (baseline), and at C_{SS1} and C_{SS2} (see Figure 3.9). The alpha level for these comparisons was set at $p < 0.05$. For methadone (trough) patients, the ratios were significantly lower than those of controls at baseline ($p = 0.003$, [95%CI, -6.9,-2.2]), C_{SS1} ($p < 0.0005$, [95%CI, -5.4,-3.1]), and C_{SS2} ($p < 0.0005$, [95%CI, -5.9,-4.1]). Methadone (peak) patients' ratios remained significantly lower than those of controls at baseline ($p < 0.0005$, [95%CI, -5.5,-3.5]), C_{SS1} ($p = 0.004$, [95%CI, -4.9,-1.5]), and C_{SS2} ($p = 0.011$, [95%CI, -6.3,-1.5]). Within group comparisons (trough vs. peak methadone) did not reveal any significant differences ($p > 0.209$) in the ratios.

Figure 3.9. Pain tolerance to pain detection ratios at pre-morphine administration (baseline), first pseudo steady state plasma morphine concentrations (C_{SS1}), and at second pseudo steady-state plasma morphine concentrations (C_{SS2}). Methadone patients at the trough session (open squares), peak session (filled squares), and matched controls (open circles).



To ascertain duration of analgesic effect after morphine administration had ceased, post-infusion pain tolerance values (ie. from 3 to 5 hours) were compared to baseline (pre-morphine administration) values. The alpha level for these comparisons was set at $p < 0.05$. Control subjects' pain tolerance values were significantly ($p < 0.020$) higher than baseline values for a period of 3 hours post-infusion. Comparing baseline pain tolerance values of the methadone (trough session) patients with those post-infusion was difficult to interpret due to the fact that the patients received their daily dose of methadone 15 minutes after the morphine infusion had ceased. However, the post-infusion pain tolerance values of the methadone (peak session) patients did not significantly ($p > 0.273$) differ from those at baseline at any time point.

3.3.4 Electrical Stimulation

3.3.4.1 Pain detection

Mean ($\pm$ SEM) pain detection values (0 to 7 h) are outlined in Table 3.6, and are also graphically illustrated in Figure 3.10. There were no significant differences for pain detection values between methadone (trough session) patients and control subjects ($F(1,6)=0.7$; $p=0.799$). However, there was a main effect of time ($F(3.1,18.5)=14.2$; $p < 0.0005$), and a significant interaction between group and time ($F(3.1,18.5)=4$; $p=0.023$), with control subjects pain detection values significantly changing across time. Compared with baseline values, control subjects' pain detection values were significantly higher at 0.5 ($p=0.002$, [95%CI, 3.9, 7.1]), 1.0 ($p=0.002$, [95%CI, 5.4, 10.6]), and 3.0 hours ($p=0.002$, [95%CI, 5.4, 10.6]).

There were no significant differences for pain detection values between methadone (peak session) patients and control subjects ($F(1,6)=0.4$; $p=0.565$). There was a main effect of time ($F(1.8,10.8)=13.8$; $p=0.001$), but no significant interaction between group and time ($F(1.8, 10.7)=1.5$; $p=0.264$).

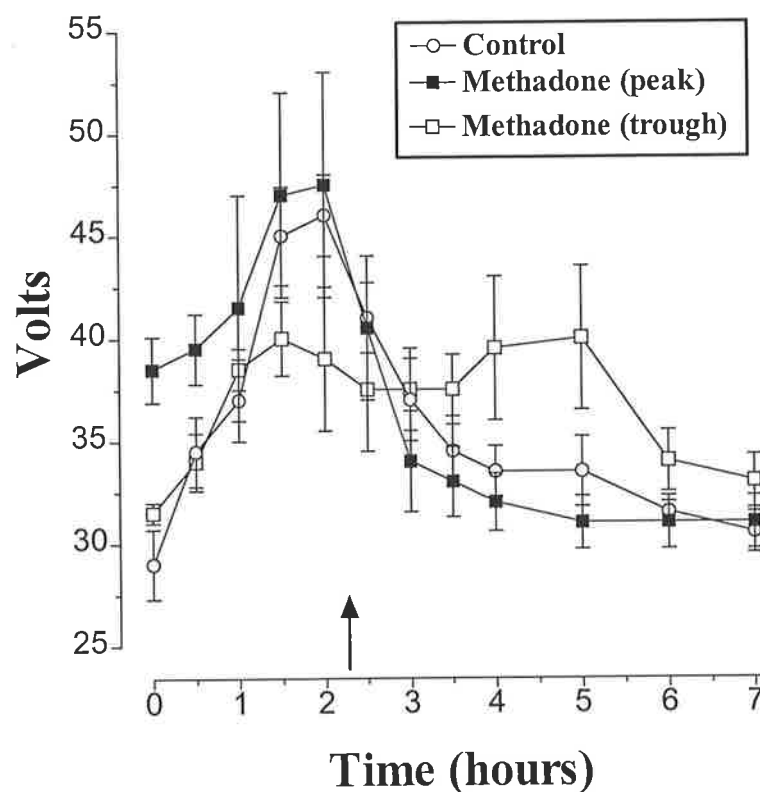
Within-group (trough vs. peak methadone) comparisons did not reveal any significant differences at any time point ($p > 0.014$).

Table 3.6. Comparison of mean ($\pm$ SEM) pain detection values (volts) for electrical stimulation amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	31.5 (0.5)	38.5 (1.5)	29 (1.7)	*p=0.215, #p=0.006,+p=0.027
0.5 h	34 (1.4)	39.5 (1.7)	34.5 (1.7)	*p=0.829, #p=0.084,+p=0.089
1.0 h	38.5 (1.0)	41.5 (5.6)	37 (1.9)	*p=0.510, #p=0.477,+p=0.595
1.5 h	40 (1.8)	47 (5.0)	45 (2.4)	*p=0.147, #p=0.733,+p=0.213
2.0 h	39 (3.5)	47.5 (5.6)	46 (2.0)	*p=0.147, #p=0.810,+p=0.246
2.5 h	37.5 (3.1)	40.5 (3.4)	41 (1.7)	*p=0.362, #p=0.900,+p=0.604
3.0 h	37.5 (2.2)	34 (2.4)	37 (1.3)	*p=0.852, #p=0.320,+p=0.402
4.0 h	39.5 (3.5)	32 (1.4)	33.5 (1.3)	*p=0.158, #p=0.458,+p=0.094
5.0 h	40 (3.7)	31 (1.3)	33.5 (1.7)	*p=0.158, #p=0.257, +p=0.042
6.0 h	34 (1.4)	31 (1.3)	31.5 (0.5)	*p=0.147, #p=0.730,+p=0.014
7.0 h	33 (1.3)	31 (1.3)	30.5 (1.0)	*p=0.171, #p=0.766,+p=0.092

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 3.10. Mean ($\pm$ SEM) pain detection responses (measured in volts) from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.



3.3.4.2 Pain tolerance

Mean ($\pm$ SEM) pain tolerance values (0 to 7 h) are summarised in Table 3.7, and are also graphically illustrated in Figure 3.11. There were no significant differences for pain tolerance values between methadone (trough session) patients and control subjects ($F(1,6)=1.6$; $p=0.255$). However, there was a main effect of time ($F(2.8,17)=16.1$; $p<0.0005$), and a significant interaction between group and time ($F(2.8,17)=10.2$; $p=0.001$); with control subjects pain tolerance values significantly changing across time. Compared with baseline values, control subjects' pain tolerance values were significantly higher at 1.5 ($p=0.002$, [95%CI, 24.8,48.2]), and 2.0 hours ($p=0.001$, [95%CI, 32.5,48.5]).

There were no significant differences for pain tolerance values between methadone (peak session) patients and control subjects ($F(1,6)=1.7$; $p=0.243$). However, there was a main effect of time ($F(2.7,16.4)=31.6$; $p<0.001$), and a significant interaction between group and time ($F(2.7,16.4)=5$; $p=0.014$), with control subjects pain tolerance values significantly changing across time as outlined above.

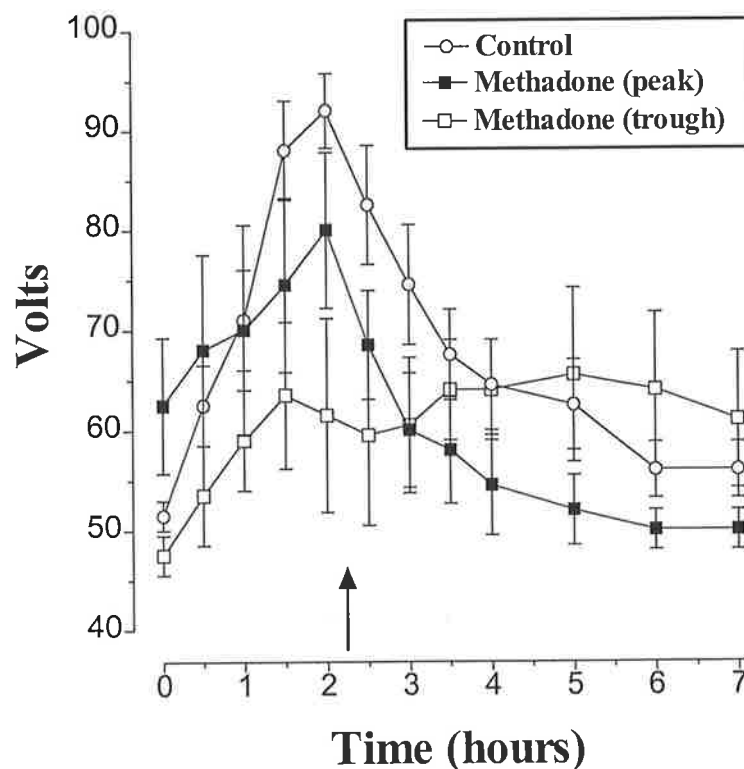
Within-group (trough vs. peak methadone) comparisons did not reveal significant differences at any time ($p>0.034$).

Table 3.7. Comparison of mean ($\pm$ SEM) pain tolerance values (volts) for electrical stimulation amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	47.5 (2.0)	62.5 (6.8)	51.5 (1.5)	*p=0.168, #p=0.238,+p=0.052
0.5 h	53.5 (5.0)	68 (9.5)	62.5 (4.3)	*p=0.220, #p=0.615,+p=0.052
1.0 h	59 (5.0)	70 (10.4)	71 (5.0)	*p=0.145, #p=0.934,+p=0.137
1.5 h	63.5 (7.3)	74.5 (8.7)	88 (5.0)	*p=0.032, #p=0.229,+p=0.093
2.0 h	61.5 (9.7)	78 (7.9)	92 (3.8)	*p=0.026, #p=0.159,+p=0.124
2.5 h	59.5 (9.2)	66.5 (5.4)	82.5 (6.0)	*p=0.083, #p=0.097,+p=0.326
3.0 h	60.5 (6.8)	58 (5.7)	74.5 (6.0)	*p=0.173, #p=0.094,+p=0.713
4.0 h	64 (5.0)	50.5 (5.0)	64.5 (4.5)	*p=0.944, #p=0.086,+p=0.141
5.0 h	65.5 (8.7)	46 (3.5)	62.5 (4.5)	*p=0.769, #p=0.027, +p=0.034
6.0 h	64 (7.7)	44.5 (2.1)	56 (2.8)	*p=0.367, #p=0.017,+p=0.041
7.0 h	61 (6.8)	44.5 (1.9)	56 (2.8)	*p=0.523, #p=0.015,+p=0.049

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 3.11. Mean ($\pm$ SEM) pain tolerance responses (measured in volts) from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.



3.3.4.3 Plasma morphine concentrations and responses

Mean ($\pm$ SEM) pain detection responses at baseline, C_{SS1} , and C_{SS2} are outlined in Table 3.8, and are also graphically illustrated in Figure 3.12a. The alpha level was set as $p < 0.05$. For methadone (trough session) patients, there were small but significant increases in pain detection values from baseline to C_{SS1} ($p = 0.019$, [95%CI, 1.5, 8.0]), and from baseline to C_{SS2} ($p = 0.044$, [95%CI, 0.4, 15.6]). In contrast for methadone (peak session) patients, there were no significant ($p > 0.153$) changes in pain detection values in relation to increasing plasma morphine concentrations. Conversely, for controls, pain detection values increased significantly from baseline to C_{SS1} ($p = 0.002$, [95%CI, 4.8, 8.8]), baseline to C_{SS2} ($p = 0.013$, [95%CI, 6.7, 26.3]), and from C_{SS1} to C_{SS2} ($p = 0.036$, [95%CI, 1.2, 18.3]).

Mean ($\pm$ SEM) pain tolerance responses at baseline, C_{SS1} , and C_{SS2} are outlined in Table 3.9, and are also graphically illustrated in Figure 3.12b. The alpha level was set as $p < 0.05$.

Pain tolerance values for methadone (trough and peak session) patients did not significantly change with the increasing plasma morphine concentrations ($p > 0.083$ and $p > 0.092$, respectively). In contrast, for control subjects there were significant increases in pain tolerance values from baseline to C_{SS1} ($p = 0.017$, [95%CI, 5.2, 25.3]), baseline to C_{SS2} ($p = 0.001$, [95%CI, 28.7, 48.3]), and from C_{SS1} to C_{SS2} ($p < 0.0005$, [95%CI, 20, 26.5]).

Table 3.8 Within group comparison of mean ($\pm$ SEM) pain detection responses (volts) for electrical stimulation at baseline (0 h), C_{SS1} , and C_{SS2} amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

	0 h	C_{SS1}	C_{SS2}	
Methadone (trough)	31.5 (0.5)	36.25 (0.5)	39.5 (2.6)	*p=0.019, #p=0.044
Methadone (peak)	38.5 (1.5)	40.5 (1.3)	47.25 (1.2)	
Controls	29(1.7)	35.75 (1.8)	45.5 (1.6)	*p=0.002, #p=0.013, +p=0.036

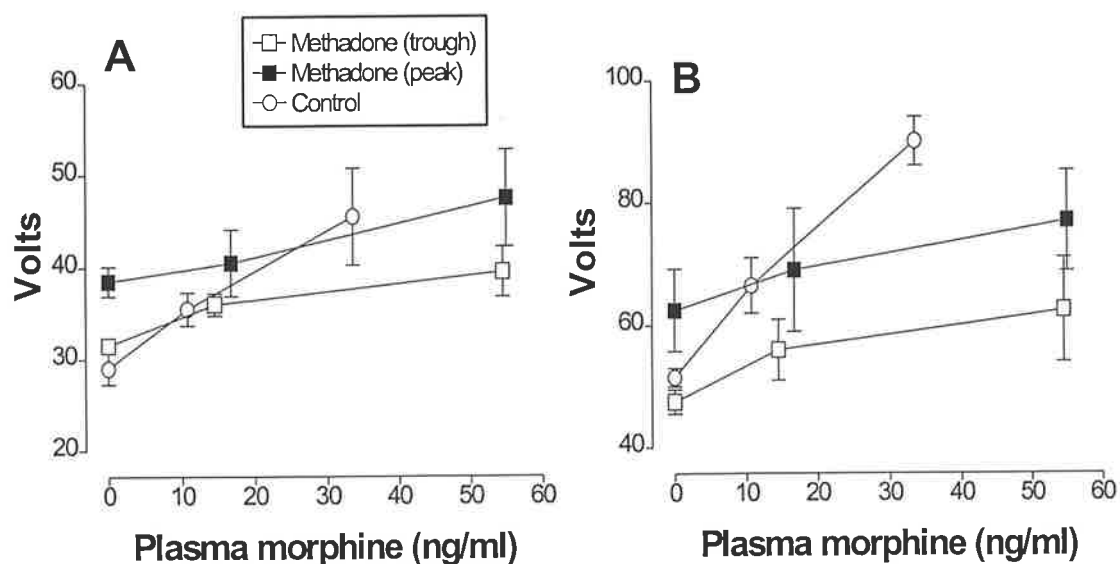
* denotes 0 h vs. C_{SS1} , # denotes 0 h vs. C_{SS2} , + denotes C_{SS1} vs. C_{SS2}

Table 3.9 Comparison of mean ($\pm$ SEM) pain tolerance responses (volts) for electrical stimulation at baseline (0 h), C_{SS1} , and C_{SS2} amongst methadone (trough) patients, methadone (peak) patients, and control subjects.

	0 h	C_{SS1}	C_{SS2}	
Methadone (trough)	47.5 (2.1)	56.25 (5.1)	62.5 (8.5)	*p=0.017, #p=0.001, +p<0.0005
Methadone (peak)	62.5 (6.8)	69 (9.8)	76.25 (8.3)	
Controls	51.5 (1.5)	67.75 (4.6)	90 (4.4)	

* denotes 0 h vs. C_{SS1} , # denotes 0 h vs. C_{SS2} , + denotes C_{SS1} vs. C_{SS2}

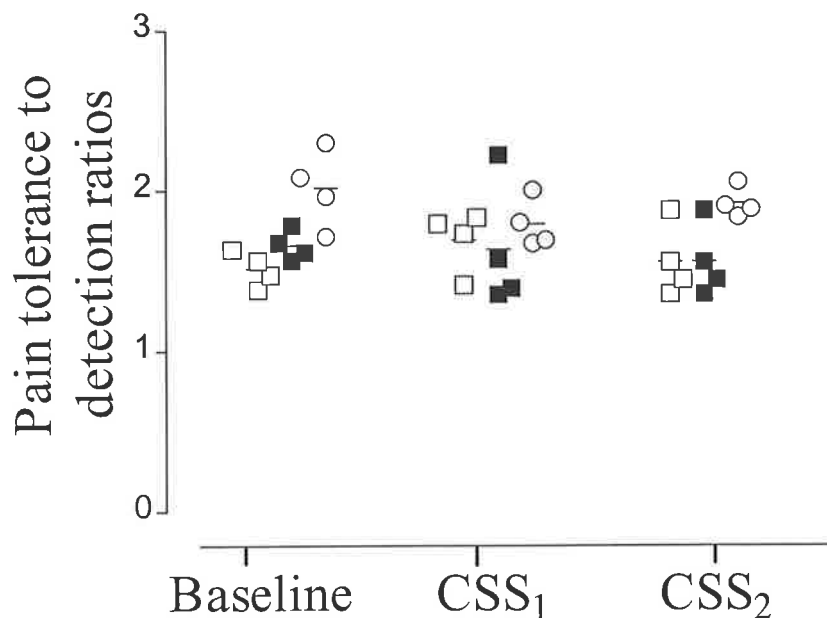
Figure 3.12. Mean (SEM) pain responses (measured in volts) relative to steady-state plasma morphine concentrations of methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Panel A: pain detection. Panel B: pain tolerance.



3.3.4.4 Pain tolerance to detection ratios

Pain tolerance to detection ratios (methadone patients versus controls) were calculated from data collected prior to morphine administration (baseline), and at C_{SS1} and C_{SS2} (see Figure 3.13). The alpha level for these comparisons was set at $p < 0.05$. For methadone (trough) patients, the ratios were significantly lower than controls' at baseline ($p = 0.024$, [95%CI, -0.5, -0.1]), C_{SS1} ($p = 0.017$, [95%CI, -0.7, -0.1]), and C_{SS2} ($p = 0.033$, [95%CI, -0.9, -0.5]) respectively. Ratios were also compared between methadone (peak) patients and controls, there were no significant ($p > 0.98$) differences at baseline and C_{SS1} . At C_{SS2} , methadone (peak) patients' ratios were significantly lower than those of controls ($p = 0.035$, [95%CI, -0.7, -0.3]). Within group comparisons (trough vs. peak) did not reveal any significant differences ($p > 0.217$) in the ratios.

Figure 3.13. Pain tolerance to pain detection ratios at pre-morphine administration (baseline), first pseudo steady state plasma morphine concentrations (C_{SS1}), and at second pseudo steady-state plasma morphine concentrations (C_{SS2}). Methadone patients at the trough session (open squares), peak session (filled squares), and matched controls (open circles).



3.3.4.5 Duration of effect post-infusion

To ascertain duration of analgesic effect after morphine administration had ceased, post-infusion pain tolerance values (ie. from 2.5 h to 5 hours) were compared to baseline (pre-morphine administration) values. The alpha level for these comparisons was set at $p < 0.05$. Control subjects' pain tolerance values were significantly ($p < 0.032$) higher than baseline values for a period of 2 hours post-infusion. Comparing baseline pain tolerance values of the methadone (trough session) patients with those post-infusion was difficult to interpret due to the fact that the patients received their daily dose of methadone 15 minutes after the morphine infusion had ceased. However, the post-infusion pain tolerance values of the methadone (peak session) patients did not significantly ($p > 0.434$) differ from those at baseline at any time point.

3.4 Adverse events

All control subjects experienced mild nausea for very brief periods (< 20 minutes) during the morphine infusion. Two control subjects vomited 3-5 hours after the infusion had ceased. All control subjects completed testing. None of the methadone patients experienced any adverse events.

3.5 Discussion

This study sought to compare the intensity and duration of the antinociceptive effects of morphine at two target controlled plasma concentrations in a sample of methadone maintenance patients and matched controls. Furthermore, in methadone patients, I set out to determine if the antinociceptive effects of morphine are affected by changes in plasma methadone concentrations that occur during an inter-dosing interval. Despite significantly greater plasma morphine concentrations, methadone patients experienced minimal if any antinociception in comparison with control subjects in relation to the cold pressor test. Furthermore, in methadone (peak session) patients the antinociception ceased when the infusion ended, but in methadone (trough session) patients, the small degree of post-infusion antinociception was probably due to increasing plasma (-)-(R)-methadone concentrations. In comparison, the duration of effect in all of the control subjects was 3 hours. In methadone patients, the antinociceptive effects of morphine were not significantly affected by either of the two extremes of plasma methadone concentration (trough and peak).

3.5.1 Antinociceptive effects of morphine

There were marked differences in responses between methadone patients and controls using the cold pressor test but not with electrical stimulation. The most pronounced difference was observed for pain tolerance, with methadone patients exhibiting hyperalgesic responses, as has been reported in the preceding chapter. Pain tolerance to pain detection ratios in the methadone patients, for the cold pressor test, were also markedly lower than the controls, as reported in the preceding chapter.

The method of morphine administration was adapted from that of Hill *et al.* (1990). This method facilitates the achievement of target controlled plasma drug concentrations. The dosing regimen was aimed to achieve plasma morphine concentrations of 20ng/mL and 80ng/mL (methadone patients), and 20ng/mL and 60ng/mL (control subjects). These concentrations were chosen based on evidence that a plasma morphine concentration of approximately 15ng/mL is adequate for minimum effective post-surgical analgesia (Dahlström *et al.*, 1982; Gourlay *et al.*, 1986) and that plasma morphine concentrations in the region of 50ng/mL provide analgesia for moderate to severe post-surgical pain (Berkowitz *et al.*, 1975). Control subjects achieved 55% of the target plasma concentrations and methadone patients achieved 70-80%. I am unable to explain why the target concentrations were not achieved in control subjects or methadone patients. Perhaps future studies should consider using a computer-controlled infusion design. This method of drug administration has been used successfully in other studies (Bowdle *et al.*, 1998; Hill *et al.*, 1990; Kerr *et al.*, 1991; Leung *et al.*, 2001; Persson *et al.*, 1999). Individually tailored computer-controlled infusion models use a bolus-elimination transfer (BET) algorithm to facilitate achievement of target concentrations (Schuttler *et al.*, 1988; Glass *et al.*, 1990; Shafer *et al.*, 1990). Specifically, after administration of a loading dose (bolus), the computer-controlled infusion pump delivers the additional drugs at exponentially declining rates calculated to balance drug loss from the central compartment to tissue, and hepatic, renal and other elimination processes. Such a model requires each subject to undergo a pre-study pharmacokinetic tailoring session to determine their specific drug pharmacokinetics to be used in the study (Hill *et al.*, 1990). The infusion model in the present study did not specifically adjust drug dose in relation to the varying pharmacokinetic parameters and weights of patients and control subjects. This may explain why actual concentrations were considerably lower than the target concentrations. I would recommend that individual pharmacokinetic tailoring and use of a computer-controlled infusion pump are used in future studies investigating concentration-response relationships.

In control subjects, mean plasma morphine concentrations of 11 and 33ng/mL significantly and substantially increased the antinociceptive responses. At 33ng/mL, the cold pressor response increased by over 100% indicating the sensitivity of the cold pressor test to respond to morphine. However, at these and higher plasma morphine concentrations, morphine was ineffective in altering the response to this test in methadone patients. This indicates that methadone patients are cross-tolerant to the antinociceptive effects of morphine at plasma concentrations known to produce analgesia in opioid-naïve patients in acute pain. To my knowledge, this is the first such report involving humans. Similar results, as reflected by flat log dose-response curves, were reported in rats receiving chronic high dose morphine administration (Mucha *et al.*, 1978; Mucha *et al.*, 1979; Mucha & Kalant, 1980).

The M3G: M6G ratio of methadone patients and control subjects (approximately 5:1 and approximately 4:1, respectively) is comparable with those outlined in previous reports in healthy subjects and non-addict patients (Osborne *et al.*, 1990; Milne *et al.*, 1992; Westerling *et al.*, 1995). Therefore, whilst the M3G: M6G ratio of methadone patients in the present study was slightly higher than that of healthy control subjects, the data were obtained from a small sample. Thus, it is difficult to definitively state that methadone patients appear to be experiencing altered morphine metabolism compared with control subjects. Further, and more detailed pharmacokinetic studies should be considered to investigate the effects of chronic methadone treatment on morphine metabolism and clearance.

A possible criticism of the current study is that because no placebo was used, the time-related effects may represent a placebo reaction to the systemic administration of morphine. I would speculate that a placebo effect is not likely to be a significant factor in this scheme of measurements. In addition, I would suggest that volunteer control subjects, unlike patients who are seeking relief of pain, have no incentive to endure pain any longer than is tolerable. Another possible criticism of the present study is that the number of subjects is small. Whilst acknowledging this, there were very significant differences in response to morphine administration between methadone patients and the control group. Hence, in light of the clear difference in analgesic response between the groups, further experimentation exposing more control subjects to intravenous morphine may have been unethical. Nonetheless, it would be valuable to replicate and extend this experiment on larger numbers of methadone maintenance patients.

Data from the current study concur with previous reports (Dyer *et al.*, 1999) that there is a small increase in antinociception from trough to peak plasma methadone concentrations that occurs during a methadone inter-dosing interval. Furthermore, the increases in the plasma concentrations of the pharmacologically active (-)-(R)-methadone from trough to peak in my subjects are similar to those earlier reports (Dyer *et al.*, 1999; Foster *et al.*, 2000), and in the preceding chapter. In addition, in the present study, the peak to trough plasma concentration ratio of (-)-(R)-methadone was approximately 80% of that obtained for (+)-(S)-methadone. This is very similar to that reported by Foster *et al.* (2000), and is also consistent with results reported in the preceding chapter. In methadone patients, although there were small baseline differences in nociceptive values between trough and peak methadone concentrations, there was virtually no difference in the antinociceptive response to morphine at either extreme of the plasma (-)-(R)-methadone concentration within the inter-dosing interval.

The finding that methadone patients are hyperalgesic to pain induced by a cold pressor test but not to electrical stimulation supports results from the preceding chapter. There was a three to four-fold difference in pain tolerance values between methadone patients and control subjects during the period of morphine administration. The methods of pain induction used in the present study have been demonstrated to be sensitive to the administration of opioid drugs (Wolff *et al.*, 1966; Ho & Dole, 1979; Posner *et al.*, 1985; Jones *et al.*, 1988; Compton, 1994; Dyer *et al.*, 1999). Both models of pain induction were shown to be sensitive to morphine administration in the present study. However, methadone patients clearly remained hyperalgesic to pain induced by the cold pressor test despite the addition of analgesic plasma concentrations of morphine. Similar to the results in this study albeit in an animal model, others have shown that cold hyperalgesia, is relatively resistant to morphine (Jasmin *et al.*, 1998). Further, as I pointed out in the preceding chapter, cold hyperalgesia is a phenomenon that is present after chronic nerve injury (Fruhstorfer & Lindblom, 1984; Frost *et al.*, 1998; Ochoa & Yarnitsky, 1994), and is frequently encountered in central pain syndromes that follow thalamic infarction (Craig *et al.*, 1994; Vestergaard *et al.*, 1995). Once again I would speculate that the central plasticity that occurs with chronic opioid treatment, such as those changes involved in opioid tolerance, may be responsible for methadone patients' hyperalgesic responses to pain induced by a cold pressor test. Undoubtedly further research is needed.

I reported in the preceding chapter that for the cold pressor test a low pain tolerance to detection ratio may be a marker of hyperalgesia in methadone patients. The present study confirms this ratio as being a sensitive marker of hyperalgesia. In addition, the ratio does not appear to be influenced by the magnitude of the plasma morphine concentration in each group of tested subjects. Further research in populations maintained on opioids other than methadone is necessary to determine the validity of this ratio as a marker of hyperalgesia.

These findings indicate that methadone patients are cross-tolerant to the antinociceptive effects of morphine at plasma concentrations which have previously been reported as being adequate for minimal to severe post-surgical pain relief (Dahlström *et al.*, 1982; Gourlay *et al.*, 1986; Berkowitz *et al.*, 1975). Clinicians are likely to have to prescribe and/or administer morphine at doses that are substantially greater than those generally prescribed for non-tolerant patients for pain control. This should of course be carefully titrated to the needs of each individual.

Portenoy (1990) suggested that absolute tolerance to the analgesic effects of opioids does not occur. Others have proposed that in general, tolerance to the side effects of morphine develops more rapidly than does tolerance to the drug's analgesic effects (Savage, 1998). Savage also added that opioids can therefore be used safely and effectively at very high doses (such as several thousand mg of intravenous morphine per hour) in individuals who have gradually increased their exposure to opioids over a prolonged period of time, with virtually no limiting side-effects. Savage did however caution that all significant increases in dose should be accompanied by careful monitoring for over-sedation and respiratory depression. Portenoy and Payne (1997) reiterated, that in pain management, doses must be titrated according to patient response; adding, that there is no pre-defined appropriate morphine dose range (Portenoy & Payne, 1997; Scimeca *et al.*, 2000).

There is some evidence that non-addict patients with a history of chronic opioid consumption require at least three to four times the dose of morphine given to patients who had not used opioids prior to surgery (de Leon-Casasola *et al.*, 1993; Rapp *et al.*, 1995). It is thus likely that morphine analgesia may not be the most suitable pharmacotherapy for the treatment of acute pain amongst methadone patients. Further research is required to ascertain whether considerably higher doses and plasma concentrations of morphine, or other drugs, such as NMDA-receptor antagonists in combination with opioids, tramadol or non steroidal anti-inflammatory drugs, such as ketorolac, are more effective than morphine in managing acute pain in this patient population.

Portenoy and colleagues (1997) suggested that ignorance and stigma compromise the management of pain amongst patients receiving methadone maintenance therapy. Others have suggested that under-treatment of pain in methadone patients is a serious problem (Payte & Zweben, 1998). We are now in an era where we are guided, in most clinical arenas, by the paradigm of evidence-based medicine. Hopefully the evidence from this study will help inform clinicians that methadone maintenance patients have distinct needs with regard to the management of acute pain. I would suggest that fear and prejudices be cast aside, and that in light of these findings, albeit in a clinical laboratory setting, clinicians should aggressively treat complaints of pain amongst patients in this population. Cousins (2000) pointed out that there is a need for more focus on acute pain, with a general view that relief of acute severe pain is a basic human right. This should be no different for methadone maintenance patients.

It has been suggested that there are fewer adverse sequelae (nausea and vomiting) associated with morphine when the subject is in bed as opposed to when ambulatory (Comroe & Dripps, 1948; Price *et al.*, 1985). These sequelae, which were evident in the healthy volunteers but not in methadone patients in the present experiment, may be related to reflexes in the vestibular apparatus that are activated by changes in body position (supine vs. erect) (Gutner *et al.*, 1952). All subjects in the present study were required to move from a seated position to kneeling on cushions at regular intervals; this movement could well have increased the likelihood and/or exacerbated the nausea and vomiting observed in the control subjects. The incidence of nausea and vomiting seen in the present study is not unusual when administering morphine to healthy (opioid naïve) volunteers (Zacny *et al.*, 1994; 1997). It has been suggested that these phenomena are more likely to occur when doses of morphine higher than 10mg are used (Christie *et al.*, 1958); control subjects in the present study received 12.95 mg over a 2-hour period. In an early randomised placebo controlled study comparing the effects of morphine 20mg (s.c) between 24 male post-addicts (no narcotics in the previous 6 months) and 20 healthy male volunteers, there was a significant incidence of vomiting amongst the control group, with 7 of them vomiting on at least one occasion (Fraser & Isbell, 1952).

3.5.2 Conclusions

In summary, methadone patients are cross-tolerant to the antinociceptive effects of morphine up to plasma concentrations of approximately 60ng/mL. They are hyperalgesic to a cold pressor test but not electrical stimulation. A low pain tolerance to pain detection ratio for the cold pressor test is a sensitive marker of hyperalgesia in this patient population. These findings suggest that plasma morphine concentrations, which have previously been reported as being adequate for minimal to severe post-surgical pain relief, are likely to be ineffective in managing episodes of acute pain amongst this patient group, and that large doses of morphine may be required to manage episodes of severe acute pain amongst individuals maintained on methadone. Further research is urgently needed to determine whether other drugs are more effective than morphine in managing acute pain in this patient population.

PHYSIOLOGICAL EFFECTS OF METHADONE ALONE, AND IN COMBINATION WITH INTRAVENOUS MORPHINE, IN METHADONE MAINTENANCE PATIENTS

4.1 Introduction

In the context of acute pain management of methadone maintenance patients, it is important to remember that when administering additional opioids such as morphine, antinociception is not the only pharmacodynamic effect that occurs. There are a number of other important effects that need to be monitored (as outlined previously in detail in section 1.17). These include respiratory depression (Reisine & Pasternak, 1995), cardiovascular changes (Gritz *et al.*, 1975; Platt, 1988; Rogers & Spector, 1980; Martin, 1984), miosis (Jaffe & Martin, 1992; Reisine & Pasternak, 1995), nausea and vomiting (Foley, 1993; Reisine & Pasternak, 1995), and sedation (Foley, 1993; Macintyre & Ready, 2000).

Furthermore, tolerance to various pharmacodynamic effects occurs at different rates (Ling *et al.*, 1989). This has been termed ‘selective tolerance’ (Taub, 1982). Tolerance to nausea and vomiting, sedation, euphoria and respiratory depression occur rapidly, while tolerance to constipation and miosis is minimal (Light & Torrance, 1929; Kreek, 1973; Bruera *et al.*, 1989; O’Brien, 1996). It has been suggested that tolerance to the various non-analgesic effects of opioids is characterised by large intra-individual and inter-individual variability (Jasinski, 1977; Martin, 1977).

The study in the preceding chapter investigated the antinociceptive effects of plasma morphine concentrations known to produce effective analgesia in opioid-naïve patients. However, little is known about methadone maintenance patients’ physiological and subjective responses to additionally administered opioids such as morphine. Hence, it is of clinical importance to investigate the non-antinociceptive pharmacodynamic effects of morphine in this patient group. In addition, given that physicians may have fears about the abuse potential of prescribing such drugs to this patient group, it is of interest to investigate the subjective effects of additionally administered morphine amongst these patients.

This chapter is divided into two parts: the first part deals with the physiological effects of methadone per se, whereas the second part examines both the physiological and subjective effects of intravenous morphine in a sample of methadone patients and matched control subjects.

4.2 Aims of Study 1

The aims of study 1 were to (i) examine the physiological effects of methadone in methadone maintenance patients by comparison with drug-free age- and sex- matched controls; (ii) determine if physiological responses are different at trough (23.5 hours after the previous dose) and peak (3 hours after the dose) plasma methadone concentrations in methadone patients.

Hypothesis: Increases in plasma methadone concentrations from putative trough to peak will produce significant physiological effects.

4.3 Methods

4.3.1 Patients and control subjects

As described previously in section 2.4.1. (please note that the patients and control subjects in this study are those previously mentioned in chapter 2).

4.3.2 Procedures and measures

As described previously in section 2.4.2, and section 2.5.

4.3.3 Physiological measures

Physiological parameters were measured both at trough (0 hour) and peak (3 hours); these included radial pulse rate, systolic and diastolic blood pressure, respiratory rate, and pupil diameter, and pulse oximetry. All physiological measures were recorded when the subject was sitting in an armchair; the measures are described in greater detail below. All physiological measures were collected within minutes of nociceptive testing (which has been described in chapter 2).

4.3.3.1 Pulse rate

Radial pulse rate was measured manually by me (a registered nurse) at each of the aforementioned time points. Each patient and control subject's pulse rate was measured after a two-minute period of relative rest and relaxation in an armchair.

4.3.3.2 Blood pressure

I measured this manually at each time point, using an aneroid sphygmomanometer. This was measured immediately after the pulse rate.

4.3.3.3 Pupil diameter

The entire study was conducted in conditions of constant lighting (65 lux); all windows were completely covered with 'black out' material to prevent any sunlight from entering the testing room. Pupil measurement was carried out by using a video camera using X2 magnification. Each subject held a ruler (marked in mm) against his or her bottom eyelash, I then commenced a 6 second videotape recording of the area close to (approximately 8cm from the eye) and including the eye. The videotaped images were later checked on a television screen in order to obtain precise pupil diameter measurement.

4.3.3.4 Respiration rate

Respiration rate was determined as the number of breaths subjects took in a 60 second period. I assessed this by counting the number of times the subject's chest rose and fell. Respiration rate was always measured 60 seconds after blood pressure was recorded.

4.3.3.5 Pulse oximetry

Pulse oximetry was non-invasively measured using a hand-held pulse oximeter (Novamatrix model 511, Novamatrix Medical Systems, Wallingford, CT, USA). A finger sensor was placed on an index finger during the testing session; no subjects were allowed to wear any nail polish as this is known to impede accurate measurement. The pulse oximeter, which has a range of measuring oxygen saturation (SpO_2) from 0-100%, and accuracy of $\pm 2\%$ SpO_2 , averaged the SpO_2 every 8 seconds.

The initial baseline measurement period was 30 minutes; for methadone patients these data were recorded approximately 30 minutes before they received their daily dose of methadone. Immediately after receiving their dose, methadone patients then re-placed the oximetry sensor cuff on an index finger; continuous oximetry measurement then took place for approximately 3 hours to determine the effect methadone had on SpO_2 . For control subjects pulse oximetry was measured for a period of 30 minutes, and then once again for a further 3 hours similar to the methadone patients. At the end of each testing session, all oximetry data were electronically transferred from the hand-held unit to a personal

computer for storage and later analysis by me. The first 30 minutes of SpO₂ data recording were used as a baseline measure (reported as 0 hour). Those data were compared with the data recorded for the 3 hour period (reported as 3 hours).

4.4 Plasma methadone concentrations

As described previously in section 2.9.1

4.5 Statistical and other analyses

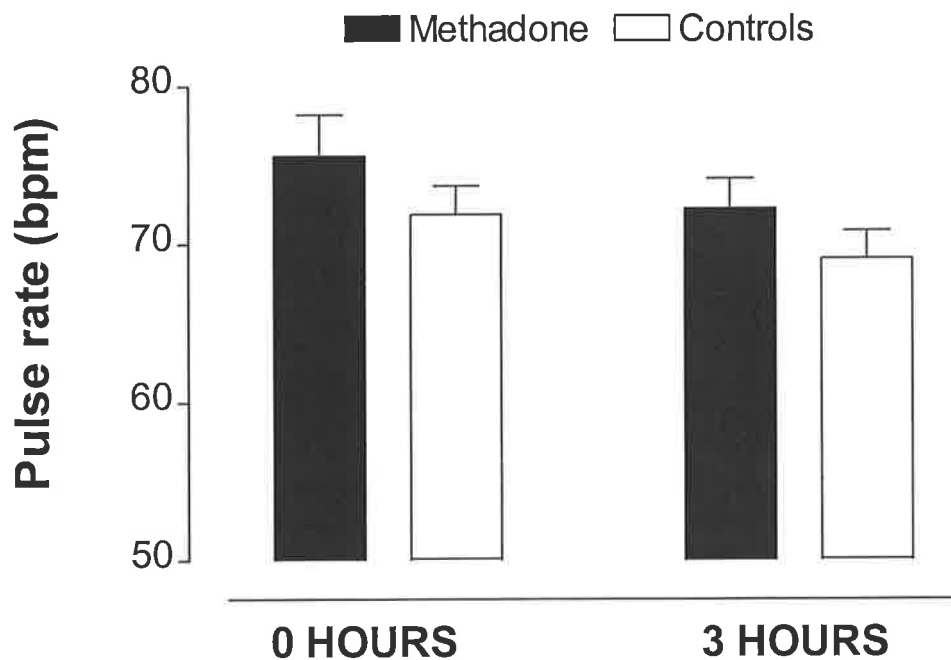
Data are presented as mean $\pm$ SEM (with 95% confidence intervals [CI of the difference]). Within-group comparisons were made using Student's *t* test (paired) and between-group comparisons using Student's *t* test (independent). The alpha level for all data was set at $p < 0.05$. All data were analysed using SPSS™ for Windows (version 10, SPSS Inc., Chicago, Illinois, USA), which carried out tests for homogeneity of variance and adjusted the *p* value accordingly. I conducted all data analysis and interpretation.

4.6 Results

4.6.1 Pulse rate

Results for methadone patients and control subjects are shown in Figure 4.1. The alpha level was set as $p < 0.05$. At 0 hours, the pulse rates of methadone patients were not significantly different from those of controls ($p = 0.246$, [95%CI, -2.7, 10.8]). Similarly at 3 hours, there were no significant differences between the groups ($p = 0.239$, [95%CI, -2.2, 8.4]). Comparisons were made between pulse rates measured at 0 and 3 hours for each group. In methadone patients, mean pulse rates at 3 hours were not significantly different from those at 0 hours ($p = 0.116$, [95%CI, -7.7, 0.9]). Similarly for controls, mean pulse rates at 3 hours were not significantly different from those at 0 hours ($p = 0.056$, [95%CI, -5.5, 0.1])

Figure 4.1. Mean ($\pm$ SEM) pulse rate in 16 methadone patients and 16 matched controls at 0 and 3 hours.

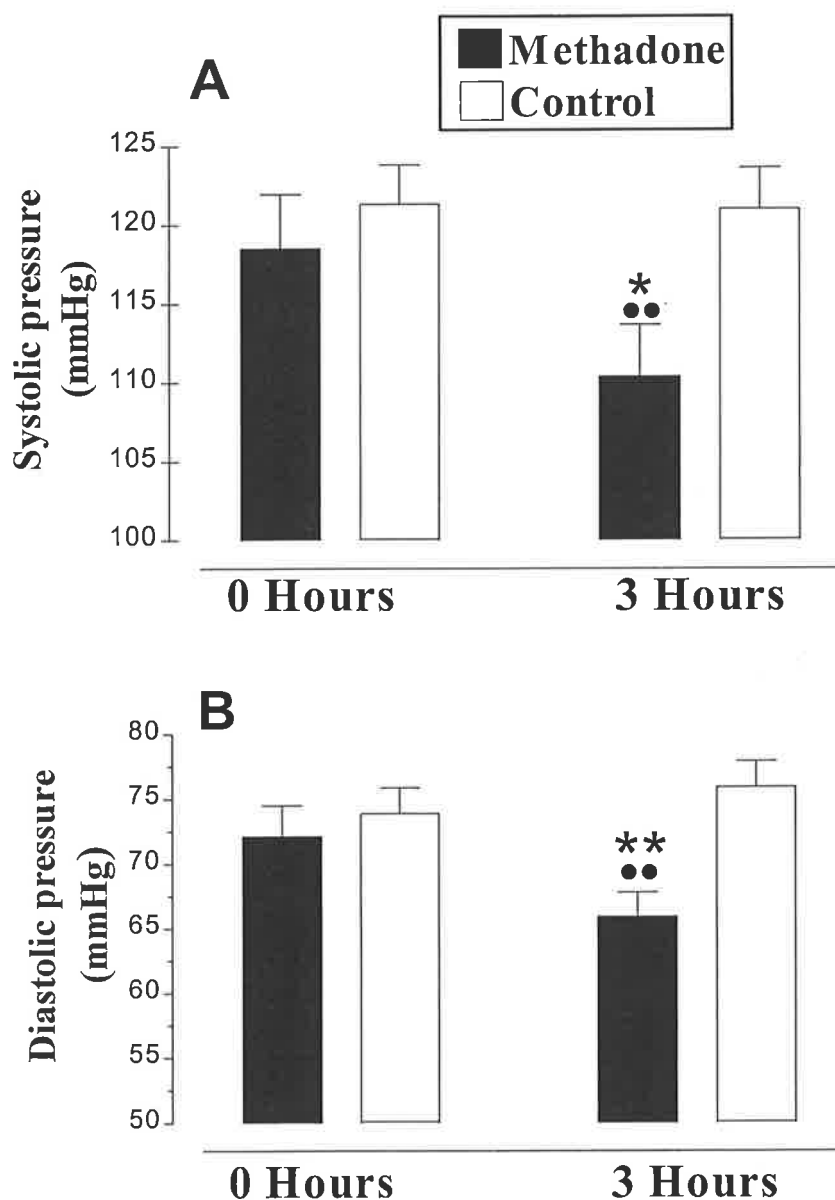


4.6.2 Blood pressure

Results for methadone patients and control subjects are shown in Figure 4.2. The alpha level was set as $p < 0.05$. At 0 hours, the mean systolic pressure of methadone patients was not significantly different from that of controls ($p = 0.579$, [95%CI, -8.1, 4.6]). In contrast at 3 hours, the mean systolic pressure of methadone patients was significantly lower than control subjects ($p = 0.001$, [95%CI, -15.6, -4.4]). Similar results were found for diastolic pressure; with no significant differences between the groups at 0 hours ($p = 0.514$, [95%CI, -11.5, 5.9]), but at 3 hours the mean diastolic pressure of methadone patient's was significantly lower than controls' ($p = 0.017$, [95%CI, -19.2, -2.1]).

Comparisons were made between systolic and diastolic pressure measured at 0 and 3 hours for each group. In methadone patients, systolic pressure at 3 hours was significantly lower than at 0 hours ($p = 0.001$, [95%CI, -12.1, -4.1]), and similarly diastolic pressure at 3 hours was significantly lower than at 0 hours ($p = 0.001$, [95%CI, -9.5, -2.9]). In contrast, for controls, systolic and diastolic pressure at 3 hours were not significantly different from those at 0 hours ($p > 0.174$).

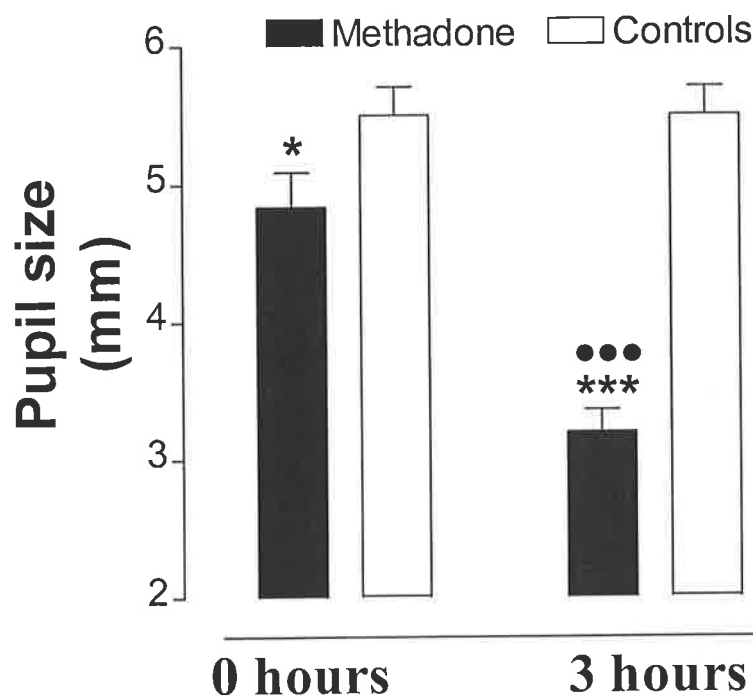
Figure 4.2. Mean ($\pm$ SEM) blood pressure in 16 methadone patients and 16 matched controls at 0 and 3 hours. Panel A: systolic pressure, methadone vs. controls, * $p=0.017$; 0 vs. 3 hours, $\bullet\bullet$ $p=0.001$ Panel B: diastolic pressure, methadone vs. controls, ** $p=0.001$; 0 vs. 3 hours, $\bullet\bullet$ $p=0.001$.



4.6.3 Pupil diameter

Results for methadone patients and control subjects are shown in Figure 4.3. The alpha level was set as $p < 0.05$. The mean pupil size for methadone patients was significantly smaller than controls at 0 hours ($p = 0.036$, [95%CI, -1.3, -0.5]), and also at 3 hours ($p < 0.0005$, [95%CI, -3.1, -1.7]). Comparisons were made between pupils sizes measured at 0 and 3 hours for each group. In methadone patients, mean pupil sizes at 3 hours were significantly smaller from those at 0 hours ($p < 0.0005$, [95%CI, -2.1, -1.3]), whereas for controls, mean pupil sizes at 3 hours were identical to those at 0 hours.

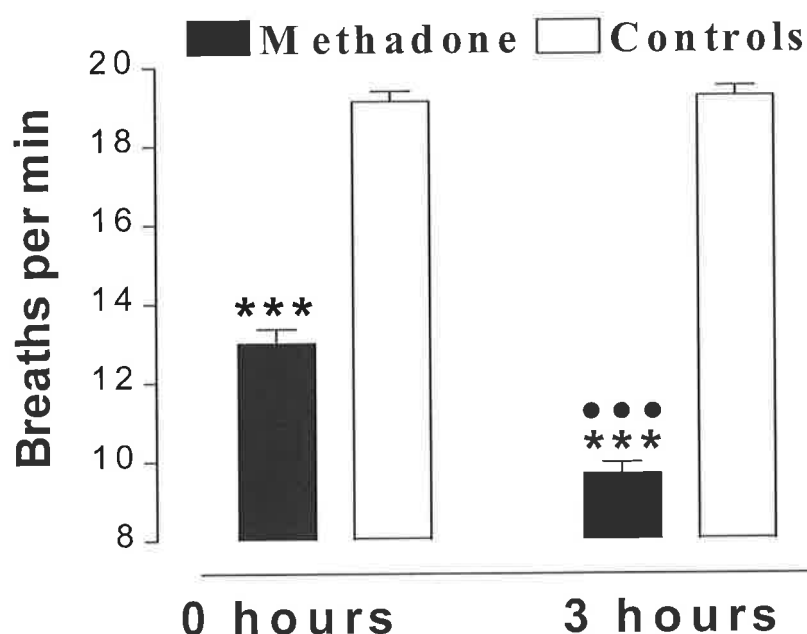
Figure 4.3. Mean ($\pm$ SEM) pupil sizes in 16 methadone patients and 16 matched controls at 0 and 3 hours. Methadone vs. controls, $*p = 0.036$, $***p < 0.0005$. 0 vs. 3 hours, $●●●p < 0.0005$.



4.6.4 Respiratory rate

Results for methadone patients and control subjects are shown in Figure 4.4. The alpha level was set as $p < 0.05$. The mean respiratory rate of methadone patients was significantly lower than controls at 0 hours ($p < 0.0005$, [95%CI, -7.1, -5.2]), and also at 3 hours ($p < 0.0005$, [95%CI, -10.3, -8.8]). Comparisons were made between respiratory rates measured at 0 and 3 hours for each group. In methadone patients, respiratory rates at 3 hours were significantly lower than those at 0 hours ($p < 0.0005$, [95%CI, -3.7, -2.9]), whereas for controls, respiratory rates at 3 hours were not significantly different from those at 0 hours ($p = 0.669$, [95%CI, -0.5, 0.7]).

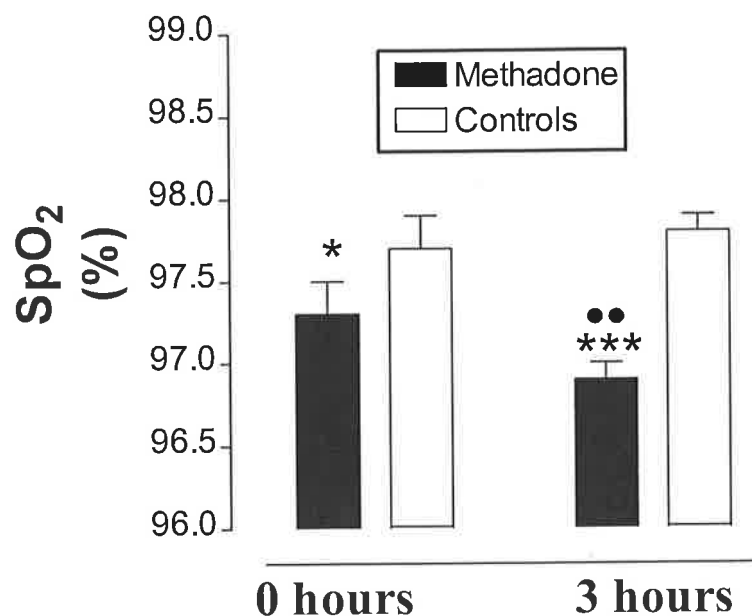
Figure 4.4. Mean ($\pm$ SEM) respiratory rates in 16 methadone patients and 16 matched controls at 0 and 3 hours. Methadone vs. controls, *** $p < 0.0005$. 0 vs. 3 hours, ●●● $p < 0.0005$.



4.6.5 Pulse oximetry

Mean SpO₂ percentages are illustrated in Figure 4.5. The alpha level was set as $p < 0.05$. SpO₂ levels of methadone patients ($97.3 \pm 0.1\%$) were significantly different from controls ($97.7 \pm 0.2\%$) at 0 hours ($p = 0.048$, [95%CI, -0.8, 0.01]), and at 3 hours mean SpO₂ levels of methadone patients ($96.9 \pm 0.1\%$) were significantly lower than controls' ($97.8 \pm 0.1\%$) ($p < 0.0005$, [95%CI, -1.3, -0.5]). Comparisons were made between mean SpO₂ levels at 0 and 3 hours for each group. For methadone patients, mean SpO₂ levels at 3 hours were significantly lower than those at 0 hours ($p = 0.007$, [95%CI, 0.1, 0.7]). In contrast there were no significant differences in control subjects ($p = 0.343$, [95%CI, -0.2, 0.1]).

Figure 4.5. Mean SpO₂ percentages in 16 methadone patients and 16 matched controls at 0 and 3 hours. Methadone vs. controls: * $p = 0.048$, *** $p < 0.0005$. 0 vs. 3 hours: ●● $p = 0.007$.



Between-group comparisons were also made between the number of episodes (one episode equals 8 seconds) at 95% SpO₂ and below (see Table 4.1 below). There were no significant differences ($p>0.113$) between the groups at any of these SpO₂ percentage levels. Comparisons were made between mean SpO₂ levels at each of the levels (outlined in Table 4.1) at 0 and 3 hours for each group. For methadone patients there were no significant differences ($p>0.069$) at any SpO₂ level at 95% or below. Similarly for controls, there were no significant differences ($p>0.143$).

Table 4.1. Arterial oxygen saturation (SpO₂). Comparisons of the mean ($\pm$ SEM, if applicable) number of episodes at oxygen saturation levels at 95% or below for methadone patients and control subjects at 0 hours (for methadone patients this was for a period of 30 minutes before their due dose) and at 3 hours (this represents continuous oximetry recording for 3 hours after methadone patients (MM) were given their daily dose of methadone). Control subjects did not receive methadone, but oximetry was measured for the same duration of time as MM patients. One episode is equivalent to 8 seconds.

SpO ₂	MM patients (0 hours)	Controls (0 hours)	MM patients (3 hours)	Control (3 hours)
	Number	of	episodes	Mean ($\pm$ SEM)
95% SpO ₂	0	0	36 (± 17)	5 (± 3)
94% SpO ₂	0	0	13 (± 7)	0 (± 0.5)
93% SpO ₂	0	0	6 (± 4)	0 (± 0.2)
92% SpO ₂	0	0	2 (± 2)	0
91% SpO ₂	0	0	1 (± 0.5)	0
90% SpO ₂	0	0	0 (± 0.25)	0

4.7 Discussion

There were marked differences between the groups for respiratory rate and pupil size; the differences were most pronounced at 3 hours, the time of putative peak plasma methadone concentrations. Furthermore, for methadone patients, increases in plasma methadone concentrations from trough to peak resulted in a small but statistically significant decrease in both systolic and diastolic blood pressure, pupil size, respiratory rate and SpO₂.

4.7.1 Physiological responses

There were no significant effects of increasing plasma methadone concentrations on the heart rates of methadone patients in this study. Very little seems to have been previously reported about the cardiovascular effects of oral methadone in the context of maintenance treatment. McCaul and colleagues (1982) reported that significant decreases in heart rate occurred during the first 4 hours after the methadone dose was administered; they concluded that the changes in heart rate were likely to parallel the changes in plasma methadone concentrations, which were not measured. Further, Gritz *et al.* (1975) reported that decreased and irregular heart rate are rarely reported effects of methadone that may occur at peak plasma methadone concentrations. The specific mechanism of these effects is unknown (Olsen, 1996; Preston, 1986). The disparity in heart rate between the respective studies could be due to the fact that the focus of the present experiment was on nociceptive responses to pain induction which may have affected cardiovascular responses of methadone patients. However, the direction of the differences in the present study, even though these were not statistically significant, was the same as others had reported (Gritz *et al.*, 1975; McCaul *et al.*, 1982).

The literature is unclear with regard to the direct effect of methadone on a patient's blood pressure, as outlined in chapter 1 (section 1.15.6). In the present study, there were small but statistically significant decreases in both systolic and diastolic blood pressure measurements of methadone patients. These small decreases were associated with increases in the plasma concentration of the pharmacologically active (-)-(R)-methadone from trough to peak. Whilst there was a statistically significant effect on methadone patients' blood pressure, it is not clinically significant in that their systolic and diastolic pressures were in the normotensive range. Furthermore, none of the patients displayed (or complained of) any symptoms consistent with hypotension. Hence, the present data appear to support the assertion within Jaffe & Martin's (1992) review that opioid 3 (mu) agonists have no major effect on blood pressure. These data are consistent with the finding by McCaul *et al.* (1982)

that stabilised methadone maintenance patients display relatively stable blood pressure. Further and more detailed investigation of the cardiovascular effects of methadone maintenance treatment, minus the influence of nociceptive stimuli, may be needed before definitive statements are put forward about the cardiovascular responses of patients on methadone maintenance treatment.

Miosis is a well known marker of opioid effect. Tress and El-Sobky (1980) reported that the measurement of pupil diameter provides the most productive information about reactions to opioid drugs in opioid dependent (heroin or methadone) and non-dependent subjects. There were significant differences in pupil sizes between control subjects and methadone patients at 0 hour, with methadone patients' pupil size being smaller (15%) than controls. This difference became more pronounced when methadone patients' plasma concentrations were at putative peak levels; with methadone patients pupils being approximately 40% smaller than control subjects'. This finding of increased miosis at the time of peak putative plasma methadone concentrations within the inter-dosing interval is consistent with previous reports (Inturrisi & Verebey, 1972; McCaul *et al.*, 1982; Dyer *et al.*, 1999).

Respiratory rates of methadone patients were markedly lower than those of control subjects. For methadone patients, the increases in plasma methadone concentration from the time of trough to putative peak resulted in significantly lower respiratory rates at the putative peak compared with those at trough, specifically by 3.3 breaths/min. This finding is consistent with results reported by Dyer *et al.* (1999) and Gritz *et al.* (1975); these reports indicate that some degree of respiratory depression, specifically a reduction in rate, occurs even in patients who have been stabilised on methadone for several months. Overall, these data suggest that, whilst participation in a methadone maintenance program may have a protective effect against opioid overdose fatalities (Hall *et al.*, 1998), methadone patients should be alerted to the significant reductions in respiration rate that occur within four hours of methadone dosing.

There are significant differences in methadone patients' respiratory rates at putative trough plasma concentrations in the present study compared with those reported by Dyer and colleagues (1999). They reported that at the time of putative trough plasma methadone concentrations, respiratory rates of methadone patients were higher than control subjects. In the present study respiratory rates of methadone patients at the time of trough plasma methadone concentrations were markedly lower than matched control subjects, and somewhat lower than the respiratory rates observed by Dyer and co-workers. I am unable to

explain the difference in respiratory rates of patients in the present study and those reported by Dyer and colleagues. However I would propose that the results of the present study accurately reflect the respiratory depressant effects of methadone within an inter-dosing period even after stabilisation on methadone has occurred. Indeed, it is well known that opioids depress respiratory rate (Sapira, 1968), and that some degree of respiratory depression has been observed in patients stabilised on methadone for several months (Gritz *et al.*, 1975). Further, Martin and colleagues (1967) suggested that this effect persists during chronic opioid administration, and is the only vital sign that falls below customary clinical limits of normal in an opioid addicted person.

Pulse oximetry was measured in this study; I am unaware of any previous reports using pulse oximetry to measure the effect of plasma methadone concentrations on arterial oxygenation levels in a sample of alert methadone maintenance patients. Although for methadone patients there was a very small but statistically significant difference in arterial oxygenation from trough to peak plasma methadone concentrations, this is not considered as being clinically significant given that arterial oxygenation levels remained within normal parameters (96-99%), but is consistent with the suggestion during opioid addiction there is a slight decrease in oxygen saturation (Sapira, 1968). Further investigation of the effect of additionally administered opioids in this patient group may yield clinically significant findings.

STUDY 2: PHYSIOLOGICAL AND SUBJECTIVE EFFECTS OF INTRAVENOUS MORPHINE IN METHADONE MAINTENANCE PATIENTS

4.8 Aims of the present study

The aims of this study were to determine the physiological and subjective effects of intravenous morphine at two pseudo steady-state plasma morphine concentrations in methadone maintenance patients and matched controls, and to determine, in methadone patients, if the physiological and subjective effects of morphine are affected by changes in plasma methadone concentration that occur during an inter-dosing interval; specifically, at the two extremes of methadone concentration: (i) at trough (approximately 23.5 hours after the previous dose), and (ii) at peak (commencing 2 hours after the dose).

Hypothesis: Plasma morphine concentrations known to result in effective antinociception in opioid-naïve patients will have minimal physiological or subjective effects in methadone maintenance patients.

4.9 Methods

4.9.1 Patients and control subjects

As described previously in section 3.2.1. (please note that the patients and control subjects in this study are those previously mentioned in chapter 3).

4.9.2 Study design

Methadone patients were tested on two occasions, separated by 7 days. They were randomly allocated into two subgroups: two patients were tested first when their methadone was at the putative trough plasma concentrations (23.5 hours after the previous dose), and the other two patients tested first when at putative peak plasma methadone concentrations (2 hours after the dose). The order was reversed for the second session. Patients in the trough session were given their scheduled daily dose of oral methadone 15 minutes after cessation of the morphine infusion (see below). All control subjects were tested on one occasion only, and did not receive any methadone.

4.9.2.1 Morphine administration

Morphine sulphate was administered intravenously as a 2 step, controlled infusion as described in detail in the preceding chapter (section 3.2.2.1). The results for this are not reported in the current chapter but are described in detail in section 3.3.1

4.9.3 Procedures and measures

As described previously in section 3.2.3.

4.9.3.1 Physiological and subjective effects measures

Various physiological measures were recorded at 0 (pre-morphine administration), 0.5, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 7.0 hours; these included respiratory rate, pupil size, heart rate, blood pressure, pulse oximetry (initially for a period of 30 minutes (baseline), and continuously for 6.5 hours after commencement of morphine administration), and sedation scores (National Health and Medical Research Council, 1999; Macintyre & Ready, 2000). The methods for measurement of respiratory rate, pupil size, heart rate, blood pressure, and pulse oximetry are described in detail earlier in this chapter (see section 4.3)

The sedation score scale used in the present study was adapted from the scale recommended by the National Health and Medical Research Council of Australia (1999); it has a maximum score of 3 indicating severe sedation, somnolence, difficult to rouse; a score of 2 indicates moderate sedation, constantly or frequently drowsy, easy to rouse; a score of 1 indicates mild sedation, occasionally drowsy, easy to rouse; a score of 0 indicates no sedation. Sedation is recognised as being one of the first signs of respiratory depression (Foley, 1993; Macintyre & Ready, 2000).

Subjective effects were measured by using the Morphine-Benzedrine Group Scale (MBG) (Haertzen & Hickey, 1987) which has been found to be a valid and reliable measure of euphoria; the MBG scale has a maximum score of 16. The Morphine Group Scale (MG) (Haertzen & Hickey, 1987) was also used; this measure has been found to be a valid and reliable measure of direct opioid effects (except euphoria). The MG scale has a maximum score of 8. Both scales (MBG and MG) were combined into one questionnaire (see appendix 1) which was completed by each patient and control subject at 0, 0.5, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 7.0 hours. Both MBG and MG scales are answered on a true-false format. Both are sub-scales of the Addiction Research Centre Inventory (ARCI), a 550 item inventory; the MBG being sub-scale 2 (ARCI #463), and the MG scale being sub-scale 3 (ARCI # 460)

4.10 Data analysis and statistics

The mean of pharmacodynamic responses at 0.5 and 1.0 hour was associated with plasma morphine concentrations at C_{ss1} , and similarly the mean of pharmacodynamic responses at 1.5 and 2.0 hours was associated with plasma morphine concentrations at C_{ss2} . Data are presented as mean $\pm$ SEM (with 95% confidence intervals [CI] of the differences). Two-way repeated measures analyses of variance (ANOVA) were used to determine differences in pharmacodynamic responses among methadone patients and control subjects. To account for sphericity, the Greenhouse-Geisser conservative F-test was used to interpret the ANOVA. As there are only two groups (methadone patients and control subjects) the statistical software used in this analysis did not conduct *post hoc* tests; hence specific between-group comparisons (methadone vs. control) were made using Student's *t* tests (independent) with an alpha level of $p < 0.0045$, and within-group comparisons were made using Student's *t* tests (paired) with an alpha level of $p < 0.005$. All such *t* tests involved multiple comparisons. Hence, I adjusted the alpha accordingly using a Bonferroni adjustment ($p < 0.05/\text{number of comparisons}$). Comparisons of SpO_2 percentages (within- and between-group) were analysed by Student's *t* tests (independent and paired). All data were analysed using SPSS™ for Windows (version 10), which carried out tests for homogeneity of variance and adjusted the *p* value accordingly.

4.11 Results

4.11.1 Respiratory rate

Mean ($\pm$ SEM) respiratory rates (0 to 7 h) are summarised in Table 4.2, and are also graphically illustrated in Figure 4.6. Comparing respiratory rates of methadone (trough session) patients with control subjects', there was a main effect of group ($F(1,6)=21.74$; $p=0.003$); methadone (trough session) patients' mean respiratory rates were significantly lower than controls' at 0 hour ($p<0.0005$, [95%CI, -6.7, -3.3]), 0.5 hour ($p<0.0005$, [95%CI, -5.4, -2.6]), 5.0 hours ($p=0.004$, [95%CI, -8.4, -2.6]), 6.0 hours ($p=0.002$, [95%CI, -9.4, -3.6]), and 7.0 hours ($p=0.002$, [95%CI, -8.4, -3.1]). There was also a main effect of time ($F(1.7,10.4)=16.6$; $p=0.001$), and significant interaction between group and time ($F(1.7,10.4)=16.6$; $p=0.004$), with control subjects respiratory rates significantly changing across time. Compared to baseline rates, control subjects' mean respiratory rates were significantly lower at 1.0 h ($p=0.003$, [95%CI, -3.04, -1.45]), and 1.5 h ($p<0.0005$, [95%CI, -5.04, -3.45]).

Comparing respiratory rates of methadone (peak session) patients with control subjects', there was a main effect of group ($F(1,6)=62.7$; $p<0.0005$); methadone patients' mean respiratory rates were significantly lower than controls' at 0 hour ($p<0.0005$, [95%CI, -10.0, -6.0]), 0.5 hour ($p<0.0005$, [95%CI, -8.1, -5.4]), 1.0 hour ($p<0.0005$, [95%CI, -7.2, -3.8]), 1.5 hours ($p=0.003$, [95%CI, -6.0, -2.0]), 6.0 hours ($p=0.002$, [95%CI, -7.4, -2.6]), and 7.0 hours ($p=0.003$, [95%CI, -7.2, -2.3]). There was also a main effect of time ($F(1.5,9.1)=14.9$; $p=0.002$), and significant interaction between group and time ($F(1.5,9.1)=6.3$; $p=0.024$), with control subjects respiratory rates significantly changing across time as outlined above.

Within-group comparisons (trough versus peak methadone) revealed that respiratory rates of methadone patients during the trough session were significantly higher than those during the peak session at 0.5 hour ($p=0.002$, [95%CI, 2.0, 3.5]), and 1.0 hour ($p=0.003$, [95%CI, 1.6, 3.4]).

Table 4.2. Comparison of mean ($\pm$ SEM) respiratory rates (breaths per minute) amongst methadone (trough) patients, methadone (peak) patients, and matched control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	14.5 (0.5)	11.5 (0.6)	19.5 (0.5)	*p<0.0005, # p<0.0005,+p=0.005
0.5 h	14.5 (0.5)	11.75 (0.5)	18.5 (0.3)	*p<0.0005, # p<0.0005,+p=0.002
1.0 h	14.25 (0.6)	11.75 (0.5)	17.25 (0.5)	*p=0.009, # p<0.0005,+p=0.003
1.5 h	13.25 (0.6)	11.5 (0.6)	15.5 (0.5)	*p=0.031, #p=0.003,+p=0.035
2.0 h	13 (0.7)	11.25 (0.5)	13.75 (0.6)	*p=0.488, #p=0.020,+p=0.035
2.5 h	12.75 (0.9)	11 (0.4)	13.5 (0.5)	*p=0.477, #p=0.008,+p=0.035
3.0 h	13.25 (0.9)	11.5 (0.6)	14.5 (1.0)	*p=0.368, #p=0.041,+p=0.188
4.0 h	11.25 (0.8)	12.25 (0.5)	16 (0.8)	*p=0.005, #p=0.007, +p=0.353
5.0 h	11 (0.7)	13.25 (0.5)	16.5 (1.0)	*p=0.004, #p=0.023, +p=0.058
6.0 h	12 (0.7)	13.5 (0.3)	18.5 (1.0)	*p=0.002, #p=0.002,+p=0.103
7.0 h	12.75 (0.5)	13.75 (0.3)	18.5 (1.0)	*p=0.002, #p=0.003,+p=0.182

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p<0.0045$) this is highlighted in bold text.

Figure 4.6. Mean ($\pm$ SEM) respiratory rates from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.

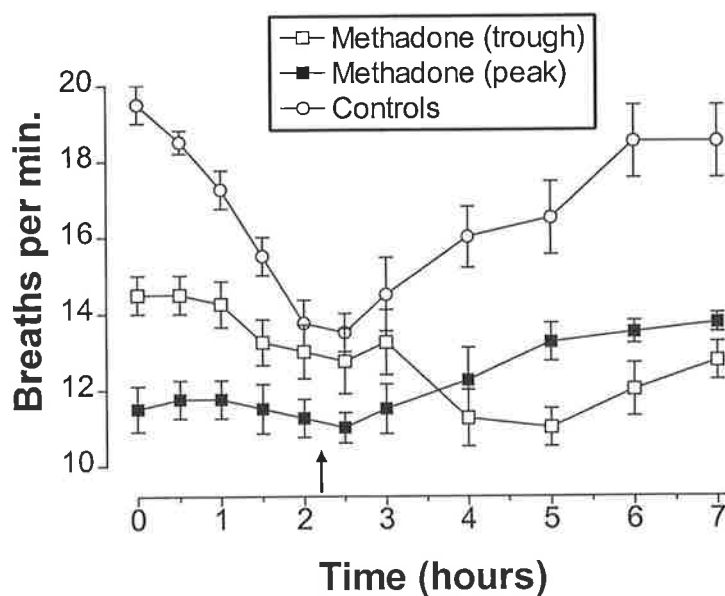
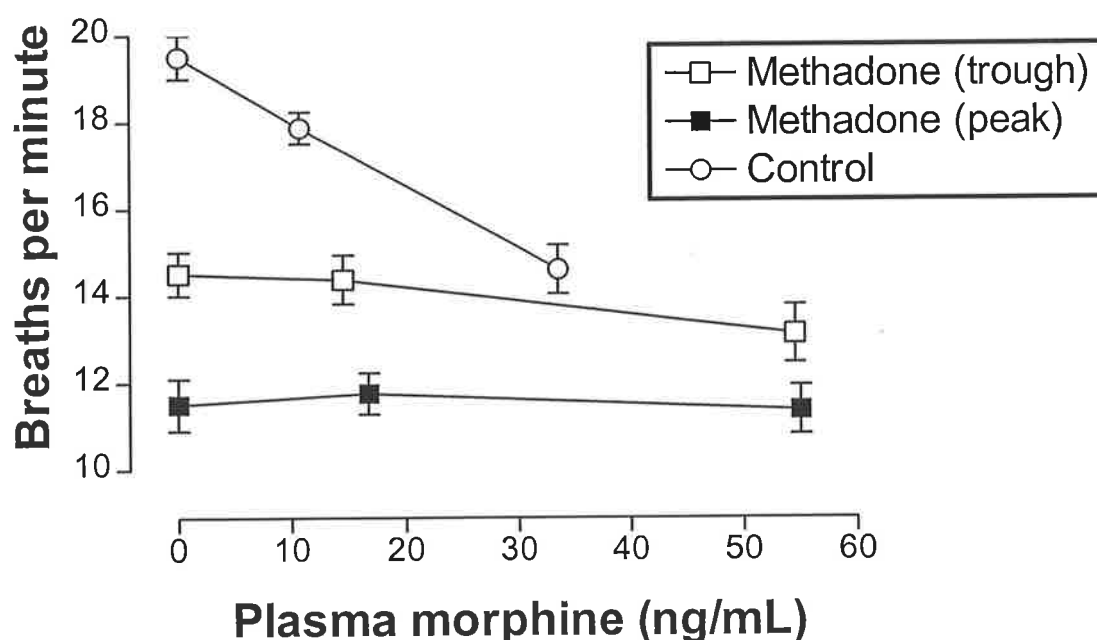


Figure 4.7 shows plasma morphine concentrations and responses on three occasions: baseline, C_{ss1} and C_{ss2} . The alpha level was set at $p < 0.05$. Respiration rates in the trough methadone session decreased significantly from C_{ss1} to C_{ss2} ($p = 0.015$, [95%CI, 0.45, 2.05]) only. There were no significant changes ($p > 0.214$) in respiratory rates with increasing plasma morphine concentrations during the peak methadone session. For control subjects, there were significant decreases in respiratory rates from baseline to C_{ss1} ($p = 0.007$, [95%CI, 0.86, 2.39]), and from C_{ss1} to C_{ss2} ($p = 0.001$ [95%CI, 2.45, 4.04]).

Figure 4.7 Mean ($\pm$ SEM) respiratory rates relative to steady-state plasma morphine concentrations of methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles).



4.11.2 Pupil size

Mean ($\pm$ SEM) pupil sizes (0 to 7 h) are outlined in Table 4.3, and are also graphically illustrated in Figure 4.8. Comparing pupil sizes of methadone (trough session) patients with control subjects', there was no main effect of group ($F(1,6)=4$; $p=0.093$). However, there was a main effect of time ($F(2.3,13.5)=21.7$; $p<0.0005$), and significant interaction between group and time ($F(2.3,13.5)=4.9$; $p=0.022$), with control subjects pupil sizes significantly changing across time. Compared to baseline values, control subjects' mean pupil sizes were significantly lower at 1.0 h ($p=0.001$, [95%CI, -2.27, -1.48]), 1.5 h ($p=0.001$, [95%CI, -3.15, -1.85]), 2.0 h ($p=0.001$, [95%CI, -3.64, -2.11]), 2.5 h ($p=0.001$, [95%CI, -3.65, -2.35]), and 3.0 h ($p=0.001$, [95%CI, -3.64, -2.11]).

Comparing pupil sizes of methadone (peak session) patients with control subjects', there was a main effect of group ($F(1,6)=9.7$; $p=0.021$); methadone patients' mean pupil sizes were significantly smaller than controls' at 0 hour ($p<0.0005$, [95%CI, -3.1, -2.2]), and 0.5 hour ($p<0.0005$, [95%CI, -2.1, -1.4]). There was a main effect of time ($F(2.2,13.4)=37.6$; $p<0.0005$), and significant interaction between group and time ($F(2.2,13.4)=17.8$; $p<0.0005$), with control subjects pupil sizes significantly changing across time as outlined above.

Within-group comparisons (trough versus peak methadone) did not reveal significant differences at any time point ($p>0.015$).

Table 4.3. Comparison of mean ($\pm$ SEM) pupil sizes amongst methadone (trough) patients, methadone (peak) patients, and matched control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	3.87 (0.13)	3.25 (0.15)	5.87 (0.1)	*p<0.0005, #p<0.0005, +p=0.015
0.5 h	3.81 (0.19)	3.25 (0.15)	5.6 (0.25)	*p=0.001, #p<0.0005, +p=0.037
1.0 h	3.5 (0.35)	2.87 (0.25)	4.6 (0.1)	*p=0.024, #p=0.001, +p=0.141
1.5 h	3.0 (0.2)	2.6 (0.25)	3.4 (0.1)	*p=0.168, #p=0.032, +p=0.058
2.0 h	2.87 (0.3)	2.5 (0.2)	3.0 (0.2)	*p=0.750, #p=0.134, +p=0.058
2.5 h	3.0 (0.2)	2.6 (0.25)	2.87 (0.1)	*p=0.620, #p=0.390, +p=0.058
3.0 h	3.0 (0.35)	2.75 (0.25)	3.1 (0.3)	*p=0.801, #p=0.387, +p=0.182
4.0 h	3.1 (0.7)	2.87 (0.3)	3.5 (0.4)	*p=0.645, #p=0.271, +p=0.703
5.0 h	2.87 (0.25)	3.25 (0.25)	3.6 (0.4)	*p=0.176, #p=0.477, +p=0.215
6.0 h	2.87 (0.25)	3.4 (0.1)	3.75 (0.3)	*p=0.072, #p=0.320, +p=0.092
7.0 h	3.1 (0.33)	3.5 (0.2)	3.75 (0.3)	*p=0.225, #p=0.537, +p=0.375

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 4.8. Mean ($\pm$ SEM) pupil sizes from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.

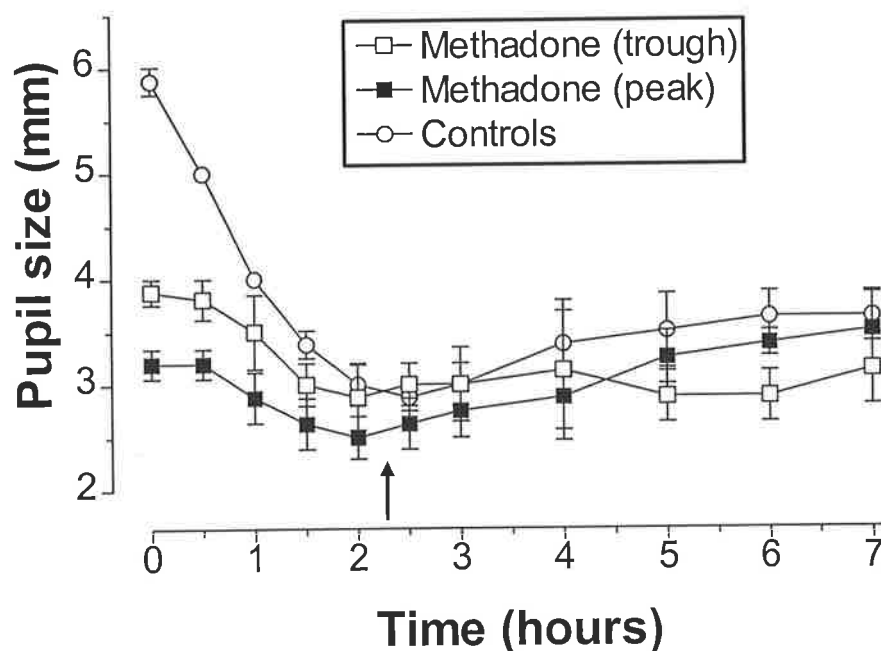
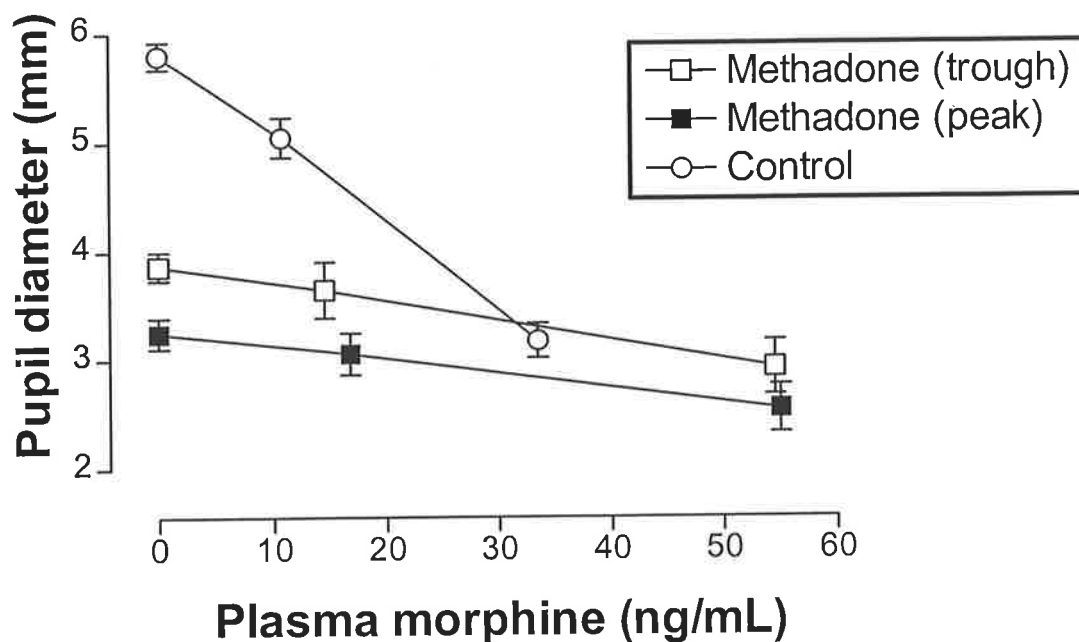


Figure 4.9 shows plasma morphine concentrations and responses on three occasions: baseline, C_{SS1} and C_{SS2} . The alpha level was set at $p < 0.05$. Pupil sizes in the trough methadone session decreased significantly with increases in plasma morphine concentration from C_{SS1} to C_{SS2} ($p = 0.007$, [95%CI, 0.38, 1.06]) only. In contrast, during the peak methadone session there were no significant changes ($p > 0.57$) in pupil size in association with increases in plasma morphine concentrations. For control subjects, the increases in plasma morphine concentration resulted in significant decreases in pupil size from baseline to C_{SS1} ($P = 0.002$, [95%CI, 0.98, 1.78]), and from C_{SS1} to C_{SS2} ($p = 0.004$, [95%CI, 0.81, 1.81]).

Figure 4.9. Mean ($\pm$ SEM) pupil sizes relative to steady-state plasma morphine concentrations of methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles).



4.11.3 Pulse rate

Mean ($\pm$ SEM) pulse rates (0 to 7 h) are outlined in Table 4.4, and are also graphically illustrated in Figure 4.10. Comparing heart rates of methadone (trough session) patients with control subjects', there was a main effect of group ($F(1,6)=7.8$; $p=0.031$). However, post hoc t-tests revealed that whilst control subjects' heart rates were lower, they were not significantly lower at any time point ($p>0.010$). There was a main effect of time ($F(3.3,19.6)=4.5$; $p=0.013$), but no significant interaction between group and time ($F(3.3,19.6)=0.8$; $p=0.517$).

Comparing heart rates of methadone (peak session) patients with control subjects', there was no main effect of group ($F(1,6)=3.3$; $p=0.118$). There was a main effect of time ($F(2.7,15.9)=4.5$; $p=0.030$), but no significant interaction between group and time ($F(2.7,15.9)=1.6$; $p=0.221$).

Within-group comparisons (trough versus peak methadone) did not reveal significant differences at any time point ($p>0.014$).

Table 4.4. Comparison of mean ($\pm$ SEM) pulse rates amongst methadone (trough) patients, methadone (peak) patients, and matched control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	76.5 (2.0)	70 (2.7)	71 (4.0)	*p=0.271, #p=0.844, +p=0.061
0.5 h	75 (1.3)	68.5 (1.5)	68 (3.6)	*p=0.150, #p=0.905, +p=0.014
1.0 h	72 (2.8)	67 (1.7)	60 (2.8)	*p=0.024, #p=0.079, +p=0.269
1.5 h	69.5 (2.4)	66 (1.4)	57 (3.9)	*p=0.033, #p=0.072, +p=0.326
2.0 h	69.5 (5.25)	63.5 (1.3)	56.5 (4.0)	*p=0.097, #p=0.148, +p=0.344
2.5 h	70 (2.5)	64 (2.8)	56.5 (2.9)	*p=0.012, #p=0.112, +p=0.069
3.0 h	69.5 (3.6)	64 (2.5)	57.5 (5.7)	*p=0.124, #p=0.334, +p=0.174
4.0 h	68 (3.0)	67 (4.4)	62.5 (5.5)	*p=0.412, #p=0.548, +p=0.848
5.0 h	68.5 (2.1)	68.5 (1.0)	61 (3.9)	*p=0.138, #p=0.109, +p=1.000
6.0 h	70 (0.8)	68.5 (3.3)	57 (3.4)	*p=0.010, #p=0.052, +p=0.718
7.0 h	67.5 (1.7)	70.5 (2.6)	57 (4.7)	*p=0.079, #p=0.045, +p=0.432

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 4.10. Mean ($\pm$ SEM) pulse rates from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose.

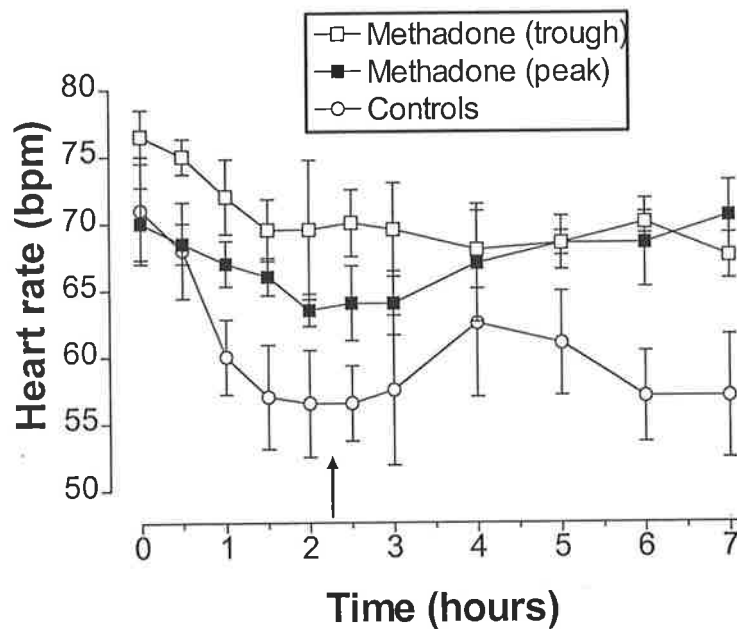
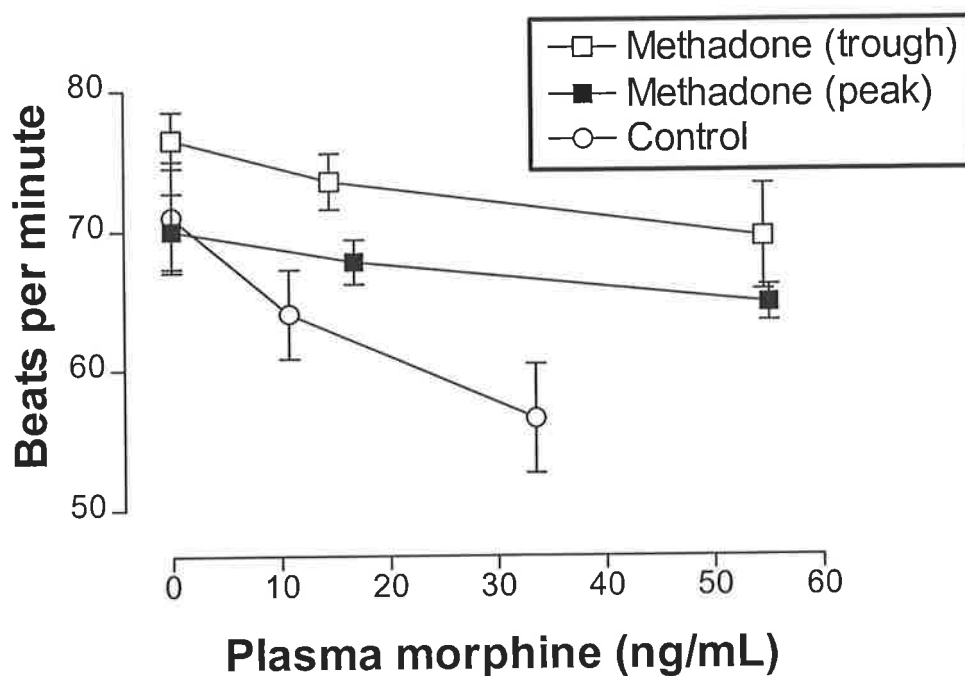


Figure 4.11 shows plasma morphine concentrations and responses on three occasions: baseline, C_{ss1} and C_{ss2} . The alpha level was set at $p < 0.05$. Methadone patients' pulse rates did not significantly change in association with increases in plasma morphine concentrations in either the trough or peak methadone sessions ($p > 0.091$ and $p > 0.102$, respectively). In contrast, control subjects' pulse rates decreased significantly from baseline to C_{ss1} ($p = 0.035$, [95%CI, 0.91, 13.1]), and from C_{ss1} to C_{ss2} ($p = 0.045$, [95%CI, 0.33, 14.2]).

Figure 4.11. Mean ($\pm$ SEM) pulse rates relative to steady-state plasma morphine concentrations of methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles).



4.11.4 Blood pressure

Mean ($\pm$ SEM) systolic and diastolic blood pressure (0 to 7 h) are outlined in Tables 4.5 and 4.6, and are also graphically illustrated in Figure 4.12. Comparing systolic pressure of methadone (trough session) patients with control subjects', there was no main effect of group ($F(1,6)=1.8$; $p=0.232$). There was no main effect of time ($F(3,17.9)=2.5$; $p=0.091$), and no significant interaction between group and time ($F(3,17.9)=1.8$; $p=0.185$). Similarly, comparing systolic pressure of methadone (peak session) patients with control subjects', there was no main effect of group ($F(1,6)=0.001$; $p=0.973$). There was no main effect of time ($F(1.2,7)=0.9$; $p=0.399$), and no significant interaction between group and time ($F(1.2,7)=1$; $p=0.368$). Within-group comparisons (trough versus peak methadone) of systolic blood pressure did not reveal significant differences ($p>0.187$) at any time point.

Comparing diastolic pressure of methadone (trough session) patients with control subjects', there was no main effect of group ($F(1,6)=0.02$; $p=0.884$). There was a main effect of time ($F(2.4,14.2)=6.8$; $p=0.007$), but no significant interaction between group and time ($F(2.4,14.2)=1$; $p=0.397$). Similarly, comparing diastolic pressure of methadone (peak session) patients with control subjects', there was no main effect of group ($F(1,6)=0.5$; $p=0.501$). There was a main effect of time ($F(2.9,17.5)=6.6$; $p=0.004$), but no significant interaction between group and time ($F(2.9,17.5)=1.1$; $p=0.397$). Within-group comparisons (trough versus peak methadone) of diastolic blood pressure did not reveal significant differences ($p>0.064$) at any time point.

Table 4.5. Comparison of mean ($\pm$ SEM) systolic pressure between methadone (trough) patients, methadone (peak) patients, and matched control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	109 (4.0)	117.5 (4.5)	120 (4.0)	*p=0.107, #p=0.689, +p=0.212
0.5 h	111 (3.0)	117.5 (4.5)	120 (4.0)	*p=0.140, #p=0.689, +p=0.239
1.0 h	109 (4.0)	117.5 (4.5)	116 (5.0)	*p=0.309, #p=0.852, +p=0.222
1.5 h	107.5 (3.0)	116 (4.0)	117.5 (5.0)	*p=0.134, #p=0.852, +p=0.188
2.0 h	107.5 (5.0)	111 (4.0)	117.5 (5.0)	*p=0.190, #p=0.368, +p=0.547
2.5 h	105 (6.0)	111 (4.0)	115 (6.5)	*p=0.304, #p=0.645, +p=0.431
3.0 h	102.5 (6.0)	112.5 (3.0)	116 (5.5)	*p=0.142, #p=0.613, +p=0.295
4.0 h	104 (5.5)	112.5 (4.0)	112 (6.0)	*p=0.323, #p=1.000, +p=0.298
5.0 h	106 (4.0)	114 (4.0)	115 (4.5)	*p=0.211, #p=0.402, +p=0.393
6.0 h	107.5 (5.0)	115 (4.0)	116 (5.5)	*p=0.294, #p=0.722, +p=0.391
7.0 h	112.5 (3.0)	115 (4.0)	116 (5.5)	*p=0.580, #p=0.722, +p=0.809

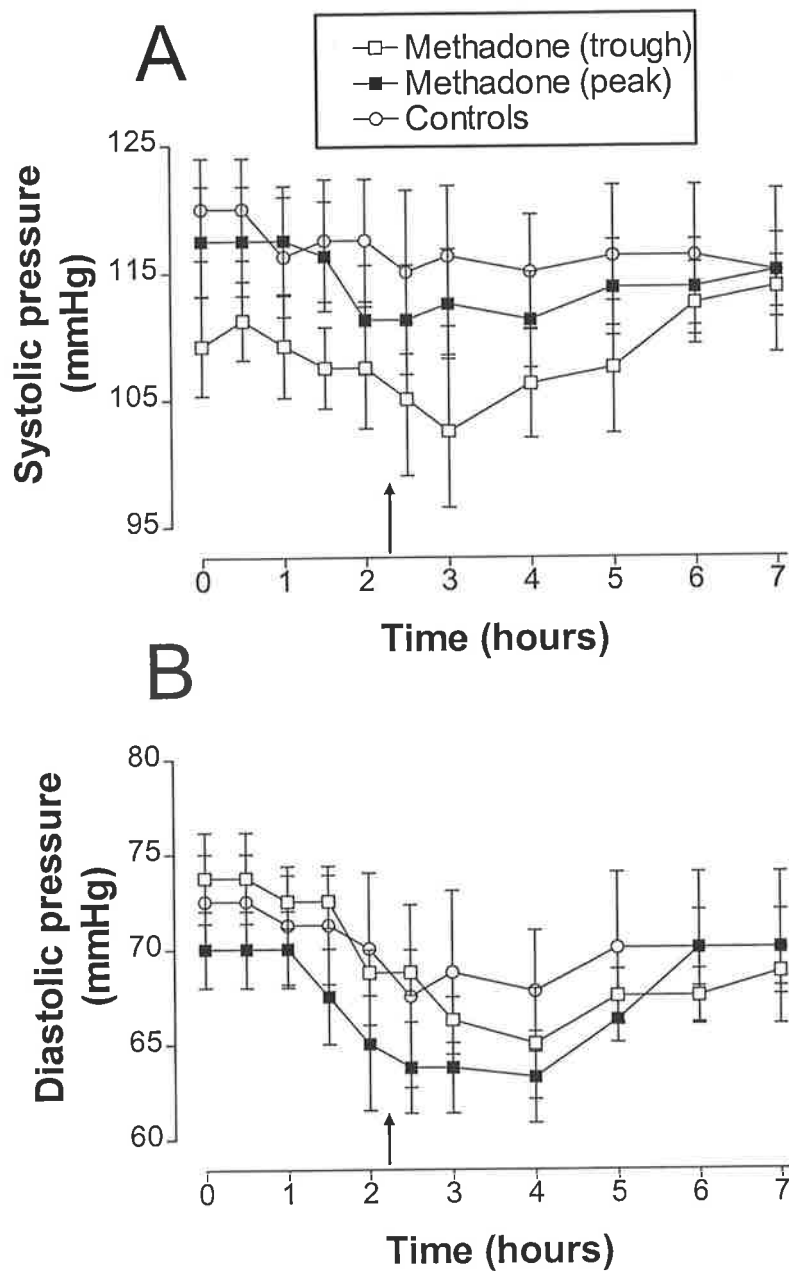
* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Table 4.6. Comparison of mean ($\pm$ SEM) diastolic pressure between methadone (trough) patients, methadone (peak) patients, and matched control subjects.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	73.75 (2.5)	70 (2.0)	72.5 (2.5)	*p=0.730, #p=0.468, +p=0.215
0.5 h	73.75 (2.5)	70 (2.0)	72.5 (2.5)	*p=0.730, #p=0.468, +p=0.215
1.0 h	72.5 (1.5)	70 (2.0)	71 (3.0)	*p=0.730, #p=0.750, +p=0.182
1.5 h	72.5 (1.5)	67.5 (2.5)	71 (3.0)	*p=0.730, #p=0.387, +p=0.092
2.0 h	68.75 (1.5)	65 (3.5)	67.5 (5.0)	*p=0.780, #p=0.390, +p=0.319
2.5 h	68.75 (1.5)	64 (2.5)	68.75 (4.5)	*p=0.815, #p=0.510, +p=0.092
3.0 h	66.25 (1.5)	64 (2.5)	65 (3.5)	*p=0.595, #p=0.346, +p=0.182
4.0 h	68 (1.25)	64 (2.5)	67.5 (3.5)	*p=0.453, #p=0.329, +p=0.581
5.0 h	65 (3.0)	66 (1.5)	70 (4.0)	*p=0.585, #p=0.435, +p=0.391
6.0 h	67.5 (1.5)	70 (2.0)	70 (4.0)	*p=0.585, #p=1.000, +p=0.412
7.0 h	68.75 (1.5)	70 (2.0)	70 (4.0)	*p=0.780, #p=1.000, +p=0.391

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p < 0.0045$) this is highlighted in bold text.

Figure 4.12. Mean ($\pm$ SEM) blood pressure from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Panel A: systolic pressure. Panel B: diastolic pressure. Arrow illustrates the time point where methadone (trough) patients received their methadone dose.



4.11.5 Sedation scores

Mean ($\pm$ SEM) sedation scores (0 to 7 h) are outlined in Table 4.7. Comparing the sedation scores of methadone (trough session) patients with control subjects', there was no main effect of group ($F(1,6)=0.2$; $p=0.670$). There was no main effect of time ($F(1.5,9.1)=1.6$; $p=0.257$), and no significant interaction between group and time ($F(1.5,9.1)=0.4$; $p=0.602$). Similarly, comparing the sedation scores of methadone (peak session) patients with control subjects', there was no main effect of group ($F(1,6)=0.2$; $p=0.693$). There was no main effect of time ($F(1.6,9.6)=2.3$; $p=0.154$), and no significant interaction between group and time ($F(1.6,9.6)=0.3$; $p=0.690$). Within-group comparisons (trough versus peak methadone) did not reveal significant differences ($p<0.390$) at any time point.

Table 4.7. Comparison of mean ($\pm$ SEM) sedation scores between methadone (trough) patients, methadone (peak) patients, and matched control subjects. Maximum possible score is 3.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	0 (0)	0 (0)	0 (0)	* $p=1.000$, # $p=1.000$, + $p=1.000$
0.5 h	0 (0)	0 (0)	0 (0)	* $p=1.000$, # $p=1.000$, + $p=1.000$
1.0 h	0.25 (0.25)	0.25 (0.25)	0 (0)	* $p=0.356$, # $p=0.356$, + $p=1.000$
1.5 h	0.25 (0.25)	0.25 (0.25)	0 (0)	* $p=0.356$, # $p=0.356$, + $p=1.000$
2.0 h	0.25 (0.25)	0.25 (0.25)	0.25 (0.25)	* $p=1.000$, # $p=1.000$, + $p=1.000$
2.5 h	0.25 (0.25)	0.25 (0.25)	0.25 (0.25)	* $p=1.000$, # $p=1.000$, + $p=1.000$
3.0 h	0.25 (0.25)	0.25 (0.25)	0.25 (0.25)	* $p=1.000$, # $p=1.000$, + $p=1.000$
4.0 h	0.25 (0.25)	0 (0)	0 (0)	* $p=0.356$, # $p=1.000$, + $p=0.356$
5.0 h	0 (0)	0 (0)	0 (0)	* $p=1.000$, # $p=1.000$, + $p=1.000$
6.0 h	0 (0)	0 (0)	0 (0)	* $p=1.000$, # $p=1.000$, + $p=1.000$
7.0 h	0 (0)	0 (0)	0 (0)	* $p=1.000$, # $p=1.000$, + $p=1.000$

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls,
+ denotes trough vs. peak methadone.

4.11.6 MBG scores

Mean ($\pm$ SEM) MBG scores (0 to 7 h) are outlined in Table 4.8, and are also graphically illustrated in Figure 4.13. Comparing the MBG scores of methadone (trough session) patients with control subjects', there was no main effect of group ($F(1,6)=1.2$; $p=0.311$). There was no main effect of time ($F(3.3, 20.1)=0.5$; $p=0.718$), and no significant interaction between group and time ($F(3.3,20.1)=0.45$; $p=0.738$). Similarly, comparing the MBG scores of methadone (peak session) patients with control subjects', there was no main effect of group ($F(1,6)=3.7$; $p=0.104$). There was no main effect of time ($F(3.5, 21.2)=1.1$; $p=0.364$), and no significant interaction between group and time ($F(3.5,21.2)=1.5$; $p=0.243$).

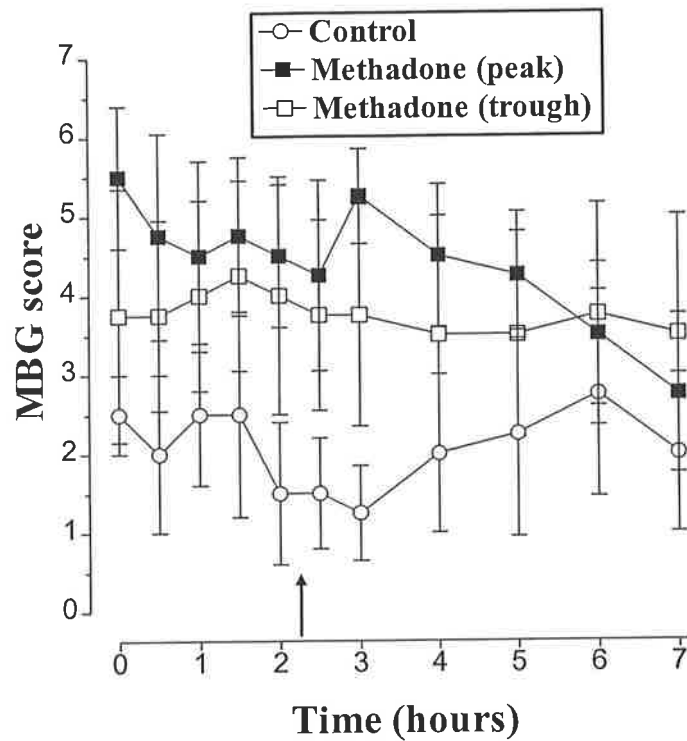
Within-group comparisons (trough versus peak methadone) did not reveal significant differences ($p<0.182$) at any time point.

Table 4.8. Comparison of mean ($\pm$ SEM) MBG scores between methadone (trough) patients, methadone (peak) patients, and matched control subjects. Maximum possible score is 16.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	3.75 (1.7)	5.5 (1.0)	2.5 (0.5)	* $p=0.514$, # $p=0.024$, + $p=0.293$
0.5 h	3.75 (1.2)	4.75 (1.3)	2.0 (1.0)	* $p=0.316$, # $p=0.157$, + $p=0.423$
1.0 h	4.0 (1.2)	4.5 (1.3)	2.5 (1.0)	* $p=0.356$, # $p=0.238$, + $p=0.731$
1.5 h	4.25 (1.3)	4.75 (1.0)	2.5 (1.3)	* $p=0.373$, # $p=0.228$, + $p=0.718$
2.0 h	4.0 (1.5)	4.5 (1.0)	1.5 (1.0)	* $p=0.194$, # $p=0.050$, + $p=0.638$
2.5 h	3.75 (1.2)	4.25 (1.3)	1.5 (0.6)	* $p=0.146$, # $p=0.098$, + $p=0.495$
3.0 h	3.75 (1.5)	5.25 (0.6)	1.25 (0.6)	* $p=0.150$, # $p=0.004$, + $p=0.182$
4.0 h	3.5 (1.5)	4.5 (1.0)	2.0 (1.2)	* $p=0.477$, # $p=0.147$, + $p=0.495$
5.0 h	3.75 (1.5)	4.25 (0.75)	2.25 (1.3)	* $p=0.461$, # $p=0.246$, + $p=0.664$
6.0 h	3.5 (1.0)	3.5 (1.0)	2.75 (1.3)	* $p=0.687$, # $p=0.651$, + $p=1.000$
7.0 h	3.5 (1.5)	2.75 (1.0)	2.0 (1.0)	* $p=0.458$, # $p=0.645$, + $p=0.391$

* denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p<0.0045$) this is highlighted in bold text.

Figure 4.13. Mean ($\pm$ SEM) MBG scores from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose. The maximum possible score is 16.



4.11.7 MG scores

Mean ($\pm$ SEM) MG scores (0 to 7 h) are outlined in Table 4.9, and are also graphically illustrated in Figure 4.14. Comparing the MG scores of methadone (trough session) patients' with control subjects', there was no main effect of group ($F(1,6)=0.9$; $p=0.781$). There was no main effect of time ($F(3.9, 23.4)=2.3$; $p=0.094$), and no significant interaction between group and time ($F(3.9,23.4)=2.1$; $p=0.111$). Similarly, comparing the MG scores of methadone (peak session) patients' with control subjects', there was no main effect of group ($F(1,6)=0.6$; $p=0.818$). There was no main effect of time ($F(3.6, 21.4)=2.6$; $p=0.067$), and no significant interaction between group and time ($F(3.6,21.4)=1.3$; $p=0.290$).

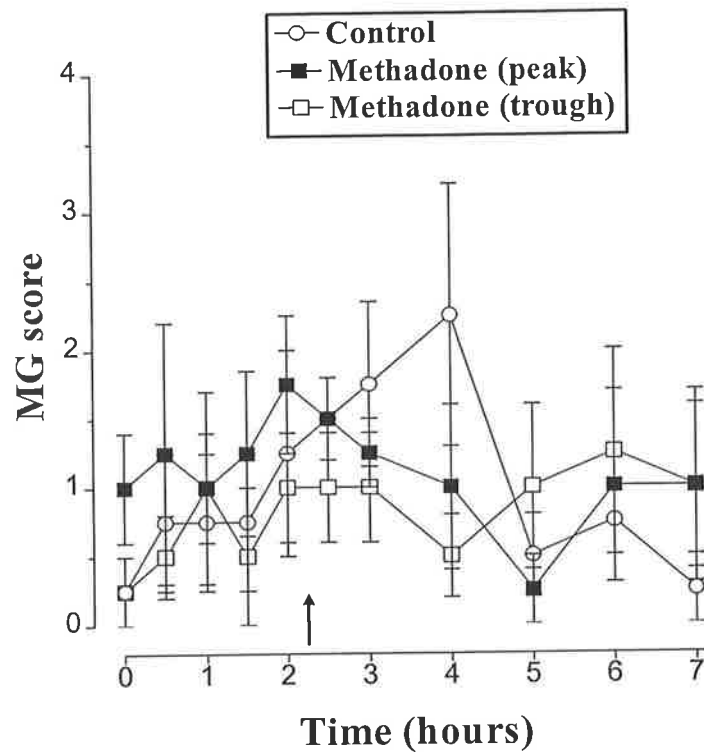
Within-group comparisons (trough versus peak methadone) did not reveal significant differences ($p<0.057$) at any time point.

Table 4.9. Comparison of mean ($\pm$ SEM) MG scores between methadone (trough) patients, methadone (peak) patients, and matched control subjects. The maximum possible score is 8.

Time point	Methadone (trough)	Methadone (peak)	Controls	
0 h	0.25 (0.25)	1.0 (0.4)	0.25 (0.25)	* $p=1.000$, # $p=0.168$, + $p=0.215$
0.5 h	0.5 (0.3)	1.25 (1.0)	0.75 (0.5)	* $p=0.670$, # $p=0.654$, + $p=0.444$
1.0 h	1.0 (0.7)	1.0 (0.4)	0.75 (0.5)	* $p=0.780$, # $p=0.705$, + $p=1.000$
1.5 h	0.5 (0.5)	1.25 (0.6)	0.75 (0.5)	* $p=0.730$, # $p=0.550$, + $p=0.058$
2.0 h	1.0 (0.4)	1.75 (0.5)	1.25 (0.75)	* $p=0.780$, # $p=0.595$, + $p=0.215$
2.5 h	1.0 (0.4)	1.5 (0.3)	1.5 (0.3)	* $p=0.356$, # $p=1.000$, + $p=0.182$
3.0 h	1.0 (0.4)	1.25 (0.25)	1.75 (0.6)	* $p=0.356$, # $p=0.488$, + $p=0.391$
4.0 h	0.5 (0.3)	1.0 (0.6)	2.25 (1.0)	* $p=0.127$, # $p=0.303$, + $p=0.182$
5.0 h	1.0 (0.6)	0.25 (0.25)	0.5 (0.3)	* $p=0.468$, # $p=0.537$, + $p=0.215$
6.0 h	1.25 (1.75)	1.0 (0.7)	0.75 (0.25)	* $p=0.550$, # $p=0.750$, + $p=0.809$
7.0 h	1.0 (0.6)	1.0 (0.7)	0.25 (0.25)	* $p=0.278$, # $p=0.356$, + $p=1.000$

*denotes methadone (trough) vs. controls, # denotes methadone (peak) vs. controls, + denotes trough vs. peak methadone. Where there is statistical significance ($p<0.0045$) this is highlighted in bold text.

Figure 4.14. Mean ($\pm$ SEM) MG scores from 0 to 7 hours in methadone patients during the trough session (open squares) and peak session (filled squares), and matched controls (open circles). Arrow illustrates the time point where methadone (trough) patients received their methadone dose. The maximum possible score is 8.



4.11.8 Pulse oximetry

Mean SpO₂ levels of methadone (trough and peak sessions) patients (97.4 ± 0.3 and 97.5 ± 0.2) were not significantly different from controls (97.3 ± 0.3) at baseline ($p=0.048$, [95%CI, -0.8, 0.01]). Similarly, mean SpO₂ levels of methadone (trough and peak sessions) patients (97.0 ± 0.2 and 97.4 ± 0.1) in the period during and post-morphine administration were not significantly different ($p=0.860$ and $p=0.642$) from those of controls in that period (97.4 ± 0.3).

Comparisons were made between mean SpO₂ levels at baseline and the period during and post-morphine administration for each group. For methadone patients (trough and peak sessions,) SpO₂ values at baseline were not significantly different from those in the period during and post-morphine administration (97.4 ± 0.3 vs 97.0 ± 0.2 , $p=0.108$ and 97.5 ± 0.2 vs. 97.4 ± 0.1 , $p=0.650$). Similarly, for control subjects there were no significant differences (97.3 ± 0.3 vs. 97.4 ± 0.3 , $p=0.530$).

Within-group comparisons (trough versus peak session) of mean SpO₂ levels at baseline did not reveal any significant differences ($p=0.594$). However, for the period during and post-morphine administration, mean SpO₂ levels in the trough session were significantly lower than those during the peak session ($p=0.034$, [95%CI, 0.1, 0.7]). Between-group comparisons were also made between the number of episodes (one episode equals 8 seconds) at 95% SpO₂ and below (see Table 4.10 below). There were no significant differences ($p>0.113$) between the groups at any of these SpO₂ percentage levels.

Comparisons were made between mean SpO₂ values at each of the levels (outlined in Table 4.10) at baseline and the period during and post-morphine administration for each group. There were no significant differences ($p>0.053$) at any level for methadone (trough session) patients. However, for methadone (peak session) patients there were significant differences at the 95% SpO₂ level ($p=0.027$, [95%CI, -32.6, -3.9]) only. For controls, there were no significant differences at any level ($p>0.069$).

Table 4.10. Arterial oxygen saturation (SpO₂). Comparisons of the mean ($\pm$ SEM) number of episodes at oxygen saturation levels at 95% or below for both methadone patients and control subjects at baseline (pre-morphine administration; a period of 30 minutes) and during the infusion (this represents continuous oximetry recording during and post-morphine administration; a period of 6.5 hours). One episode is equivalent to 8 seconds.

	CONTROL SUBJECTS		METHADONE PATIENTS			
			Trough session		Peak session	
	Baseline	Infusion	Baseline	Infusion	Baseline	Infusion
95% SpO₂	6 (6)	58 (29)	1 (1)	65 (20)	2 (2)	20 (5)
94% SpO₂	0 (0)	15 (7)	0 (0)	16 (7)	0 (0)	4 (2)
93% SpO₂	0 (0)	2 (1)	0 (0)	4 (2)	0 (0)	2 (2)
92% SpO₂	0 (0)	1 (1)	0 (0)	3 (1)	0 (0)	0 (0)
91% SpO₂	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
90% SpO₂	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)

4.12 Adverse events

As described in the preceding chapter all control subjects experienced mild nausea for very brief periods (< 20 minutes) during the morphine infusion. Two control subjects vomited 3-5 hours after the infusion had ceased. All control subjects completed testing. None of the methadone patients experienced any adverse events.

4.13 Discussion

4.13.1 Physiological effects

In the current study there were significant respiratory depressant effects associated with plasma morphine concentration in the control subjects, but not in methadone maintenance patients. This is consistent with the findings of Tress and El-Sobky (1980) who found that non-dependent volunteers had a significantly greater reduction in respiratory rate (which remained significantly lower for a longer period of time) compared with an opioid dependent group. This respiratory depression in the control subjects in response to administration of morphine is also consistent with a number of other previous reports (Jasinski & Preston, 1986a,b; Preston *et al.*, 1987; Sullivan *et al.*, 1992). However, not all studies involving administration of morphine to healthy volunteers observe these effects. Zacny and colleagues (1994) reported a dose-response analysis of the subjective and physiological effects of intravenous morphine (0, 2.5, 5.0 and 10mg/kg) in healthy volunteers using a randomised, double-blind, crossover design. They did not find a significant decrease in respiration rate. Interestingly, the current finding of morphine-induced respiratory depression amongst the healthy volunteers (in tandem with increased tolerance to experimental pain induction) is similar to that previously reported by Gal *et al.* (1982). They compared the respiratory depressant and analgesic effects of nalbuphine and morphine, given as single 0.15 mg/kg doses and as four successive doses of 0.15 mg/kg, in six healthy male subjects.

The absence of any clinically significant respiratory depressant effects related to administration of morphine in the methadone maintenance patients in the current study suggests that, at the doses used (and at the plasma morphine concentrations achieved), methadone patients have developed a degree of cross-tolerance to these effects. Despite the apparent cross-tolerance to morphine's respiratory depressant effects in the methadone patients, there was a significant within-group (trough vs. peak session) difference in respiratory rates; baseline respiratory rates in the peak session were significantly lower than those measured at baseline in the trough session. This finding is consistent with results reported by Dyer *et al.* (1999), and is in keeping with the decreases in respiratory rate in association with increases in plasma methadone concentrations from trough to peak which were reported earlier in this chapter (section 4.8.4). This suggests that there is incomplete cross-tolerance to the respiratory depressant effects of opioid drugs, and that methadone may be a more potent respiratory depressant than morphine. Further research, without involving pain stimuli, is needed to fully elucidate the comparative respiratory depressant

effects of different opioid drugs in methadone maintained patients.

Morphine-induced miosis has previously been reported in studies with healthy volunteers (Fraser & Isbell, 1952; Ghoniem *et al.*, 1984; Nicolodi & Sicuteri, 1992) and in opiate abusers (Fraser and Isbell, 1952; Jasinski & Mansky, 1972; Lamb *et al.*, 1991), and is a well known marker of opioid effect. Tress and El-Sobky (1980) suggested that the measurement of pupil diameter provides the most productive information about reactions to opioid drugs in opioid dependent (heroin or methadone) and non-dependent subjects.

In the present study morphine-induced miosis was most marked in the control subjects, but less marked in the methadone maintenance patients. This is similar to the findings of Azorlosa *et al.* (1994); they compared the effects of single dose versus repeated dose morphine (15mg/70kg) in a sample of opioid abusers (n=20) and control subjects (n=20). They found that although pupil constriction was evident in both groups, it was most marked in the control subjects. In the present study, the miosis in the control group remained marked for at least 5 hours after morphine administration had ceased. Indeed, the miosis in the control subjects remained highly significant at the end of the testing session. These findings in the control subjects are in keeping with those observed in previous studies involving the administration of morphine to opioid naïve healthy volunteers; it has been reported that miosis was induced in a dose-dependent manner, and was still evident 5 hours post injection (Zacny *et al.*, 1994; Walker & Zacny, 1999). Overall these combined findings support the conclusions of Ghoniem and colleagues (1984) that morphine-induced miosis is of long duration in healthy volunteers. Morphine-induced miosis was evident in the methadone patients, although it was somewhat less marked than in the control subjects, thus indicating that in this patient population there is incomplete cross-tolerance to this physiological marker of opioid effect. This finding is similar to that reported by Strain *et al.* (1992) who administered buprenorphine, hydromorphone, and naloxone to a group (n=6) of methadone maintained patients; they found that hydromorphone (10mg) decreased the pupil sizes of the patients.

There were statistically significant differences in heart rate between control subjects and methadone patients (trough session only) in the present study. Heart rate changes have been found in previous studies involving morphine administration (Ivy *et al.*, 1944; Foltin & Fischman, 1992) but not in others (Jasinski & Preston, 1986a,b; London *et al.*, 1990; Wright *et al.*, 1992; Zacny *et al.*, 1994). There does not seem to be a consistent effect on heart rate across studies.

There were no significant effects of morphine on systolic or diastolic blood pressure in control subjects or methadone maintenance patients in the present study. There does not appear to be a consistent effect of morphine in humans studies; in some studies there have been decreases in systolic and/or diastolic blood pressure (Ivy *et al.*, 1944; Preston *et al.*, 1987; Foltin & Fischman, 1992; London *et al.*, 1990; Sullivan *et al.*, 1992) but not in others (Jasinski & Preston, 1986a,b; Wright *et al.*, 1992; Lamb *et al.*, 1991; Zacny *et al.*, 1994). It is not clear why this variability exists across studies; dose and positioning (supine vs. erect) do not appear to be factors (Zacny *et al.*, 1994).

Cross-tolerance between methadone and other opioids has been the subject of previous investigations; Dole *et al.* (1966) and Zaks *et al.* (1971) using 100mg of methadone per day as the minimum dose, reported pronounced cross-tolerance to heroin. However, Gunne and Holmstand (1974), who administered 30mg of methadone daily, had some difficulty demonstrating cross-tolerance to morphine. Volavka *et al.* (1978) used 12 male post-addicts who had previously been drug free for at least 6 weeks. They administered methadone doses of 40 and 80mg per day for a period of 6 weeks; subjects then received injections of heroin (0.214mg/kg) and placebo at various times before and during methadone treatment. The investigators reported that subjects on both dosing schedules developed an incomplete cross-tolerance to that dose of heroin. Furthermore, their findings indicated that after 19 days on methadone, the cross-tolerance to a moderate dose of heroin was not complete (ie, the response to heroin was greater than to placebo). They suggested that pupillary constriction is a more sensitive measure of heroin effect than the subject's report. They also reported that pupil response to heroin decreased with duration of methadone treatment, irrespective of the dose or plasma level of methadone.

Sedation scores were measured in the present study for safety purposes. It has been reported that sedation is a good indicator of respiratory depression (Ready *et al.*, 1988; National Health and Medical Research Council, 1999; Macintyre & Ready, 2000). There were no significant sedation scores in either the control group or methadone patients during the period of morphine administration. Nonetheless, I would suggest that sedation scores should be used as a matter of course in all clinical experiments involving the use of opioids.

There were no clinically or statistically significant effects of morphine administration on arterial oxygenation as measured by non-invasive pulse oximetry. Methadone patients' and control subjects' mean oxygenation levels were within normal clinical parameters (96-99%).

In methadone patients, there was a small but not clinically significant effect of plasma methadone concentration on arterial oxygenation levels; interestingly SpO₂ levels were slightly lower when plasma methadone concentration was at the putative trough. Furthermore, the occurrence of occasional episodic hypoxaemia without significant respiratory depression in this study is consistent with opioid administration (National Health and Medical Research Council, 1999; Macintyre & Ready, 2000). Pulse oximetry did not reveal significant opioid effects on arterial oxygenation; indeed, others have suggested that this measure may not be a reliable method for measuring the interaction between pain, opioids and respiration (Catley *et al.*, 1985; Bulow *et al.*, 1995; Borgbjerg *et al.*, 1996; Macintyre & Ready, 2000).

It has been suggested that there are fewer adverse sequelae (nausea and vomiting) associated with morphine when the subject is in bed as opposed to when ambulatory (Comroe & Dripps, 1948; Price *et al.*, 1985). These sequelae, which were evident in the healthy volunteers but not in methadone patients in the present experiment, may be related to reflexes in the vestibular apparatus that are activated by changes in body position (supine vs. erect) (Gutner *et al.*, 1952). All subjects in the present study were required to move from a seated position to kneeling on cushions at regular intervals; this movement could well have increased the likelihood and/or exacerbated the nausea and vomiting observed in the control subjects. The incidence of nausea and vomiting seen in the present study is not unusual when administering morphine to healthy (opioid naïve) volunteers (Zacny *et al.*, 1994; 1997). It has been suggested that these phenomena are more likely to occur when doses of morphine higher than 10mg are used (Christie *et al.*, 1958); control subjects in the present study received 12.95 mg over a 2 hour period. In an early randomised placebo controlled study comparing the effects of morphine 20mg (s.c) between 24 male post-addicts (no narcotics in the previous 6 months) and 20 healthy male volunteers, there was a significant incidence of vomiting amongst the control group, with 7 of them vomiting on at least one occasion (Fraser & Isbell, 1952).

4.13.2 Subjective effects

The lack of significant subjective effects (as measured by MBG and MG scores) related to morphine administration in the present study was not unexpected, due to the frequency of pain induction (and nausea in control subjects) throughout the testing sessions. There is some evidence that experimental pain attenuates the subjective and behavioural effects of opioid drugs (Wolff *et al.*, 1940; Borgbjerg *et al.*, 1996). This suggests that in the context of acute pain management, methadone patients are unlikely to experience a classic “high” from the administration of additional opioids.

Interestingly, baseline MBG scores in methadone (peak session) patients were significantly higher than those of control subjects at baseline. This is similar to previous reports comparing MBG scores of methadone maintained patients, at putative peak plasma concentrations, with those of control subjects (Dyer *et al.*, 1999). Zacny and colleagues (1994) concluded that MBG score increases were not related to morphine dose, and were not a particularly robust measure. This suggests that in the presence of repeated nociceptive stimuli, MBG scores are not a reliable measure of subjective opioid effect. Furthermore, the fact that morphine effects were judged to be unpleasant, as reported verbally by the control subjects in the present study, is consistent with findings of earlier studies involving morphine administration to healthy volunteers (Brown, 1940; Smith & Beecher, 1962; Bourke *et al.*, 1984).

The safe use of morphine in human experimental research has been well documented (Fraser & Isbell, 1952; Jarvik *et al.*, 1981; Ghoniem *et al.*, 1984; Wright *et al.*, 1992; Zacny *et al.*, 1994; Bochner *et al.*, 1999). In terms of addiction liability, there is no evidence that once only, acute administration of sedative or analgesic drugs in a medical setting using healthy volunteers increases the risk for subsequent abuse or dependence (Porter & Hick, 1980; Schuster, 1989). Given that exposure to morphine was strictly limited to one occasion for the control subjects, I am confident that the risk of control subjects becoming addicted to morphine is very low for the following reasons: (1) the drug was administered in a controlled setting under close supervision of study personnel, (2) as outlined above the drug was given on only one occasion, (3) there is strong evidence in the literature that experimental pain attenuates subjective and behavioural effects of opioid drugs (Wolff *et al.*, 1940; Borgbjerg *et al.*, 1996), and (4) control subjects were only included in this study if they had no prior history of drug abuse.

4.13.3 Summary

The combined results from both studies presented in this chapter indicate that methadone patients have a significantly lower respiratory rate compared with healthy control subjects; the difference in respiratory rate is most pronounced when methadone patients' plasma methadone concentrations are at the putative peak. Plasma morphine concentrations known to produce analgesia in opioid-naïve patients had little effect on the respiratory rate of methadone patients, but had a marked depressant effect among the control group. These results suggest that in methadone maintenance patients, methadone itself may be a more potent respiratory depressant than morphine; further studies are needed to determine the relative respiratory depressant potencies of these drugs. With regard to miosis, methadone had a significant effect on patients' pupil sizes within the inter-dosing period; miosis was most pronounced at the time of peak plasma methadone concentrations. The administration of morphine resulted in marked reductions in the pupil sizes of control subjects, but only very small reductions in the methadone patients; this suggests that methadone patients have partial tolerance to the effects of opioid drugs. There were no clinically significant cardiovascular effects in relation to additionally administered morphine. Overall, these results suggest that plasma morphine concentrations known to produce analgesia in opioid-naïve patients have only minor physiological effects amongst methadone maintenance patients. The lack of significant changes as measured by MBG and MG scales also suggests that in the context of acute pain management, methadone patients are unlikely to experience a classic "high" from the administration of additional opioids. Further studies using substantially larger doses (and plasma concentrations) of morphine in a larger sample of methadone maintenance patients would be of value.

ANTINOCICEPTIVE, PHYSIOLOGICAL AND SUBJECTIVE EFFECTS OF (+)- (S)-KETAMINE, ALONE AND IN COMBINATION WITH MORPHINE, IN METHADONE MAINTENANCE PATIENTS.

5.1 Introduction

I previously reported in chapters two and three that methadone maintenance patients are hyperalgesic compared with age and sex-matched control subjects. This finding of hyperalgesia in methadone patients is, to the best of my knowledge, the first controlled study demonstrating this phenomenon in humans. This supports earlier evidence of altered pain sensitivity related to chronic opioid exposure in rats (Mao *et al.*, 1994, 1995a, 1995b; Laulin *et al.*, 1999). Overall, these combined results suggest that chronic opioid exposure in general may result in hyperalgesia. In addition, in the preceding chapter, I also reported that methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine.

The NMDA (N-methyl-D-aspartate) ion channel receptor is regarded as being principally responsible for the induction and maintenance of hyperalgesia (Dickenson, 1994). Mao and colleagues (1995b) suggested that both hyperalgesia and the development of opioid tolerance involve activation of the NMDA receptor; specifically the intracellular processes thought to be linked to NMDA receptor activation (eg. synthesis of NO, increases in the levels of protein kinases such as protein kinase C, increased levels of Ca^{++}). Others have proposed that activation of the NMDA ion channel receptor following chronic opioid treatment may reduce the magnitude and duration of opioid-induced antinociception (Wiesenfeld-Hallin, 1998). Chronic opioid treatment could be indirectly activating this receptor via an increase in protein kinase C, which removes the Mg^{2+} blockade of the NMDA receptor (Chen & Huang, 1992; Mayer & Mao, 1999). Dickenson (1997) proposed that this activation will itself contribute to poor opioid sensitivity because it will increase excitation in the pain transmitting systems.

Interestingly, the co-administration of NMDA receptor antagonists with opioids has been shown to reduce and/or reverse the development of tolerance to opioids in rats (Trujillo & Akil, 1991 & 1994; Tiseo & Inturrisi, 1993; Elliott *et al.*, 1994; Mao *et al.*, 1996; Shimoyama *et al.*, 1996). Whilst methadone itself is a non-competitive NMDA receptor

antagonist (Gorman *et al.*, 1997; Ebert *et al.*, 1998) the clinical implications of this for humans chronically administered methadone are unknown. In particular, the magnitude of NMDA antagonist activity achieved at normal therapeutic concentrations is unknown.

Clinically, there is considerable evidence that NMDA receptor antagonists are effective adjuncts to opioids for the relief of pain. There are indications that a ketamine-opioid combination could provide superior analgesia compared to an opioid alone (Parkhouse & Marriott, 1977; Bristow & Orlikowski, 1989; Javery *et al.*, 1996; Stubhaug *et al.*, 1997; Suzuki *et al.*, 1999), and that such a combination will reduce opioid tolerance, further enhancing treatment efficacy (Bell, 1999). Furthermore, there is evidence that these combinations result in a significant reduction in opioid consumption (Cherry *et al.*, 1995; Chia *et al.*, 1998). Indeed, it has even been suggested that NMDA antagonists such as ketamine may be effective in improving opioid analgesia in difficult pain syndromes, such as neuropathic pain (Mercadante *et al.*, 2000).

Ketamine is a non-competitive NMDA ion channel-blocking drug (Church & Lodge, 1990) that is used in clinical practice (White, 1988). Ketamine, first approved for clinical use in 1970 (Schmid *et al.*, 1999), is generally used as a racemate that contains equal amounts of the two enantiomers (+)-(S)- and (-)-(R)-ketamine. These enantiomers differ in their pharmacokinetics and pharmacodynamic effects (Kharasch & Labroo, 1992). In animals and humans, (+)-(S)-ketamine is approximately 2-4 times more potent than (-)-(R)-ketamine for pain relief (Marietta *et al.*, 1977; Ryder *et al.*, 1978; White *et al.*, 1985; Øye *et al.*, 1992; Geisslinger *et al.*, 1993; Mathison *et al.*, 1995; Arendt-Nielsen *et al.*, 1996). Furthermore, it has been suggested that, at equianalgesic doses, (+)-(S)-ketamine produces fewer psychotomimetic disturbances and less agitation than (-)-(R)-ketamine or the racemate (White *et al.*, 1980; Calvey, 1995). However, others suggest that (+)-(S)-ketamine is a more potent psychedelic than (-)-(R)-ketamine (Jansen, 2000). Nevertheless, it has been concluded that in the clinical environment using (+)-(S)-ketamine is more rational than using the racemic compound (Arendt-Nielsen *et al.*, 1995; Geisslinger *et al.*, 1993; Shimoyama *et al.*, 1996).

Evidence of the psychotogenic properties of ketamine emerged initially from general anaesthetic use where clinicians documented post-anaesthetic reactions that were characterised by confusional states, vivid dreaming and hallucinations (Siegel, 1978). These 'emergence' phenomena limited the clinical use of ketamine as an anaesthetic. Recent studies (Krystal *et al.*, 1994; Malhotra *et al.*, 1996) have assessed sub-anaesthetic doses of

ketamine in healthy volunteers. The findings from those studies included a range of positive and negative schizophrenic-like symptoms, as well as perceptual changes similar to dissociative states (eg. altered body perceptions, distorted sensory perceptions, and depersonalisation). In a study involving the administration of ketamine to chronic, but stable schizophrenic patients, there was a re-emergence of symptoms typical of acute schizophrenia (Lahti *et al.*, 1993).

I am unaware of any studies in which ketamine or (+)-(S)-ketamine have been administered to methadone maintenance patients. Hence, apart from investigating its antinociceptive effects, it would be of clinical interest to ascertain other physiological and subjective effects.

5.1.1 Aims of present study

The aims of the current experiment were to investigate (1) the antinociceptive effects, and (2) the physiological and subjective effects, of low dose (+)-(S)-ketamine alone and in combination with morphine, at consecutive pseudo steady-state plasma concentrations in a sample of methadone maintenance patients and age and sex-matched control subjects.

Hypotheses:

1. (+)-(S)-ketamine alone will induce antinociception in methadone maintenance patients, but not in control subjects.
2. (+)-(S)-ketamine in combination with morphine will have greater antinociceptive effects than (+)-(S)-ketamine alone in control subjects, but not methadone maintenance patients.
3. (+)-(S)-ketamine alone, or in combination with morphine will not have significant physiological or subjective effects amongst methadone patients.

5.2 Methods

5.2.1 Patients and control subjects

Approval for this open label study was given by the Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia. Four patients (3 male and 1 female), age range 34 – 42 (mean=37) years, who had been enrolled in the South Australian Public Methadone Maintenance Program for at least 9 months (range 9 months to 20 years), with no dose changes in the previous four months were recruited. The average dose of methadone was $52.5\text{mg} \pm 25$ (mean $\pm$ SEM) (range 30-75 mg; 0.45–1.60 mg/kg). Methadone patients who self-reported intravenous heroin use at a frequency of more than once per month but less than once per week, were recruited, as it was deemed more ethical to administer (+)-

(S)-ketamine and morphine to individuals who continued to use illicit heroin, rather than giving these drugs to patients who were abstaining from using opioids other than their prescribed dose of methadone. Four age and sex-matched healthy volunteers were recruited as control subjects.

Exclusion criteria for both groups included those currently receiving therapy for pain, those with a history of cardiac, pulmonary (particularly asthma), hepatic or renal disease, neurological disorders (eg. epilepsy), HIV positive serology, a major psychiatric condition that would prevent giving informed consent, pregnancy and/or lactation. A urine sample was collected from each participant for the detection of opioids (other than methadone), benzodiazepines, sympathomimetic amines, cannabinoids and barbiturates. None of the control subjects had taken any known psychoactive substance, other than caffeine, nicotine and/ or alcohol, in the month before commencement of the study. One of the methadone patients tested positive (on one occasion) for morphine; indeed this patient's baseline plasma morphine concentration, during the (+)-(S)-ketamine plus morphine session (outlined below), was 9.75 ng/mL. None of the other patients tested positive to any other opioid drug except their prescribed methadone. Three of the methadone patients admitted to smoking cannabis at least twice per week. None of the four patients baseline samples contained any ketamine. All 4 methadone patients smoked cigarettes daily. None of the control subjects' baseline plasma samples contained morphine or ketamine. One of the 4 control subjects smoked cigarettes. All subjects were paid for their participation in this study.

5.2.2 Study design

Methadone patients and control subjects were tested on two occasions (0900-2000), separated by 7-10 days. They were randomly allocated into two sub-groups: two patients and two control subjects were given (+)-(S)-ketamine alone first, and the other two patients and controls were given (+)-(S)-ketamine and morphine first. The order was reversed for the second session. Methadone patients commenced testing when their plasma methadone was at putative peak concentrations (ie. commencing 2 hours after their methadone dose was administered). Control subjects did not receive methadone.

5.2.2.1 Drug administration

Both drugs were administered intravenously as a 2 step, controlled infusion designed to produce consecutive target plasma concentrations (see section 3.2.2.1), using a Harvard 22 Basic Syringe Pump® (Harvard Apparatus, South Natick, MA, USA). The (+)-(S)-ketamine (Ketanest®) used in this study was kindly donated to the Department of Clinical and Experimental Pharmacology by Parke Davis (Freiburg, Germany). The details of the present design are as follows: in both treatment sessions methadone patients and control subjects were given an initial bolus dose of (+)-(S)-ketamine 1.1mg, followed by a constant infusion rate of 0.6 mg/hour for one hour to achieve the first target pseudo steady-state plasma (+)-(S)-ketamine concentration (C_{ss1}) of 10ng/mL. At 60 minutes, methadone patients and control subjects were given an additional bolus dose of (+)-(S)-ketamine 2.1mg and the infusion rate increased to 1.8mg/hour for one hour to achieve the second pseudo steady-state plasma (+)-(S)-ketamine concentration (C_{ss2}) of 30ng/mL.

During the drug combination session ((+)-(S)-ketamine plus morphine), in addition to the (+)-(S)-ketamine regimen described above, at 0 hour, methadone patients and controls also received a bolus dose of morphine 2.2mg, followed by an infusion rate of 1.2mg/hour for two hours to achieve and maintain a pseudo steady-state (C_{ss}) plasma morphine concentration of 20ng/mL (in the period from 0.5 hour to 2.0 hours). The total period of drug administration in both treatment sessions was two hours.

5.2.3 Procedures and measures

The study was conducted in a temperature-controlled room (24 °C) under constant illumination (75 lux). Each testing session occurred over 10 hour periods, approximately 0900-2100. Only one subject was tested per session. Two indwelling venous catheters were inserted into the two best available, but opposite, peripheral arm veins; one (22 gauge catheter, Insyte™, Becton Dickinson, Franklin Lakes, NJ, USA) on the dominant arm, for drug administration and the other (18 gauge catheter, Optiva™, Critikon, Rome, Italy) on the non-dominant arm for blood sampling. Venous blood samples (6mL) were collected at 0 hour (pre-intravenous drug administration), 0.5, 0.75, 1.0, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 4.0, 5.0, 6.0 and 7.0 hours after the beginning of the infusion. The blood samples were centrifuged, and the plasma stored at -20° C until assay.

5.2.3.1 Pain induction

Two methods of pain induction were used to determine nociceptive responses, electrical stimulation via an ear lobe, and a cold pressor test using the non-dominant arm as previously described in detail in chapter two (section 2.5). Two indices for measuring pain were used: (1) when subjects first perceived pain (detection), and (2) when they could no longer tolerate the stimulus intensity (tolerance). These indices were quantified as volts for the electrical stimulation, and as seconds for the cold pressor test. Nociceptive responses were recorded at 0 hour, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 7.0 hours after beginning the morphine infusion.

5.2.3.2 Physiological and subjective measures

A number of physiological and subjective measures were recorded at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 7.0 hours; these included respiratory rate, pupil size, heart rate, blood pressure, sedation scores, pulse oximetry (initially for 30 minutes (baseline), and continuously for 6.5 hours after commencement of intravenous drug administration), the MBG scale, the MG scale, and the lysergic acid diethylamide (LSD) scale (appendix 2). All of those measures, except the LSD scale, have been described in detail in section 4.3 and section 4.11.3.1.

The LSD scale is a sub-scale of the Addiction Research Centre Inventory. It is a 14-item scale, which is answered on a true-false format; 4 items are false and 10 items are true, therefore the maximum score is 10. This scale estimates dysphoric and psychotomimetic changes (Martin *et al.*, 1971). Furthermore, unplanned (*ad hoc*) records of methadone patients' and control subjects' verbal comments during the period of drug administration, are presented in the results section.

5.2.4 Plasma (+)-(S)-ketamine concentrations

Plasma (+)-(S)-ketamine concentrations were quantified by Mr. Andrew Menelaou (Research Assistant, Department of Clinical and Experimental Pharmacology, Adelaide University) using a high-performance liquid chromatographic (HPLC) method with UV (ultra violet) detection. The method has a limit of quantification of 2 ng/mL. Intra- and inter-assay precision and inaccuracies were less than 6% for all quality control samples. For each subject, I collected all blood samples from an indwelling catheter, and then centrifuged each sample. The plasma was then stored at -20 °C in pre-labeled plastic containers in

preparation for later analysis. Methadone and/or morphine did not interfere with this method. Mr. Menelaou gave me a list of the actual plasma concentrations for every sample. I then used these data for subsequent analysis and interpretation.

5.2.5 Plasma morphine concentrations

Plasma morphine concentrations were quantified by Mr. Andrew Menelaou (Research Assistant, Department of Clinical and Experimental Pharmacology, Adelaide University), using a high-performance liquid chromatographic (HPLC) – electrochemical detection method. High (20ng/ml) and low (2ng/ml) quality control samples were assayed with each set of subject's plasma samples, and were within 10 and 15% respectively of the nominal concentrations. Methadone and/or (+)-(S)-ketamine did not interfere with this method. For each subject, I collected all blood samples from an indwelling catheter, and centrifuged each sample. The plasma was then stored at –20 °C in pre-labelled plastic containers in preparation for later analysis. Mr. Menelaou gave me a list of the actual plasma concentrations for every sample. I then used these data for subsequent analysis and interpretation.

5.2.6 Plasma methadone concentrations

(-)-(R)- and (+)-(S)-methadone were quantified in plasma by Mr. Andrew Menelaou (Research Assistant, Department of Clinical and Experimental Pharmacology, Adelaide University) using high-performance liquid chromatography (HPLC) as described by Foster *et al.* (2000). The method has a limit of quantification of 15ng/ml for each enantiomer. Inter- and intra-day precision and accuracy data, of low, medium and high quality control concentration, as assessed by the coefficients of variation, were less than 12%. For each subject, I collected all blood samples from an indwelling venous catheter, and centrifuged each sample. The plasma was then stored at –20 °C in pre-labelled plastic containers in preparation for later analysis. (+)-(S)-ketamine and morphine did not interfere with this method. I then used these data for subsequent analysis and interpretation

5.2.7 Statistical and other analyses

Data are presented as mean $\pm$ SEM (with 95% confidence intervals, CI). Two-way repeated measures analyses of variance (ANOVA) were used to determine differences in pharmacodynamic responses among methadone patients and control subjects. To account for sphericity, the Greenhouse-Geisser conservative F-test was used to interpret the ANOVA. As there are only two groups (methadone patients and control subjects), the statistical software used in this analysis did not conduct *post hoc* tests; hence, specific between-group comparisons (methadone vs. control) were made using Student's *t* tests (independent) with an alpha level of $p < 0.0045$, and within-group comparisons were made using Student's *t* tests (paired) with an alpha level of $p < 0.005$. All such *t* tests involved multiple comparisons. Hence, I adjusted the alpha accordingly using a Bonferroni adjustment ($p < 0.05/n$). The relevant alpha level is outlined in each part of the results section of this chapter. Pain tolerance to detection ratios were also calculated. Comparisons of SpO₂ percentages (within- and between-group) were analysed by Student's *t* tests (independent and paired). All data were analysed using SPSS™ for Windows (version 10, SPSS Inc., Chicago, Illinois, USA), which carried out tests for homogeneity of variance and adjusted the *p* value accordingly.

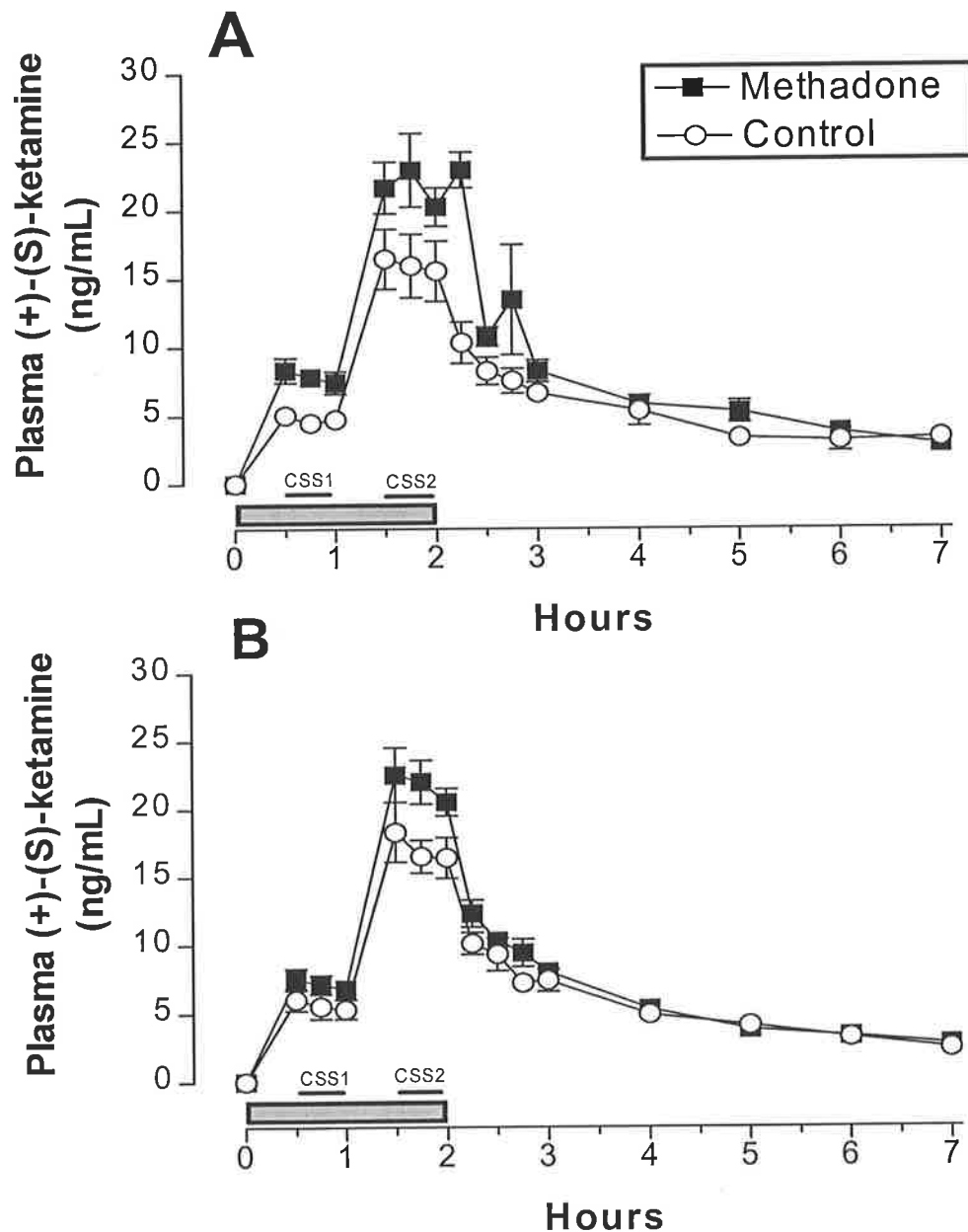
5.3 Results.

5.3.1 Plasma (+)-(S)-ketamine concentrations.

Mean (+)-(S)-ketamine concentrations are illustrated in Figure 5.1. During C_{ss1} in the (+)-(S)-ketamine only session, methadone patients' mean ($\pm$ SEM) (+)-(S)-ketamine concentrations, 7.84 ($\pm$ 0.7) ng/mL, was significantly greater ($p=0.012$, [95% CI, 0.99,5.24]) than the control subjects' mean of 4.72 ($\pm$ 0.5) ng/mL. During C_{ss2} there were no significant differences ($p=0.092$) between the groups; methadone patients' mean ($\pm$ SEM) (+)-(S)-ketamine concentrations was 21.6 ($\pm$ 1.8) ng/mL, whereas controls' for the same period was 15.9 ($\pm$ 4.4) ng/mL.

In the (+)-(S)-ketamine plus morphine session, there were no significant differences during either C_{ss} period ($p>0.083$); methadone patients' mean ($\pm$ SEM) (+)-(S)-ketamine concentrations during C_{ss1} was 7.2 ($\pm$ 0.5) ng/mL, whereas for controls, mean (+)-(S)-ketamine concentrations during the same period was 5.6 ($\pm$ 0.8) ng/mL. During C_{ss2} , methadone patients' mean ($\pm$ SEM) (+)-(S)-ketamine concentrations was 21.7 ($\pm$ 1.5) ng/mL, whereas controls' for the same period was 17.1 ($\pm$ 1.6) ng/mL.

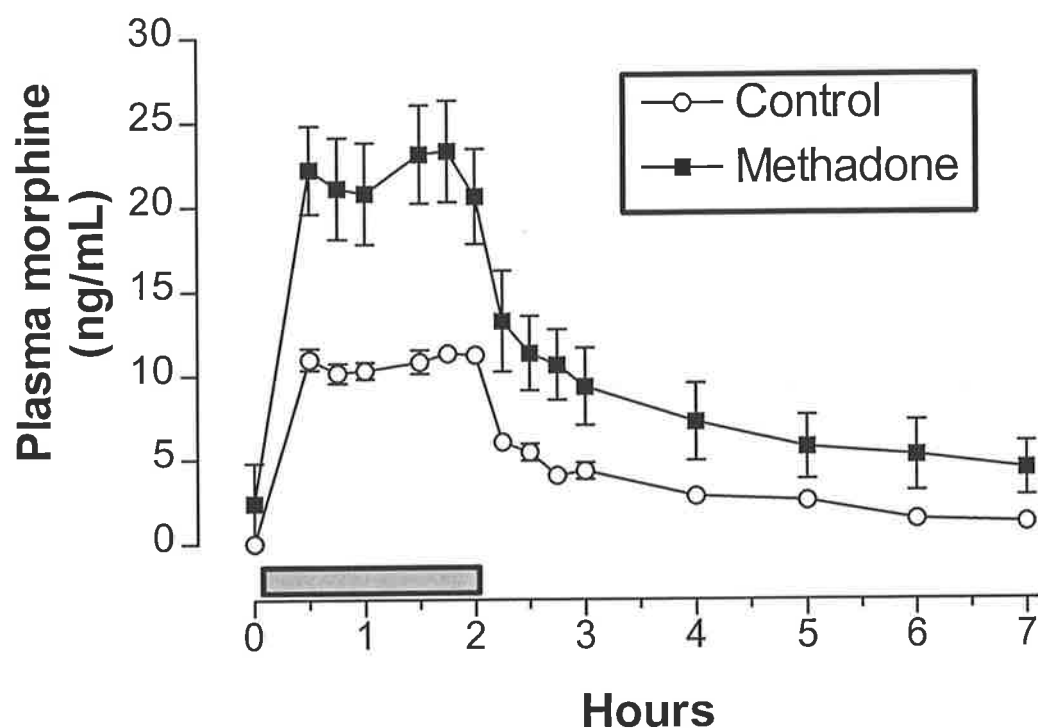
Figure 5.1. Mean ($\pm$ SEM) plasma (+)-(S)-ketamine concentrations (0 to 7 hours) in methadone patients (filled squares) and matched controls (open circles). Panel A: during (+)-(S)-ketamine only session. Panel B: during (+)-(S)-ketamine plus morphine session. Grey shaded rectangle illustrates the period in which additional drugs were administered; C_{SS1} and C_{SS2} periods are also highlighted.



5.3.2 Plasma morphine concentrations.

Mean ($\pm$ SEM) plasma morphine concentrations are illustrated in Figure 5.2. Methadone patients' mean ($\pm$ SEM) plasma morphine concentration, 21.9 ($\pm$ 2.7) ng/mL, during the C_{ss} period (0.5 to 2.0 hours) was significantly higher ($p=0.007$, [95% CI, 4.3, 17.9]) than that of control subjects, 10.8 ($\pm$ 0.5) ng/mL.

Figure 5.2. Mean ($\pm$ SEM) plasma morphine concentrations (0 to 7 hours) in methadone patients (filled squares) and matched controls (open circles). Grey shaded rectangle illustrates the period of the morphine infusion.

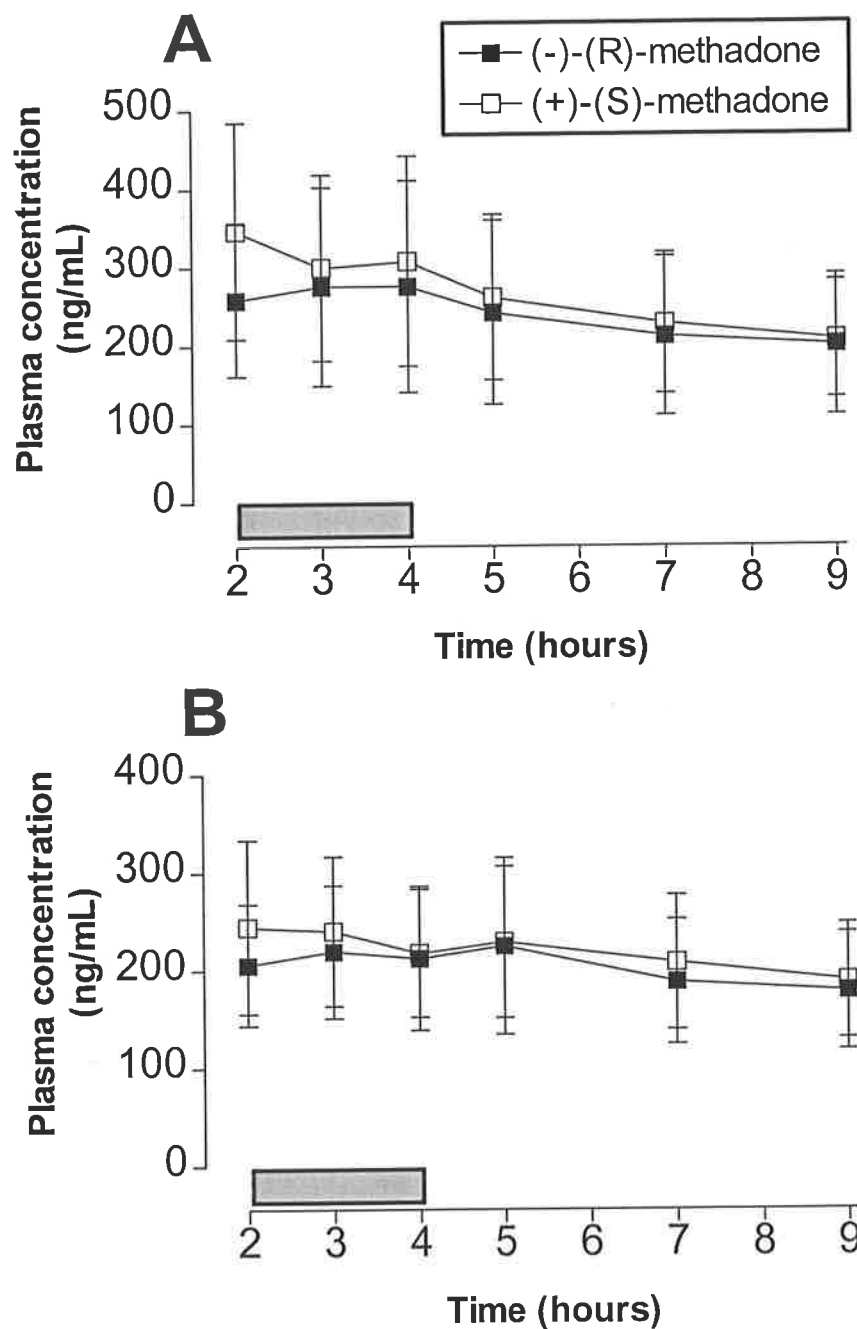


5.3.3 Plasma methadone concentrations

Mean plasma (-)-(R)- and (+)-(S)-methadone concentrations during both treatment sessions are shown in figure 5.3. The range of mean ($\pm$ SEM) plasma (-)-(R)- and (+)-(S)- methadone concentrations during the 2 hour period of (+)-(S)-ketamine administration in the (+)-(S)-ketamine only session was 259 ($\pm$ 97) to 276 ($\pm$ 135) ng/mL for the (-)-(R)- enantiomer, and 300 ($\pm$ 118) to 347 ($\pm$ 138) ng/mL for the (+)-(S)- enantiomer. The range of mean ($\pm$ SEM) plasma (-)-(R)- and (+)-(S)- methadone concentrations during the 2 hour period of (+)-(S)-ketamine plus morphine administration was 206 ($\pm$ 62) to 219 ($\pm$ 68) ng/mL for the (-)-(R)- enantiomer, and 218 ($\pm$ 65) to 245 ($\pm$ 89) ng/mL for the (+)-(S)- enantiomer.

Within-group and between session ((+)-(S)-ketamine alone versus (+)-(S)-ketamine plus morphine) comparisons of (-)-(R)- and (+)-(S)-methadone concentrations were also made; there were no significant differences for the (-)-(R)-enantiomer ($p > 0.373$; range, $p = 0.374$ to 0.688) or for the (+)-(S)- enantiomer ($p = 0.358$; range, $p = 0.359$ to 0.718) at any time point.

Figure 5.3. Mean ($\pm$ SEM) plasma methadone concentrations in the period 2 to 9 hours after the methadone dose was administered. Panel A: during (+)-(S)-ketamine only session. Panel B: during (+)-(S)-ketamine plus morphine session. Grey shaded rectangle illustrates the period in which additional drugs were administered.



5.3.4 Cold Pressor Test

5.3.4.1 Pain detection

Mean ($\pm$ SEM) pain detection responses (0 to 7 h) are outlined in Table 5.1, and are also graphically illustrated in Figure 5.4. Comparing the pain detection values of methadone patients with control subjects' during the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=11.3$; $p=0.015$); post hoc analysis revealed that methadone patients' pain detection values were lower, but not significantly, than those of control subjects ($p>0.005$). There was no main effect of time ($F(3.1,18.8)=2.3$; $p=0.112$), nor was there a significant interaction between group and time ($F(3.1,18.8)=1$; $p=0.409$)

Comparing the pain detection values of methadone patients with control subjects' during the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=8.2$; $p=0.028$); specifically, methadone patients' pain detection values were significantly lower than those of control subjects at 7 h ($p<0.0005$, [95%CI, -4.4, -2.1]) only. There was a main effect of time ($F(3.2,19.4)=11.8$; $p<0.0005$), but no significant interaction between group and time ($F(3.2,19.4)=2.3$; $p=0.104$)

Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) revealed that for methadone patients there were no significant differences ($p>0.057$) at any time point. Similarly, there were no significant differences between the treatment sessions for control subjects ($p>0.040$).

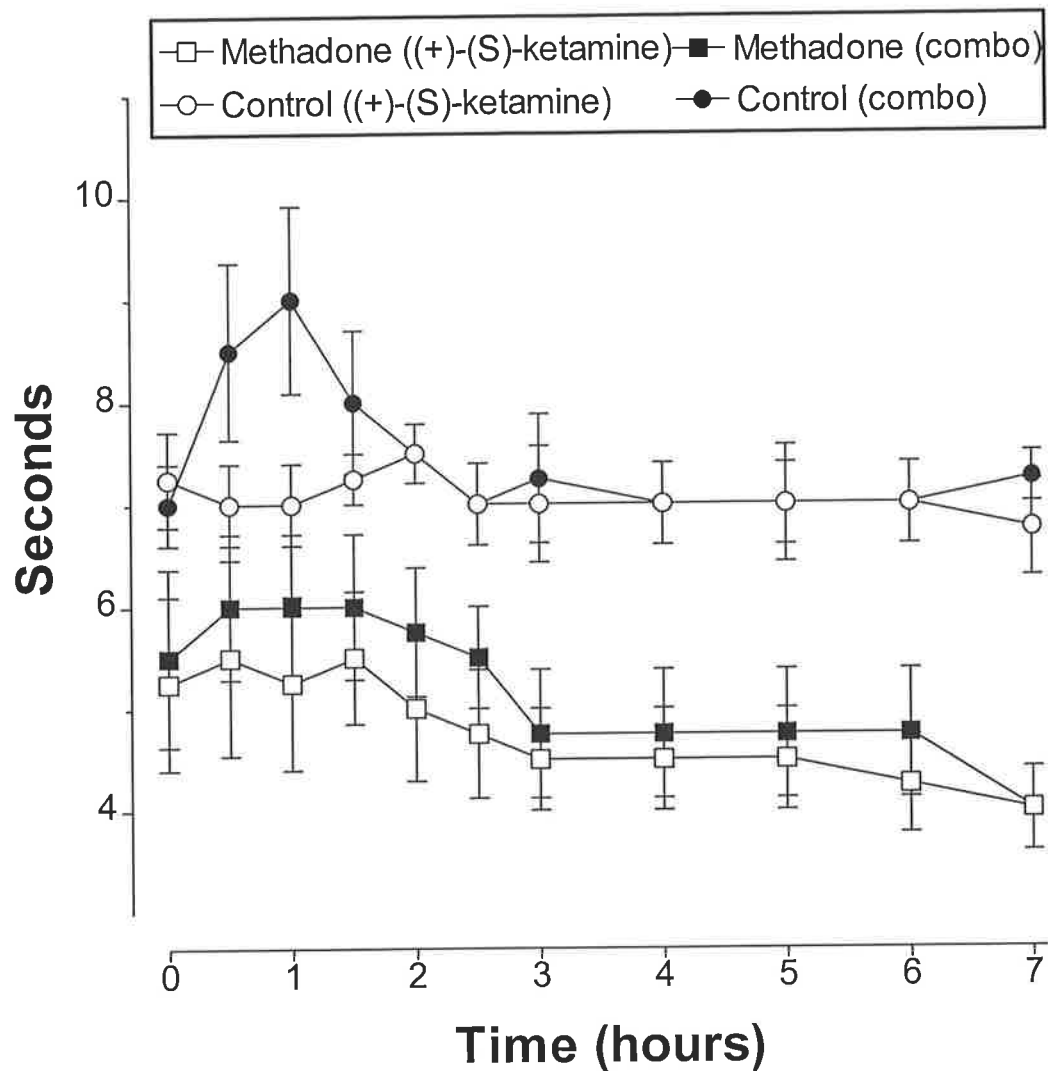
Table 5.1. Cold pressor test: mean ($\pm$ SEM) pain detection values (seconds) for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket denotes the (+)-(S)-ketamine only session, and combo denotes the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	5.25 (0.9)	5.5 (0.9)	7.25 (0.5)	7.0 (0.4)	*p=0.391, #p=0.087, +p=0.168, \$p=0.391
0.5 h	5.5 (1.0)	6.0 (0.7)	7.0 (0.4)	8.5 (0.9)	*p=0.495, #p=0.200, +p=0.067, \$p=0.058
1.0 h	5.25 (0.9)	6.0 (0.7)	7.0 (0.4)	9.0 (0.9)	*p=0.319, #p=0.114, +p=0.041, \$p=0.041
1.5 h	5.5 (0.6)	6.0 (0.7)	7.25 (0.3)	8.0 (0.7)	*p=0.495, #p=0.045, +p=0.192, \$p=0.215
2.0 h	5.0 (0.7)	5.75 (0.6)	7.5 (0.3)	7.5 (0.3)	*p=0.215, #p=0.017, +p=0.045, \$p=1.000
2.5 h	4.75 (0.6)	5.5 (0.5)	7.0 (0.4)	7.0 (0.4)	*p=0.058, #p=0.024, +p=0.059, \$p=1.000
3.0 h	4.5 (0.5)	4.75 (0.6)	7.0 (0.6)	7.25 (0.6)	*p=0.391, #p=0.017, +p=0.031, \$p=0.638
4.0 h	4.5 (0.5)	4.75 (0.6)	7.0 (0.4)	7.0 (0.4)	*p=0.391, #p=0.008, +p=0.024, \$p=1.000
5.0 h	4.5 (0.5)	4.75 (0.6)	7.0 (0.6)	7.0 (0.4)	*p=0.391, #p=0.017, +p=0.024, \$p=1.000
6.0 h	4.25 (0.5)	4.75 (0.6)	7.0 (0)	7.0 (0.4)	*p=0.182, #p=0.010, +p=0.024, \$p=1.000
7.0 h	4.0 (0.4)	4.0 (0.4)	6.75 (0.5)	7.25 (0.3)	*p=1.000, #p=0.005, +p<0.0005 \$p=0.182

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.4 Cold pressor test. Mean ($\pm$ SEM) pain detection values (seconds) during the (+)-(-S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(-S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(-S)-ketamine plus morphine session.



5.3.4.2 Pain tolerance

Mean ($\pm$ SEM) pain tolerance responses (0 to 7 h) are outlined in Table 5.2, and are also graphically illustrated in Figure 5.5. Comparing the pain tolerance values of methadone patients with control subjects' during the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=11.3$; $p=0.015$); *post hoc* analysis revealed that methadone patients' pain detection values were significantly lower than those of control subjects at 0 h (baseline) ($p=0.001$, [95%CI, -60.9, -28.1]), 0.5 h ($p=0.002$, [95%CI, -63.6, -22.9]), 1.0 h ($p=0.001$, [95%CI, -59.5, -26.1]), 1.5 h ($p=0.001$, [95%CI, -62.3, -28.7]), 2.0 h ($p=0.001$, [95%CI, -62.8, -25.7]), 2.5 h ($p=0.001$, [95%CI, -66.1, -28.4]), 3.0 h ($p=0.001$, [95%CI, -65.4, -29.6]), 4.0 h ($p<0.0005$, [95%CI, -65.6, -30.9]), 5.0 h ($p=0.001$, [95%CI, -67.7, -27.8]), 6.0 h ($p<0.0005$, [95%CI, -67.7, -32.8]), and 7.0 h ($p=0.001$, [95%CI, -67.7, -28.3]). There was no main effect of time ($F(2.6, 15.5)=2.96$; $p=0.071$), but there was a significant interaction between group and time ($F(2.6, 15.5)=3.6$; $p=0.044$); with methadone patients' pain tolerance values decreasing across time. Compared with baseline values, methadone patient's pain tolerance values were lower but not significantly at any time point ($p>0.029$).

Comparing the pain tolerance values of methadone patients with control subjects' during the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=39.6$; $p=0.001$). Specifically, methadone patients' pain tolerance values were significantly lower than those of controls at 0 h (baseline) ($p=0.001$, [95%CI, -60.8, -27.7]), and 7.0 h ($p=0.004$, [95%CI, -72.7, -28.8]). There was a significant effect of time ($F(1.6,9.7)=9.5$; $p=0.007$, and also a significant interaction between group and time ($F(1.6,9.7)=4.6$; $p=0.045$), with control subjects pain tolerance values increasing across time. However, compared to baseline values, control subjects' pain tolerance values were not significantly higher at any specific time point ($p>0.043$).

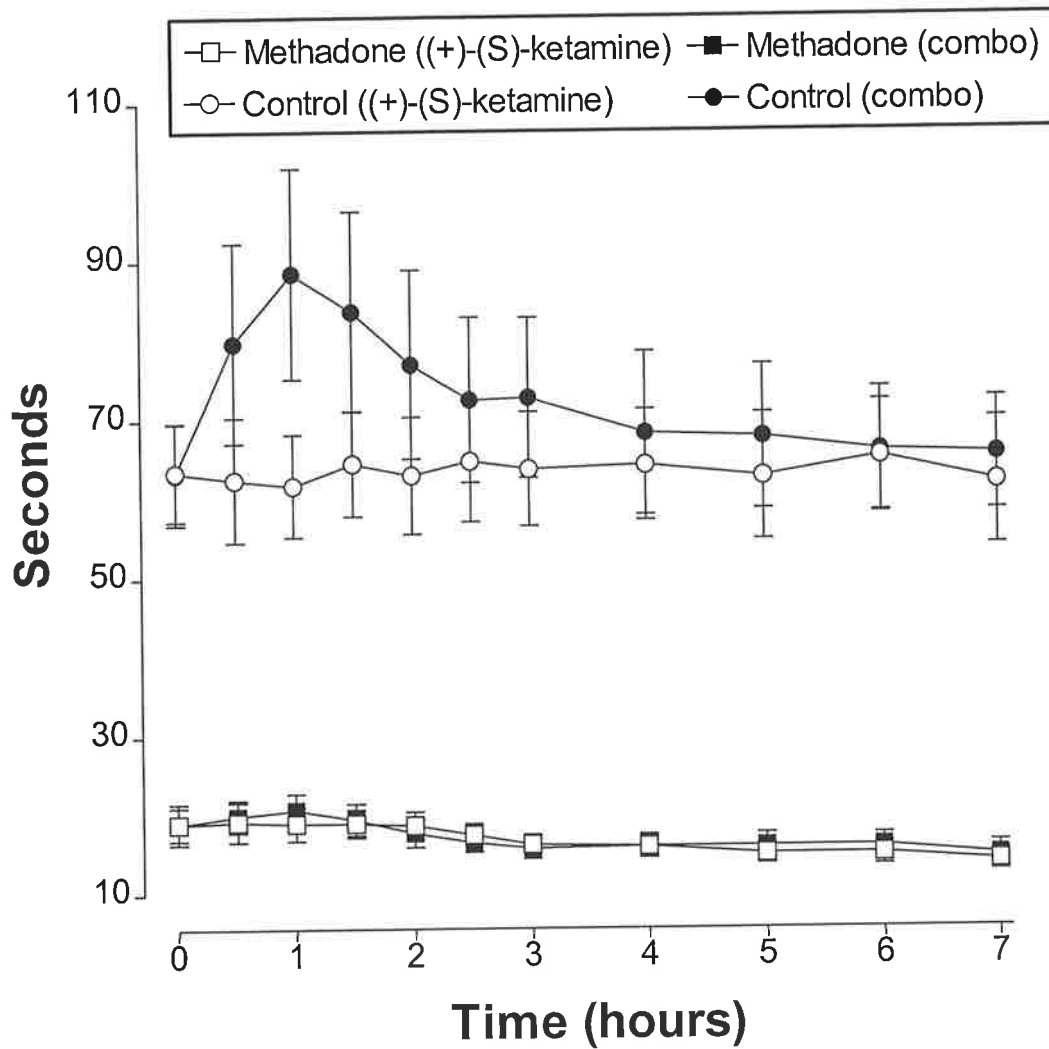
Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) revealed that there were no significant differences in the pain tolerance values in either group at any time point.

Table 5.2. Cold pressor test: mean ($\pm$ SEM) pain tolerance values (seconds) for methadone (S-ket.) patients, methadone (combo) patients, control (S-ket.) and control (combo) subjects. Please note that the abbreviation S-ket denotes the (+)-(S)-ketamine only session, and the abbreviation combo denotes the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	19 (2.5)	19 (2.0)	63.5 (6.2)	63 (6.5)	*p=1.000, #p=0.001, +p=0.001, \$p=0.836
0.5 h	19.3 (2.5)	20 (2.0)	62.5 (8.0)	80 (12.5)	*p=0.391, #p=0.002, +p=0.016, \$p=0.130
1.0 h	19 (2.2)	20.8 (2.0)	61.5 (6.5)	88.5 (13)	*p=0.162, #p=0.001, +p=0.013, \$p=0.052
1.5 h	19 (1.8)	19.5 (2.0)	64.5 (6.7)	84 (12.5)	*p=0.664, #p=0.001, +p=0.014, \$p=0.084
2.0 h	18.8 (1.7)	17.8 (1.8)	63 (7.5)	77 (12)	*p=0.308, #p=0.001, +p=0.014, \$p=0.094
2.5 h	17.5 (1.5)	16.5 (1.2)	64.5 (7.5)	73 (10.5)	*p=0.308, #p=0.001, +p=0.012, \$p=0.212
3.0 h	16.3 (1.5)	15.8 (1.3)	63.5 (7.0)	73 (10)	*p=0.391, #p=0.001, +p=0.010, \$p=0.069
4.0 h	16 (1.3)	16 (1.5)	64.5 (7.0)	68 (10.5)	*p=1.000, #p<0.0005, +p=0.014, \$p=0.397
5.0 h	15 (1.5)	16 (1.6)	63 (8.0)	68 (9.0)	*p=0.182, #p=0.001, +p=0.010, \$p=0.267
6.0 h	15 (1.5)	16 (1.5)	65.5 (7.0)	66 (8.0)	*p=0.252, #p<0.0005, +p=0.007, \$p=0.764
7.0 h	14 (1.3)	14.8 (1.7)	62 (8.0)	65 (7.0)	*p=0.391, #p=0.001, +p=0.004, \$p=0.077

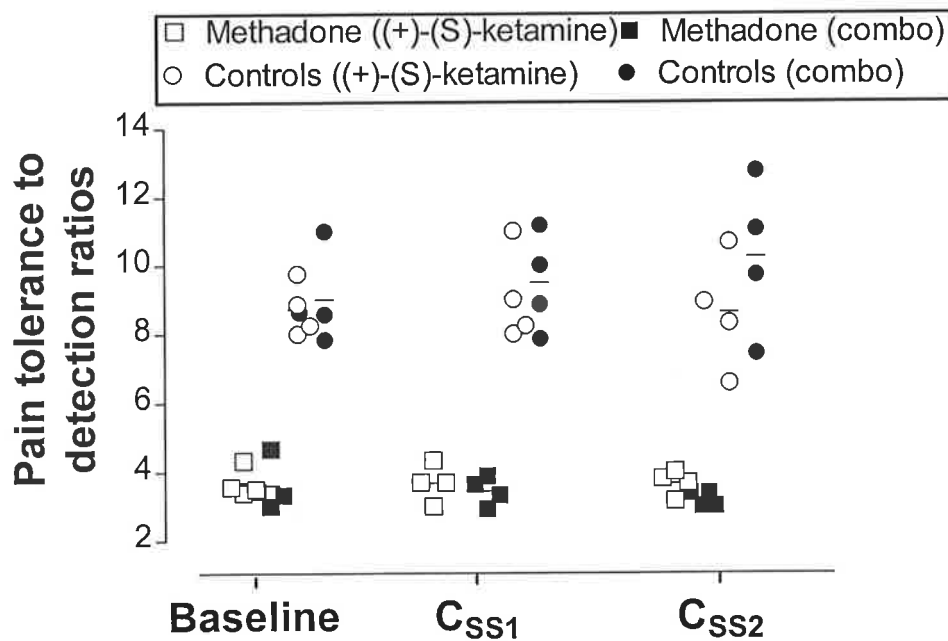
* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)
+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.5 Cold pressor test. Mean ($\pm$ SEM) pain tolerance values (seconds) during the (+)-(*S*)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(*S*)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(*S*)-ketamine plus morphine session.



Pain tolerance to detection ratios (methadone patients versus controls) were calculated from the data collected prior to intravenous drug administration (baseline), and at C_{SS1} and C_{SS2} (see Figure 5.6). The alpha was set as $p < 0.05$. In the (+)-(S)-ketamine only session, the ratios of methadone patients were significantly lower than those of controls at baseline ($p < 0.0005$, [95%CI, -6.1,-3.9]), C_{SS1} ($p = 0.001$, [95%CI, -7.3,-3.0]), and C_{SS2} ($p = 0.001$, [95%CI, -7.1,-2.8]). Similarly, in the (+)-(S)-ketamine plus morphine session, the ratios of methadone patients were significantly lower than those of controls at baseline ($p < 0.0005$, [95%CI, -7.3,-3.5]), C_{SS1} ($p < 0.0005$, [95%CI, -7.8,-4.2]), and C_{SS2} ($p = 0.008$, [95%CI, -9.8,-4.3]). Within-group comparisons ((+)-(S)-ketamine only versus (+)-(S)-ketamine plus morphine) did not reveal any significant differences ($p > 0.052$) for the methadone patients at any of these time points. For control subjects there was a small but statistically significant difference ($p = 0.043$, [95%CI, 0.93, 3.14]) at C_{SS2} only.

Figure 5.6 Pain tolerance to detection ratios at baseline, C_{SS1} , and C_{SS2} during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session



5.3.5 Electrical stimulation

5.3.5.1 Pain detection

Mean ($\pm$ SEM) pain detection responses (0 to 7 h) are outlined in Table 5.3, and are graphically illustrated in Figure 5.7. Comparing the pain detection values of methadone patients and control subjects during the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=26.6$; $p=0.002$). Specifically, methadone patients' pain detection values were significantly higher than those of controls at 0 h (baseline) ($p<0.0005$, [95%CI, 6.3, 11.6]), 0.5 h ($p<0.0005$, [95%CI, 6.0, 10.0]), 1.0 h ($p<0.0005$, [95%CI, 6.8, 12.2]), 1.5 h ($p=0.003$, [95%CI, 4.0, 12.0]), and 2.0 h ($p<0.0005$, [95%CI, 6.1, 12.9]). There was a main effect of time ($F(3.3, 20)=8.2$; $p=0.001$), and also a significant interaction between group and time ($F(3.3, 20)=6.2$; $p=0.003$), with methadone patients' pain detection values decreasing across time. Compared with baseline values, methadone patients' pain detection values were significantly lower at 4.0 ($p=0.002$, [95%CI, -3.9, -7.1]) and 7.0 hours ($p=0.002$, [95%CI, -6.5, -12.5]).

Comparing the pain detection values of methadone patients and control subjects during the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=7.4$; $p=0.035$). Specifically, pain detection values for methadone patients were significantly higher than those of controls at 0 h (baseline) ($p=0.001$, [95%CI, 5.3, 12.7]) only. There was a main effect of time ($F(4.1, 24.5)=16.6$; $p<0.0005$), and also a significant interaction between group and time ($F(4.1, 24.5)=9.7$; $p<0.0005$), with methadone patients' pain detection values decreasing across time. Compared with baseline values, methadone patients' pain detection values were significantly lower at 7.0 hour ($p=0.003$, [95%CI, -5.4, -11.5]) only.

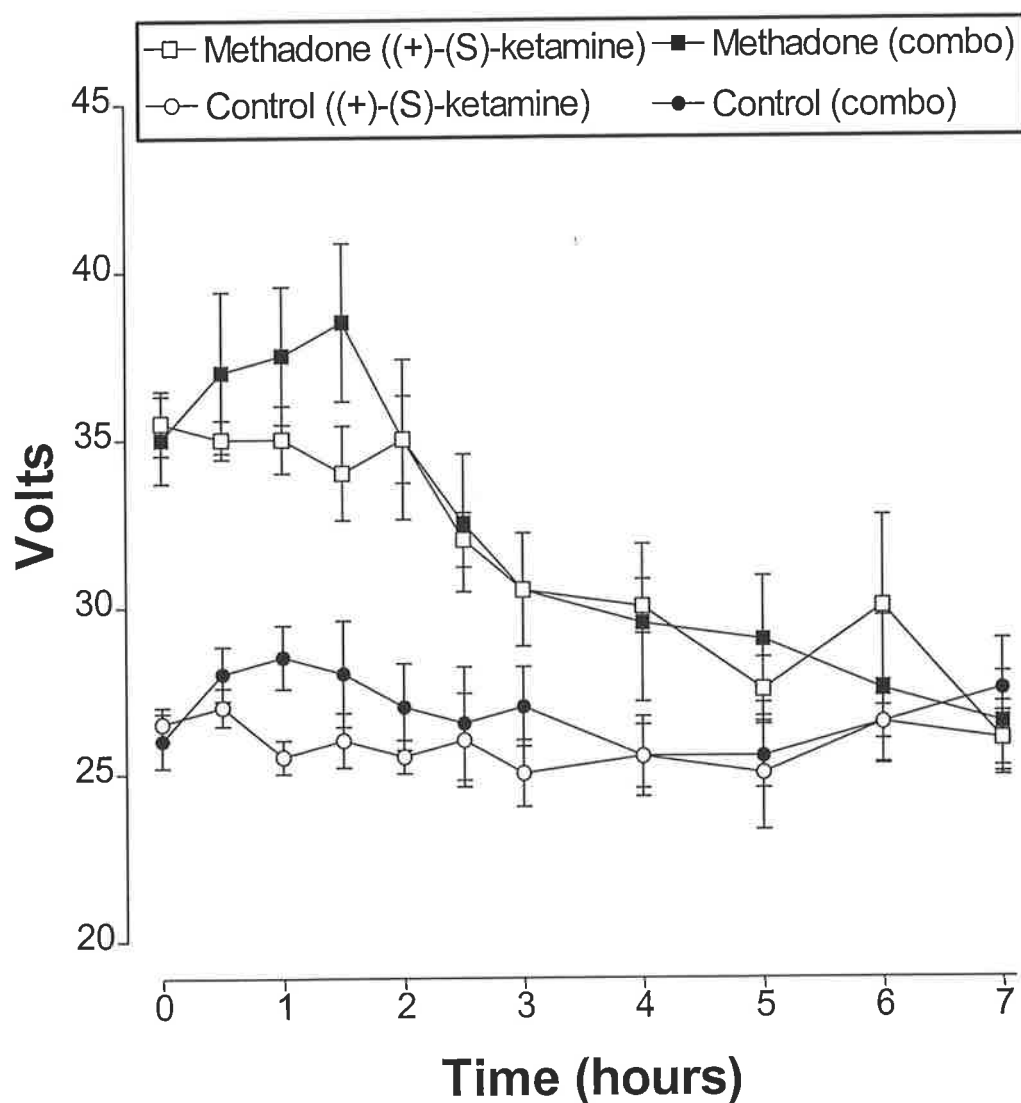
Within-group comparisons, (+)-(S)-ketamine only versus (+)-(S)-ketamine and morphine, revealed pain detection values for methadone patients and control subjects did not significantly differ ($p>0.079$ and $p>0.090$, respectively) at any time point.

Table 5.3. Electrical stimulation: mean ($\pm$ SEM) pain detection values (volts) for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket means the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	35.5 (1.0)	35 (1.3)	26.5 (0.5)	26 (0.8)	*p=0.391, #p<0.0005, +p=0.001, \$p=0.638
0.5 h	35 (0.6)	37 (2.4)	27 (0.6)	28 (0.8)	*p=0.353, #p<0.0005, +p=0.027, \$p=0.495
1.0 h	35 (1.0)	37.5 (2.0)	25.5 (0.5)	28.5 (1.0)	*p=0.278, #p<0.0005, +p=0.015, \$p=0.103
1.5 h	34 (1.4)	38.5 (2.4)	26 (0.8)	28 (1.6)	*p=0.170, #p=0.003, +p=0.011, \$p=0.252
2.0 h	35 (1.3)	35 (2.4)	25.5 (0.5)	27 (1.3)	*p=1.000, #p<0.0005, +p=0.035, \$p=0.391
2.5 h	32 (0.8)	32.5 (2.0)	26 (1.4)	26.5 (1.7)	*p=0.761, #p=0.010, +p=0.066, \$p=0.854
3.0 h	30.5 (1.7)	30.5 (1.7)	25 (1.0)	27 (1.3)	*p=1.000, #p=0.032, +p=0.153, \$p=0.092
4.0 h	30 (0.8)	29.5 (2.4)	25.5 (1.0)	25.5 (1.3)	*p=0.836, #p=0.012, +p=0.186, \$p=1.000
5.0 h	27.5 (1.0)	29 (2.0)	25 (1.7)	25.5 (1.0)	*p=0.391, #p=0.253, +p=0.153, \$p=0.718
6.0 h	30 (2.7)	27.5 (2.2)	26.5 (1.3)	26.5 (0.5)	*p=0.080, #p=0.286, +p=0.675, \$p=1.000
7.0 h	26 (0.8)	26.5 (1.5)	26 (1.2)	27.5 (1.5)	*p=0.638, #p=1.000, +p=0.654, \$p=0.519

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)
+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.7 Electrical stimulation. Mean ($\pm$ SEM) pain detection values (volts) during the (+)-(-S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(-S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(-S)-ketamine plus morphine session.



5.3.5.2 Pain tolerance

Mean ($\pm$ SEM) pain tolerance responses (0 to 7 h) are outlined in Table 5.4, and are graphically illustrated in Figure 5.8. There were no significant differences in pain tolerance values between methadone patients and control subjects in the (+)-(S)-ketamine only session ($F(1,6)=0.003$; $p=0.957$). However, there was a main effect of time ($F(3,18)=18.6$; $p<0.0005$), and also a significant interaction between group and time ($F(3,18)=6.6$; $p=0.003$), with methadone patients' pain tolerance values decreasing across time. Compared with baseline values, methadone patients' pain tolerance values were significantly lower at 6.0 ($p=0.003$ [95%CI, -6.9, -15.1]), and 7.0 hours ($p=0.003$, [95%CI, -7.5, -16.5]).

There were no significant differences in pain tolerance values between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session ($F(1,6)=0.06$; $p=0.821$). However, there was a main effect of time ($F(3,18.2)=17.6$; $p<0.005$), but no significant interaction between group and time ($F(3,18.2)=1.8$; $p=0.184$).

Within-group comparisons ((+)-(S)-ketamine only versus (+)-(S)-ketamine plus morphine) revealed methadone patients' pain tolerance values were not significantly different ($p>0.034$) at any time point. For controls, pain tolerance values in the (+)-(S)-ketamine only session were significantly lower than those in the (+)-(S)-ketamine plus morphine session at 7 h ($p=0.003$, [95%CI, 0-6.1, -2.9]) only.

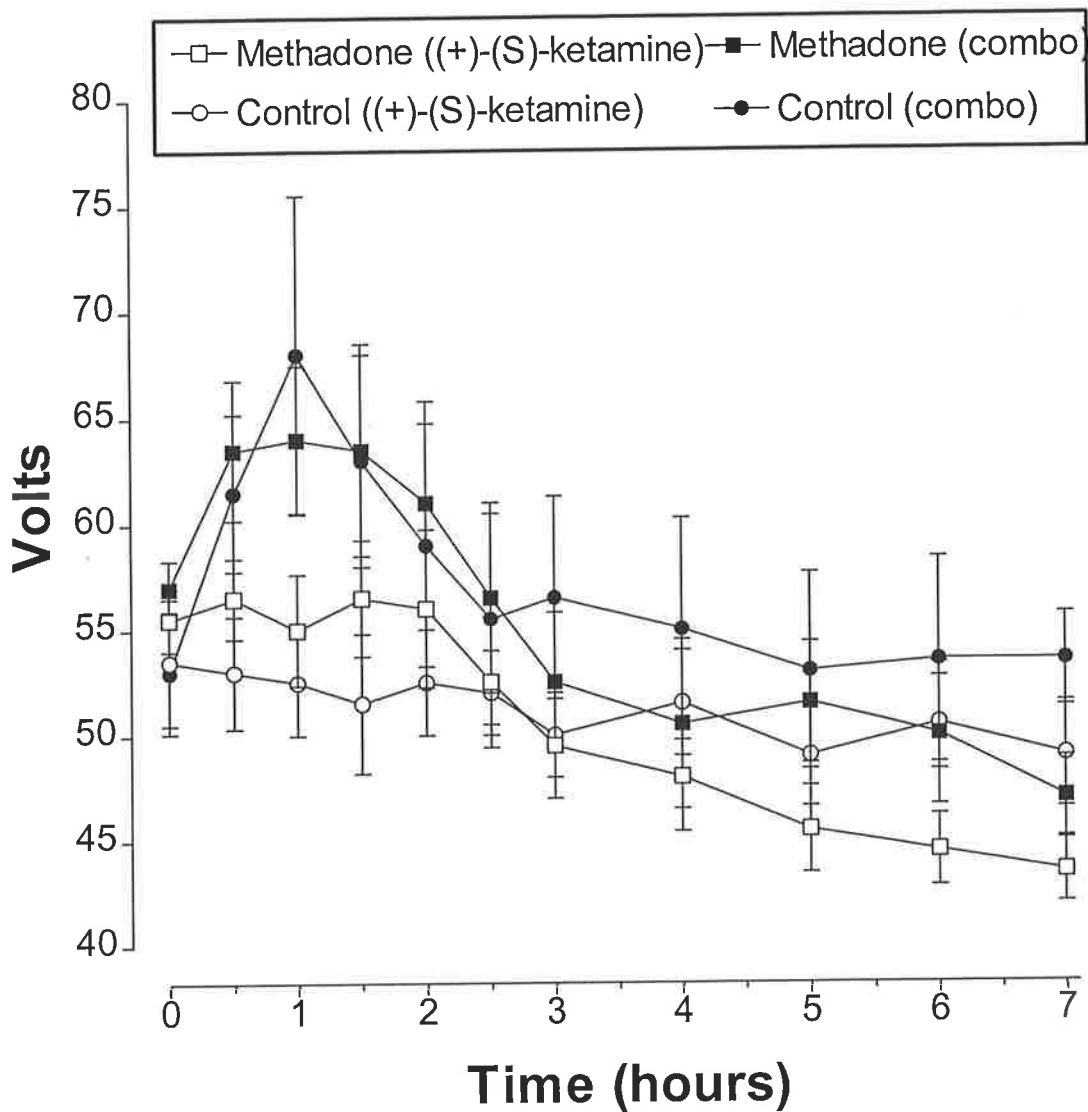
Table 5.4. Electrical stimulation: mean ($\pm$ SEM) pain tolerance values (volts) for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket means the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	55 (1.5)	57 (1.3)	53.5 (3.0)	53 (3.0)	*p=0.215, #p=0.571, +p=0.253, \$p=0.638
0.5 h	56.5 (2.0)	63.5 (3.3)	53 (2.5)	61.5 (3.7)	*p=0.069, #p=0.323, +p=0.700, \$p=0.016
1.0 h	55 (2.5)	64 (3.5)	52.5 (2.5)	68 (7.5)	*p=0.073, #p=0.518, +p=0.645, \$p=0.057
1.5 h	56.5 (2.8)	63.5 (5.0)	51.5 (3.3)	63 (5.0)	*p=0.289, #p=0.289, +p=0.947, \$p=0.019
2.0 h	56 (3.8)	61 (4.8)	52.5 (2.5)	59 (5.8)	*p=0.269, #p=0.466, +p=0.798, \$p=0.219
2.5 h	52.5 (3.0)	56 (4.5)	52 (2.0)	55.5 (5.0)	*p=0.116, #p=0.899, +p=0.888, \$p=0.340
3.0 h	49.5 (2.5)	52.5 (3.3)	50 (2.0)	56.5 (4.8)	*p=0.319, #p=0.885, +p=0.517, \$p=0.090
4.0 h	48 (2.5)	50.5 (4.0)	51.5 (2.5)	55 (5.0)	*p=0.537, #p=0.368, +p=0.522, \$p=0.310
5.0 h	45.5 (2.0)	51.5 (3.0)	49 (2.4)	53 (4.7)	*p=0.035, #p=0.309, +p=0.793, \$p=0.252
6.0 h	44.5 (2.7)	50 (3.5)	50.5 (2.0)	53.5 (5.0)	*p=0.102, #p=0.076, +p=0.575, \$p=0.406
7.0 h	43.5 (1.5)	47 (2.0)	49 (2.5)	53.5 (2.0)	*p=0.069, #p=0.110, +p=0.068, \$p=0.003

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

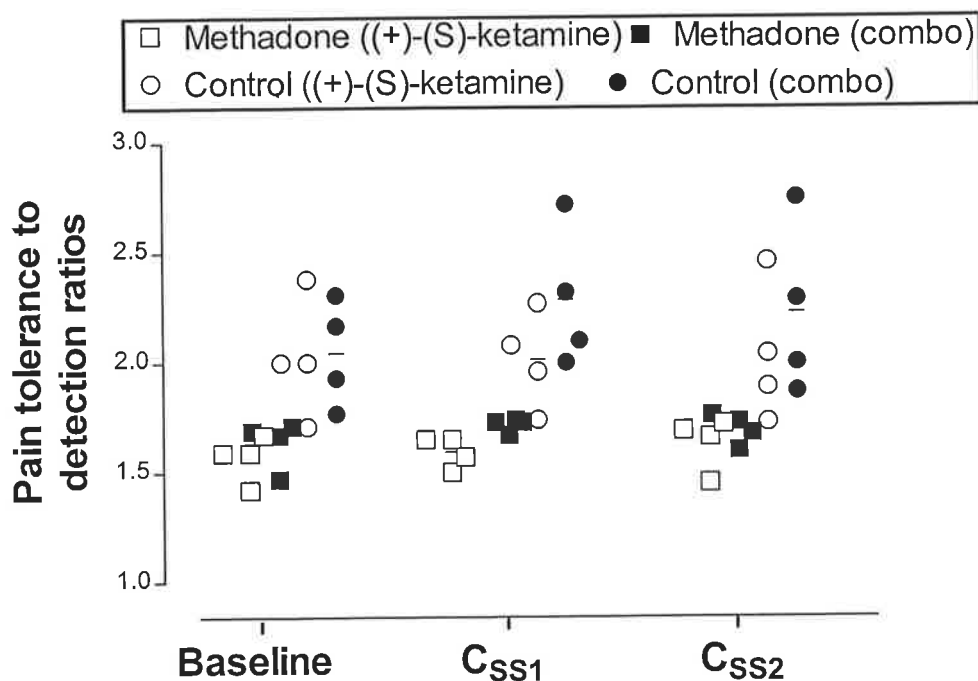
+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo) Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.8 Electrical stimulation. Mean ($\pm$ SEM) pain tolerance values (volts) during the (+)-(*S*)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(*S*)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(*S*)-ketamine plus morphine session.



Pain tolerance to detection ratios (methadone patients versus controls) were calculated prior to intravenous drug administration (baseline), C_{SS1} and C_{SS2} (see Figure 5.9). The alpha was set as $p < 0.05$. In the (+)-(S)-ketamine only session, the ratios of methadone patients were significantly lower than those of control subjects at baseline ($p = 0.021$, [95%CI, -0.8, -0.1]) and at C_{SS1} ($p = 0.11$, [95%CI, -0.7, -0.1]). Similarly in the (+)-(S)-ketamine plus morphine session there were small but significant differences; methadone patients ratios were lower than controls' at baseline ($p = 0.021$, [95%CI, -0.7, -0.1]), and at C_{SS1} ($p = 0.037$, [95%CI, -0.9, -0.2]). Within-group comparisons ((+)-(S)-ketamine only versus (+)-(S)-ketamine plus morphine) revealed that the mean pain tolerance to detection ratio of methadone patients in the (+)-(S)-ketamine plus morphine session was significantly higher than in the (+)-(S)-ketamine only session ($p = 0.049$, [95%CI, 0.001, 0.243]) at C_{SS1} only; it should be noted that whilst the difference in the ratio was statistically significant it was very small (1.72 vs. 1.59). For controls, there was also a small but significant difference, with the ratio in the (+)-(S)-ketamine plus morphine session higher than in the (+)-(S)-ketamine only session ($p = 0.025$, [95%CI, 0.064, 0.484]) at C_{SS1} only; it should be noted that whilst the difference in the ratio was statistically significant it was very small (2.32 vs. 2.0).

Figure 5.9. Pain tolerance to detection ratios at baseline, C_{SS1} , and C_{SS2} during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session



5.3.6 Physiological and subjective responses

5.3.6.1 Respiratory rate

Mean ($\pm$ SEM) respiratory rates (0 to 7 h) are outlined in Table 5.5, and are graphically illustrated in Figure 5.10. Comparing the respiratory rates of methadone patients and controls subjects in the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=102.9$; $p<0.0005$); with methadone patients' respiratory rates being significantly lower than those of controls at 0 hour ($p<0.0005$, [95%CI, -6.7, -3.3]), 0.5 hour ($p<0.0005$, [95%CI, -6.7, -3.3]), 1.0 hour ($p<0.0005$, [95%CI, -7.2, -3.8]), 1.5 hours ($p<0.0005$, [95%CI, -8.9, -4.1]), 2.0 hours ($p<0.0005$, [95%CI, -8.7, -5.3]), 2.5 hours ($p<0.0005$, [95%CI, -8.9, -4.5]), 3.0 hours ($p<0.0005$, [95%CI, -9.6, -4.4]), 4.0 hours ($p=0.003$, [95%CI, -10.5, -5.1]), 5.0 hours ($p=0.001$, [95%CI, -11.1, -6.4]), 6.0 hours ($p<0.0005$, [95%CI, -10.3, -6.2]), and 7.0 hours ($p<0.0005$, [95%CI, -9.2, -4.8]). There was also a main effect of time ($F(3.2,19.1)=7.6$; $p=0.001$), and a significant interaction between group and time ($F(3.2,19.1)=5.5$; $p=0.006$), with methadone patients' respiratory rate decreasing across time. Compared with baseline rates, methadone patients' respiratory rates were significantly lower at 6.0 ($p=0.001$, [95%CI, -2.6, -4.4]) and 7.0 hours ($p=0.003$, [95%CI, -1.6, -3.4]).

Comparing the respiratory rates of methadone patients and controls subjects in the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=125.8$; $p<0.0005$); with methadone patients' respiratory rates being significantly lower than those of controls at 0 hour ($p=0.001$, [95%CI, -10.6, -6.4]), 0.5 hour ($p<0.0005$, [95%CI, -8.7, -5.3]), 1.0 hour ($p<0.0005$, [95%CI, -7.3, -4.7]), 1.5 hours ($p<0.0005$, [95%CI, -7.6, -3.4]), 2.0 hours ($p<0.0005$, [95%CI, -6.9, -3.6]), 2.5 hours ($p<0.0005$, [95%CI, -7.7, -4.3]), 3.0 hours ($p<0.0005$, [95%CI, -7.9, -4.6]), 4.0 hours ($p<0.0005$, [95%CI, -9.4, -3.1]), 5.0 hours ($p<0.0005$, [95%CI, -8.1, -3.4]), 6.0 hours ($p<0.0005$, [95%CI, -7.6, -3.9]), and 7.0 hours ($p<0.0005$, [95%CI, -7.1, -3.9]). There was a main effect of time ($F(2.3,13.8)=7.7$; $p=0.005$), but no significant interaction between group and time ($F(2.3,13.8)=2.3$; $p=0.131$).

Within-group comparisons revealed that the respiratory rates of control subjects during the (+)-(S)-ketamine plus morphine session were significantly lower than those during the (+)-(S)-ketamine only session at 2.5 hours ($p=0.003$, [95%CI, -3.4, -1.6]) only. For methadone patients, respiratory rates in the (+)-(S)-ketamine plus morphine session were significantly lower than those during the (+)-(S)-ketamine only session at 0.5 hour ($p=0.002$, [95%CI, -3.5, -1.9]), 1.0 hour ($p=0.003$, [95%CI, -3.4, -1.6]).

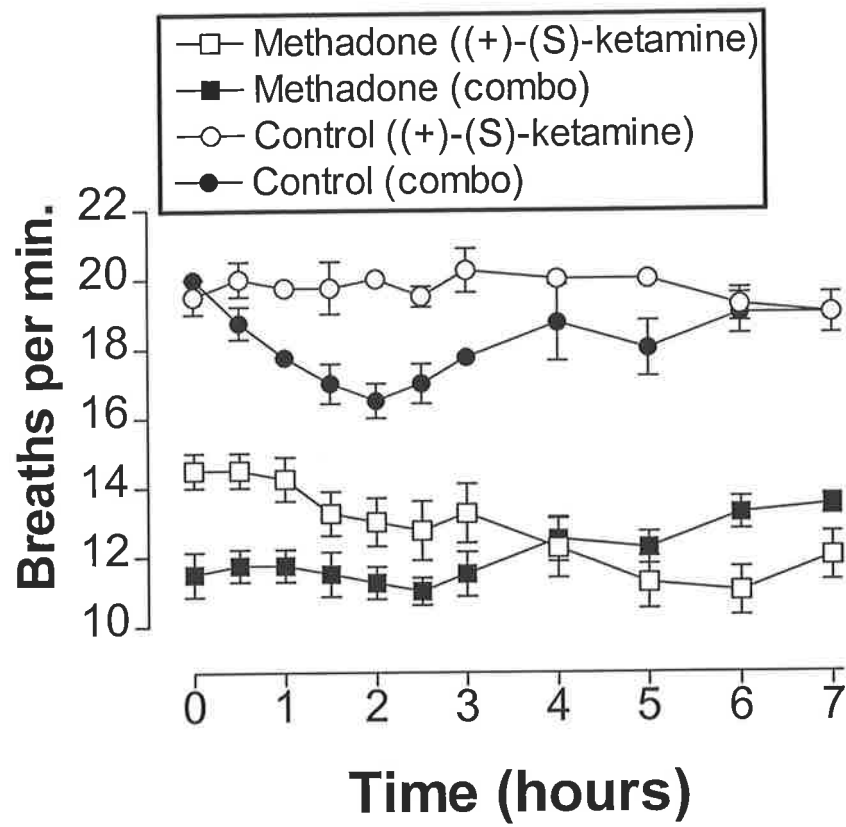
Table 5.5. Respiratory rate: mean ($\pm$ SEM) breaths per minute for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket means the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	14.5 (0.5)	11.5 (0.6)	19.5 (0.5)	20 (0)	*p=0.005, #p<0.0005, +p=0.001, \$p=0.391
0.5 h	14.5 (0.5)	11.75 (0.5)	20 (0)	18.75 (0.5)	*p=0.002, #p=0.002, +p<0.0005, \$p=0.080
1.0 h	14.25 (0.6)	11.75 (0.5)	19.75 (0.3)	17.75 (0.3)	*p=0.003, #p<0.0005, +p<0.0005, \$p=0.016
1.5 h	13.25 (0.6)	11.5 (0.6)	19.75 (0.8)	17 (0.6)	*p=0.035, #p=0.001, +p=0.001, \$p=0.022
2.0 h	13 (0.7)	11.25 (0.5)	20 (0)	16.5 (0.5)	*p=0.035, #p<0.0005, +p<0.0005, \$p=0.006
2.5 h	12.75 (0.9)	11 (0.4)	19.5 (0.3)	17 (0.6)	*p=0.035, #p<0.0005, +p<0.0005, \$p=0.003
3.0 h	13.25 (0.9)	11.5 (0.6)	20.25 (0.6)	17.75 (0.3)	*p=0.188, #p=0.001, +p<0.0005, \$p=0.030
4.0 h	12.25 (0.9)	12.5 (0.6)	20 (0)	18.75 (1.0)	*p=0.861, #p=0.003, +p=0.003, \$p=0.342
5.0 h	11.25 (0.8)	12.25 (0.5)	20 (0)	18 (0.8)	*p=0.353, #p=0.001, +p=0.001, \$p=0.092
6.0 h	11 (0.7)	13.25 (0.5)	19.25 (0.5)	19 (0.6)	*p=0.058, #p<0.0005, +p<0.0005, \$p=0.789
7.0 h	12 (0.7)	13.5 (0.3)	19 (0.6)	19 (0.6)	*p=0.103, #p<0.0005, +p<0.0005, \$p=1.000

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo) Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.10 Mean ($\pm$ SEM) respiratory rates during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.2 Pupil size

Mean ($\pm$ SEM) pupil sizes (0 to 7 h) are outlined in Table 5.6, and are also graphically illustrated in Figure 5.11. Comparing the sizes of pupils between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=60$; $p<0.0005$); with methadone patients' pupil sizes being significantly smaller than those of controls at 0 hour ($p<0.0005$, [95%CI, -2.2, -1.1]), 0.5 hour ($p=0.001$, [95%CI, -2.4, -1.0]), 1.0 hour ($p=0.003$, [95%CI, -3.0, -1.0]), 1.5 hours ($p<0.0005$, [95%CI, -3.2, -1.8]), 2.0 hours ($p<0.0005$, [95%CI, -3.5, -1.7]), 2.5 hours ($p<0.0005$, [95%CI, -3.2, -1.8]), 3.0 hours ($p=0.001$, [95%CI, -3.4, -1.3]), 4.0 hours ($p<0.0005$, [95%CI, -3.5, -1.7]), 5.0 hours, 6.0 hours ($p<0.0005$, [95%CI, -3.1, -1.7]), and 7.0 hours ($p<0.0005$, [95%CI, -3.3, -1.7]). There was no main effect of time ($F(1.9,11.2)=3.4$; $p=0.075$, and no significant interaction between group and time ($F(1.9,11.2)=2.1$; $p=0.166$).

Comparing the sizes of pupils between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=9.9$; $p=0.020$); with methadone patients' pupil sizes were significantly lower than those of control subjects at 0 hour ($p<0.0005$, [95%CI, -2.9, -1.6]) only. There was also a main effect of time ($F(3.8,23)=28$; $p<0.0005$), and a significant interaction between group and time ($F(3.8,23)=10$; $p<0.0005$); with control subjects' pupil sizes being significantly smaller across time. Compared with baseline sizes, control subjects' pupil sizes were significantly smaller at 0.5 h ($p=0.001$, [95%CI, -1.2, -2.0]), 1.5 h ($p=0.003$, [95%CI, -1.4, -3.0]), 2.0 ($p=0.001$, [95%CI, -1.8, -2.7]), 2.5 h ($p=0.001$, [95%CI, -1.8, -2.7]), 3.0 h ($p=0.001$, [95%CI, -1.8, -2.7]), 4.0 h ($p=0.001$, [95%CI, -1.8, -2.7]), 5.0 h ($p=0.001$, [95%CI, -1.8, -2.7]), and 6.0 h ($p=0.003$, [95%CI, -1.4, -2.9]).

Within-group comparisons revealed that pupil sizes of control subjects during the (+)-(S)-ketamine plus morphine session were significantly lower than those during the (+)-(S)-ketamine only session at 0.5 hour ($p=0.001$, [95%CI, -2.0, -1.2]), 1.0 hour ($p=0.003$, [95%CI, -2.9, -1.4]), 1.5 hours ($p=0.001$, [95%CI, -2.7, -1.8]), 2.0 hours ($p=0.003$, [95%CI, -3.1, -1.5]), 2.5 hours ($p=0.001$, [95%CI, -2.7, -1.8]), 3.0 hours ($p=0.003$, [95%CI, -2.9, -1.4]), 4.0 hours ($p=0.003$, [95%CI, -2.9, -1.4]), 5.0 hours ($p=0.001$, [95%CI, -2.8, -1.9]), 6.0 hours ($p=0.001$, [95%CI, -2.3, -1.5]). For methadone patients, pupil sizes during the (+)-(S)-ketamine plus morphine session were not significantly different ($p>0.014$) than those during the (+)-(S)-ketamine only session at any time point.

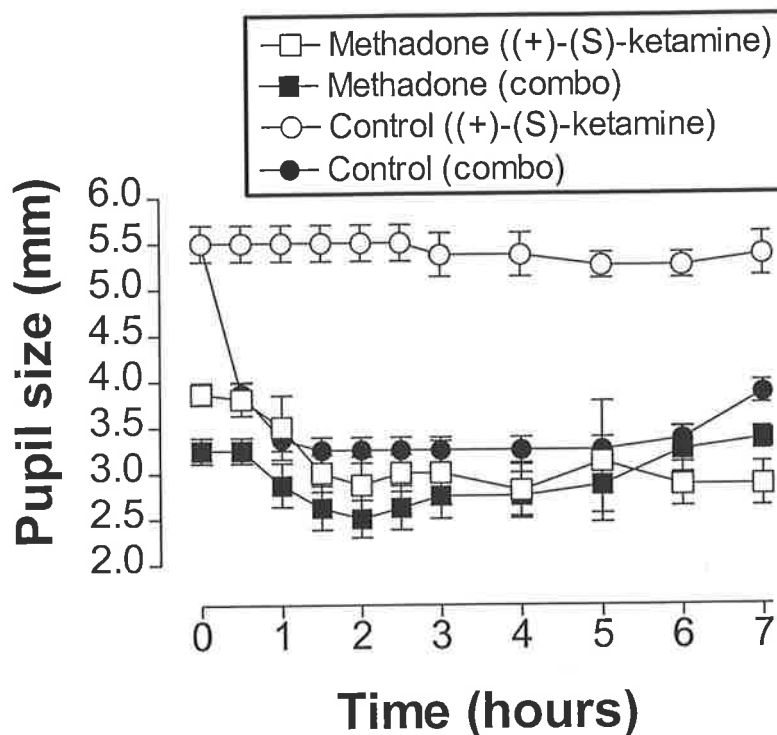
Table 5.6. Pupil sizes: mean ($\pm$ SEM) pupils sizes (mm) for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket means the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	3.9 (0.1)	3.25 (0.1)	5.5 (0.2)	5.5 (0.2)	*p=0.015, #p<0.0005, +p<0.0005, \$p=1.000
0.5 h	3.8 (0.2)	3.25 (0.1)	5.5 (0.2)	3.87 (0.1)	*p=0.037, #p=0.001, +p=0.017, \$p=0.001
1.0 h	3.5 (0.4)	2.87 (0.2)	5.5 (0.2)	3.37 (0.1)	*p=0.141, #p=0.003, +p=0.114, \$p=0.003
1.5 h	3 (0.2)	2.6 (0.2)	5.5 (0.2)	3.25 (0.1)	*p=0.058, #p<0.0005, +p=0.067, \$p=0.001
2.0 h	2.9 (0.25)	2.5 (0.2)	5.5 (0.2)	3.25 (0.1)	*p=0.058, #p<0.0005, +p=0.024, \$p=0.003
2.5 h	3 (0.2)	2.6 (0.3)	5.5 (0.2)	3.25 (0.1)	*p=0.058, #p<0.0005, +p=0.067, \$p=0.001
3.0 h	3 (0.4)	2.75 (0.3)	5.37 (0.3)	3.25 (0.1)	*p=0.182, #p=0.001, +p=0.134, \$p=0.003
4.0 h	2.8 (0.25)	2.75 (0.3)	5.37 (0.3)	3.25 (0.1)	*p=0.391, #p<0.0005, +p=0.134, \$p=0.003
5.0 h	3.1 (0.7)	2.9 (0.3)	5.25 (0.1)	3.25 (0.1)	*p=0.703, #p=0.020, +p=0.320, \$p=0.001
6.0 h	2.9 (0.25)	3.25 (0.3)	5.25 (0.1)	3.37 (0.1)	*p=0.215, #p<0.0005, +p=0.670, \$p=0.001
7.0 h	2.9 (0.25)	3.37 (0.1)	5.37 (0.3)	3.87 (0.1)	*p=0.092, #p<0.0005, +p=0.030, \$p=0.005

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo) Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.11 Mean ($\pm$ SEM) pupil sizes (mm) during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.3 Heart rate

Mean ($\pm$ SEM) heart rates (0 to 7 h) are outlined in Table 5.7, and are also graphically illustrated in Figure 5.12. Comparing the heart rates between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was no main effect of group ($F(1,6)=4.7$; $p=0.074$). There was no main effect of time ($F(3.6,21.9)=0.7$; $p=0.593$), and no significant interaction between group and time ($F(3.6,21.9)=0.9$; $p=0.463$). During the (+)-(S)-ketamine plus morphine session, there was no main effect of group ($F(1,6)=1$; $p=0.346$). There was a main effect of time ($F(3.4,20.5)=4.8$; $p=0.009$), but no significant interaction between group and time ($F(3.4,20.5)=0.7$; $p=0.570$).

Within-group comparisons revealed that for methadone patients, mean heart rates during the (+)-(S)-ketamine plus morphine session were not significantly ($p>0.060$) different from those during the (+)-(S)-ketamine only session at any time point. Similarly, for controls there were no significant differences ($p>0.006$) between the treatment sessions.

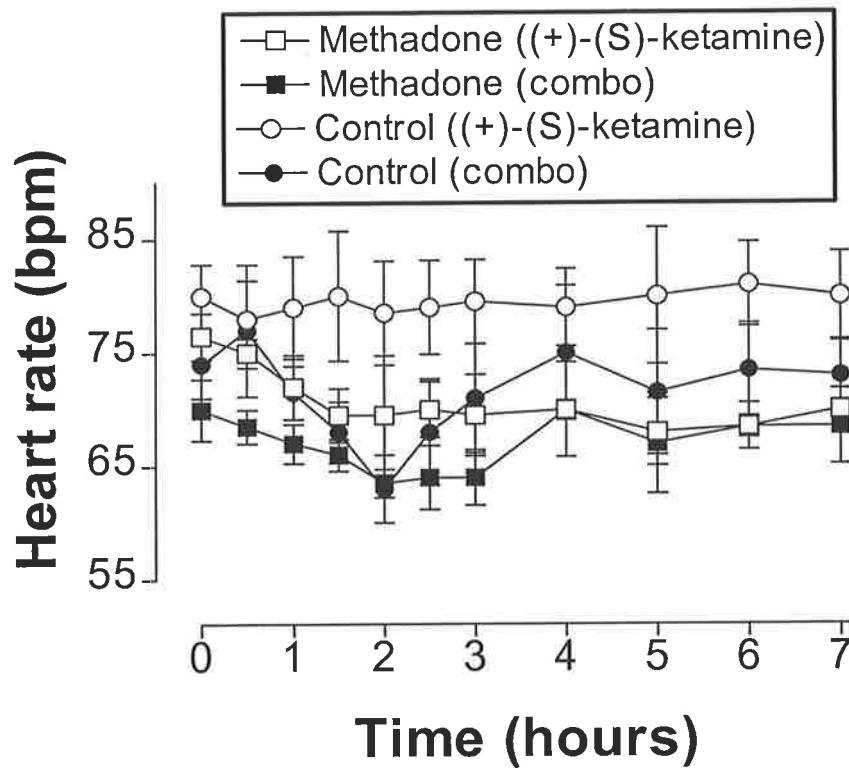
Table 5.7. Heart rate: mean ($\pm$ SEM) beats per minute for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket denotes the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	76.5 (2.0)	70 (2.7)	80 (2.8)	74 (3.0)	*p=0.061, #p=0.356, +p=0.356, \$p=0.046
0.5 h	75 (1.3)	68.5 (1.5)	78.5 (3.4)	77 (5.8)	*p=0.014, #p=0.393, +p=0.241, \$p=0.661
1.0 h	72 (2.8)	67 (1.7)	79.5 (4.5)	71.5 (2.4)	*p=0.269, #p=0.208, +p=0.175, \$p=0.066
1.5 h	69.5 (2.3)	66 (1.4)	80 (5.7)	68 (2.7)	*p=0.326, #p=0.140, +p=0.537, \$p=0.116
2.0 h	69.5 (5.3)	63.5 (1.3)	78.5 (4.5)	63 (3.0)	*p=0.344, #p=0.244, +p=0.885, \$p=0.007
2.5 h	70 (2.5)	64 (2.8)	79 (4.0)	68 (4.7)	*p=0.069, #p=0.110, +p=0.494, \$p=0.066
3.0 h	69.5 (3.5)	64 (2.5)	79.5 (3.7)	71 (4.8)	*p=0.174, #p=0.100, +p=0.257, \$p=0.042
4.0 h	70 (0.8)	70 (4.0)	79 (3.4)	75 (5.9)	*p=1.000, #p=0.043, +p=0.515, \$p=0.415
5.0 h	68 (3.0)	67 (4.0)	80 (6.0)	71.5 (5.5)	*p=0.848, #p=0.123, +p=0.550, \$p=0.169
6.0 h	68.5 (2.0)	68.5 (1.0)	81 (3.7)	73.5 (4.0)	*p=1.000, #p=0.026, +p=0.314, \$p=0.043
7.0 h	70 (0.8)	68.5 (3.3)	80.5 (4.0)	73 (3.0)	*p=0.718, #p=0.070, +p=0.352, \$p=0.022

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.12 Mean ($\pm$ SEM) heart rates (beats per minute) during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.4 Blood pressure

Mean ($\pm$ SEM) systolic and diastolic blood pressures (0 to 7 h) are shown in Figure 5.13. Comparing systolic blood pressure between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was no main effect of group ($F(1,6)=2.9$; $p=0.138$). There was no main effect of time ($F(3,18)=2.4$; $p=0.099$), and no significant interaction between group and time ($F(3,18)=2.2$; $p=0.120$).

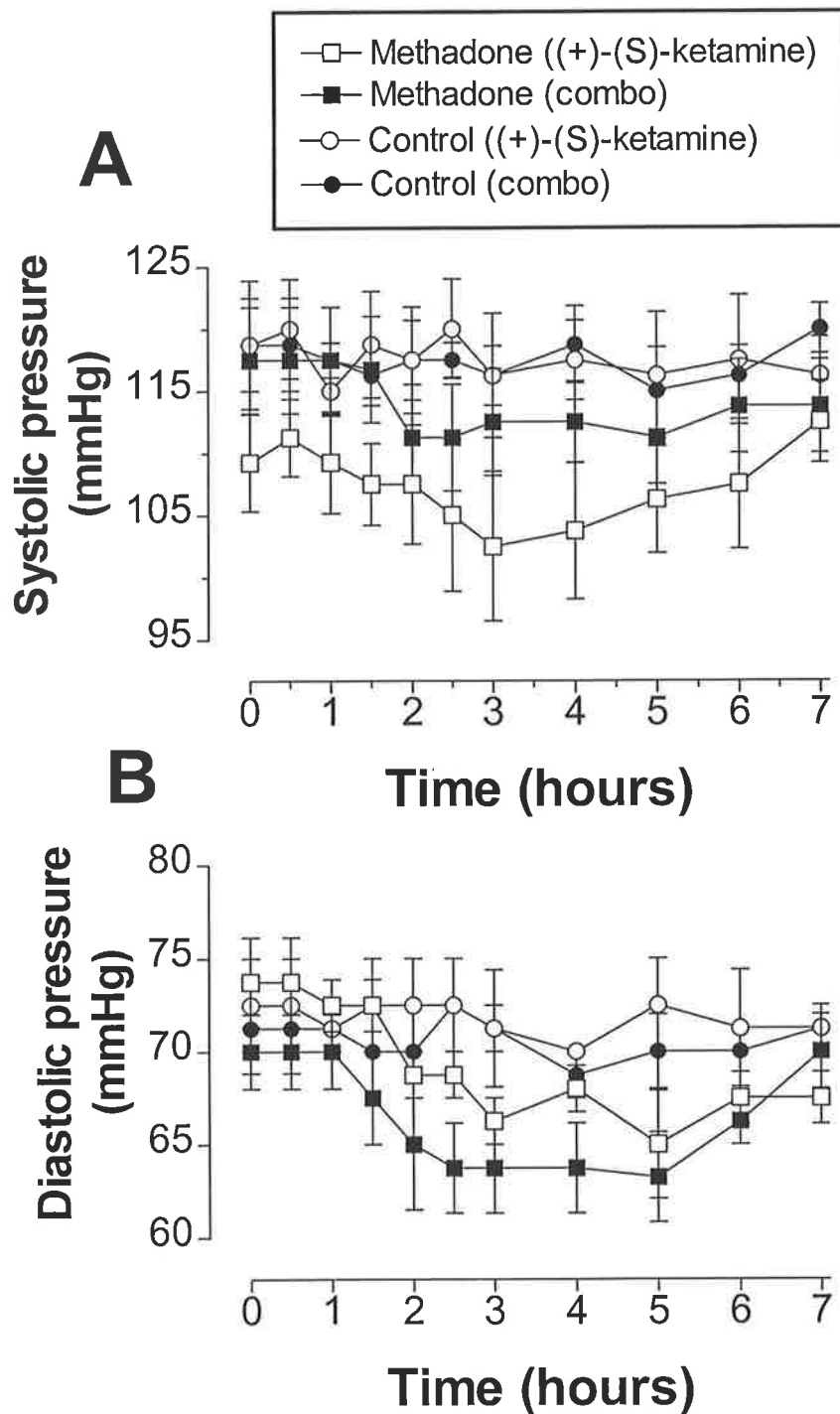
Similarly, comparing systolic blood pressure between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session, there was no main effect of group ($F(1,6)=0.7$; $p=0.444$). There was no main effect of time ($F(2.3,13.7)=1.5$; $p=0.264$), and no significant interaction between group and time ($F(2.3,13.7)=0.8$; $p=0.466$).

Comparing diastolic blood pressure between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was no main effect of group ($F(1,6)=0.8$; $p=0.403$). However, there was a main effect of time ($F(3.2,19.3)=6$; $p=0.004$), and a significant interaction between group and time ($F(3.2,19.3)=4.2$; $p=0.017$); with methadone patients' diastolic pressure decreasing over time. However, compared with diastolic pressure at baseline, there were no significant differences in methadone patients' diastolic pressure at any time point ($p>0.006$).

Comparing diastolic blood pressure between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session, there was no main effect of group ($F(1,6)=2.9$; $p=0.140$). However, there was a main effect of time group ($F(3.6,21.9)=4.4$; $p=0.011$), and a significant interaction between group and time ($F(3.6,21.9)=2.9$; $p=0.048$), with methadone patients' diastolic blood pressure decreasing across time. However, compared with diastolic pressure at baseline, there were no significant differences in methadone patients' diastolic pressure at any time point ($p>0.010$).

Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) for methadone patients revealed that there were no significant differences in systolic pressure ($p>0.187$) or diastolic pressure ($p>0.091$). Similarly for control subjects, there were no significant differences in systolic pressure ($p>0.058$) or diastolic pressure ($p>0.181$) between each session.

Figure 5.13 Mean ($\pm$ SEM) blood pressure values (mmHg) during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Panel A: systolic pressure. Panel B: diastolic pressure. Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.5 LSD scores

Mean ($\pm$ SEM) LSD scores (0 to 7 h) are outlined in Table 5.8, and are also graphically illustrated in Figure 5.14. Comparing the LSD scores between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was a main effect of group ($F(1,6)=24$; $p=0.003$), with methadone patients' LSD scores being significantly higher than those of control subjects at 1.5 hours ($p<0.0005$, [95%CI, 2.6, 4.4]) only. There was also a main effect of time ($F(2.7,16.1)=35.7$; $p<0.0005$), and also a significant interaction between group and time ($F(2.7,16.1)=13$; $p<0.0005$); compared with baseline scores, methadone patients' LSD score was significantly higher at 1.5 h ($p<0.0005$, [95%CI, 3.95, 5.6]) only.

Similarly, comparing the LSD scores between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session, there was a main effect of group ($F(1,6)=32$; $p=0.001$); with methadone patients' LSD scores being significantly higher than controls' at 1.5 hours ($p=0.001$, [95%CI, 2.7, 5.8]). There was also a main effect of time ($F(2.5, 14.9)=36.7$; $p<0.0005$), and also a significant interaction between group and time ($F(2.5, 14.9)=16.1$; $p<0.0005$); compared with baseline scores, methadone patients' LSD score was significantly higher at 0.5 h ($p=0.003$ [95%CI, 1.6, 3.4]), and 1.5 h ($p=0.004$ [95%CI, 3.2, 7.2]).

Within group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) revealed that there were no significant differences for methadone patients ($p>0.214$) or control subjects ($p>0.390$) between the treatment sessions.

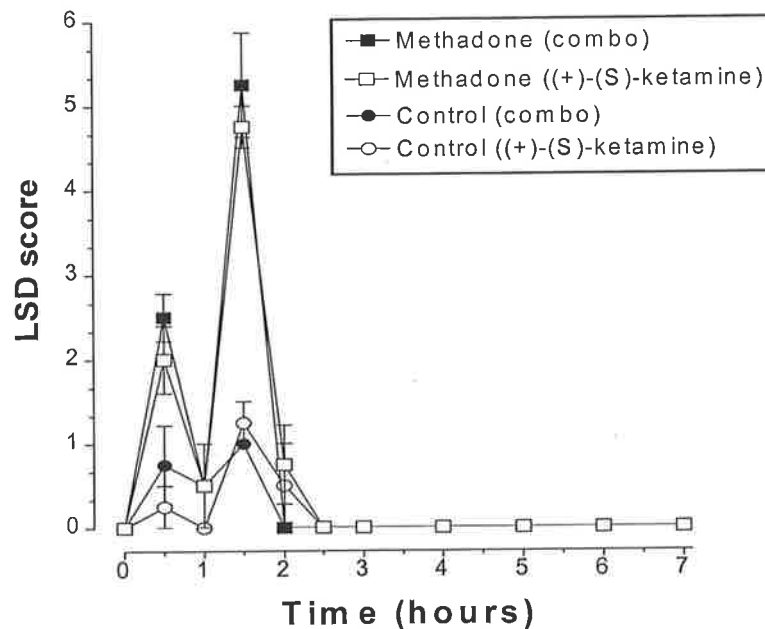
Table 5.8. Mean ($\pm$ SEM) LSD scores for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket denotes the (+)-(S)-ketamine only session, and combo denotes the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
0.5 h	2.0 (0.4)	2.5 (0.3)	0.25 (0.3)	0.75 (0.5)	*p=0.182, #p=0.011, +p=0.020, \$p=0.182
1.0 h	0.5 (0.5)	0.5 (0.5)	0 (0)	0.5 (0.5)	*p=0.391, #p=0.356, +p=1.000, \$p=0.391
1.5 h	4.75 (0.3)	5.25 (0.6)	1.25 (0.3)	1.0 (0)	*p=0.391, # p<0.0005 , + p=0.001 , \$p=0.391
2.0 h	0.75 (0.5)	0 (0)	0 (0)	0.5 (0.5)	*p=0.391, #p=0.730, +p=1.000, \$p=0.391
2.5 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
3.0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
4.0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
5.0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
6.0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000
7.0 h	0 (0)	0 (0)	0 (0)	0 (0)	*p=1.000, p=1.000 +p=1.000, \$p=1.000

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.14 Mean ($\pm$ SEM) LSD scores during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.5.6.1 Subjective comments related to drug administration

5.3.5.6.1.1 (+)-(S)-ketamine only session

Methadone patients' subjective awareness of altered sensations commenced within 30- 60 seconds of the first bolus dose (1.1mg) being administered and the infusion (0.6 mg/hour) being commenced, and lasted between 6 and 15 minutes. Spontaneous comments from the four methadone patients are outlined as follows:

“feels like I am floating” “this is wonderful” “my eyesight seems much sharper ...things seem so much brighter...” “its like being really light headed...a lovely feeling” “I feel light headed” “I have a slightly numb sensation in my lips” “there is a numbness around my face and lips” “colours and sounds seem to be a lot more intense” “this is good”

Similarly, for control subjects, their subjective awareness of altered sensations generally commenced within 30 seconds of initial drug administration: these lasted up to 17 minutes later. Spontaneous comments from the four control subjects' comments after the first part of the drug administration regimen are as follows:

“feeling a little bit woozy in the head” “are you sure this wasn't a placebo?” “I don't feel any different at all” “there is a slight sensation of numbness on my forehead” “its like the feeling you've had when you've had a couple of beers”

The drug regimen (as described in section 5.2.2.1) then involved the administration of second bolus dose (2.1mg), and the infusion rate increased to 1.8mg/hour for one hour. Within 30 seconds of the second bolus dose and the infusion rate being increased, methadone patients began to verbalise their experiences; these lasted for up to 35 minutes. Methadone patients' comments are as follows:

"this is fantastic...its like a cross between cocaine, heroin and GHB (Gamma Hydroxy Butyrate) its like having each of the great feelings those drugs give you....and no bad bits" "wow...this is great" "the colours are so much brighter" "everything seems much clearer and sharper" "this is fucking yummy" "an excellent feeling" "can I buy this stuff from you?" "my vision seems a bit weird...things look distorted" "this is like a fantastic acid trip without any bad bits" "this is absolutely fantastic" "I feel really floaty" "I have a sense of sensational well being" "its clouding my thinking, if you know what I mean" "this is a lot more pleasant than last week (referring to the combination session)" "my hearing seems much more acute" "I am worried that my words are coming out all jumbled up" "its like being wrapped up in warm cotton wool and floating around" "can I have more?" "this is one of the best feelings I have ever had" "I'd love to get my hands on this stuff" "this has to be the best ever drug experience" (repeated in all 4 patients) "I wish I felt like this all of the time" "they'd charge a fortune for this on the streets"

Control subjects generally reported sensory/perceptual alterations commencing within 1-2 minutes after the second part of the regimen was administered; these lasted for up to 24 minutes. Comments of controls are outlined below:

"it feels like I've just had one beer too many" "It feels like I am nearly drunk"
"when I look around the room it seems to take my vision a little bit of time to catch up with my head" (visual distortion repeated in 3 control subjects)

5.3.5.6.1.2 (+)-(S)-ketamine plus morphine session

During this session the amount S(+)-ketamine administered was identical to that in the (+)-(S)-ketamine only session. However, morphine sulphate was administered in conjunction with (+)-(S)-ketamine (as described in detail in section 5.2.2.1). Methadone patients' subjective sensations generally commenced within 30-60 seconds of first bolus doses being administered and the infusion being commenced; these lasted up to 14 minutes later. Methadone patients' comments are as follows:

"a kind of stoned feeling" "I feel a bit groggy but not too groggy" "it's a slightly weird"

feeling ..really quite nice” “the muscles in my face seem really relaxed” “I can feel tingles in my arm...like morphine tingles when you jack up (inject drugs)” “oh yes...I feel nice and relaxed now”.

In the control group, subjective sensations commenced within 30-60 seconds of the first bolus doses being administered and the infusion being commenced; these lasted up to 18 minutes later. Comments from control subjects are outlined below:

“my arm is itching” “I have a light-headed feeling” “I just feel slightly different, its difficult to describe” “my neck seems to be a bit stiffer” “there is tingling around my face” “I feel slightly light headed”

At the 60 minute time point a second bolus dose of (+)-(S)-ketamine (2.1mg) was administered, as well as the (+)-(S)-ketamine infusion rate being increased to 1.8mg/hour. Morphine administration did not change at this time point; there was no second bolus dose of morphine, and the infusion rate remained at 1.2mg/hour.

Once again, methadone patients’ began to verbalise their experiences within 60 seconds of the second bolus dose of (+)-(S)-ketamine being administered; these lasted for up to 24 minutes. Methadone patients’ comments are as follows:

“my lips and parts of my face are starting to tingle” “its better than cocaine” “I feel like I am glowing inside” “its nearly like an acid trip before the hallucinations kick in” “everything seems so much more colourful and bright” “its like someone has turned up the lights” “it feels like I am floating even though I know I’m not!” “this is a good weird feeling” “yeah this is great.....its like cocaine without all the noise and speediness” “a fantastic feeling but not a rush” “my thoughts seem to be slow but its okay.....does that make sense?” “its like cocaine without the excitement” “my colour perception seems really different” “I feel like I am floating” “this stuff should be called Super Special K” “my head feels like its been wrapped up in something nice and warm”

Similarly, control subjects began to verbalise their experiences within 60 seconds of the second bolus dose of (+)-(S)-ketamine being administered; these lasted for up to 16 minutes. Control subjects’ comments are as follows:

“it feels like I’ve had one drink too many....you know slightly intoxicated” “its a very mild sort of strange feeling” “its like my concentration is slightly impaired” “I feel slightly drunk but not too bad” “a floaty kind of sensation” “a slightly fuzzy sensation”

All of the methadone patients indicated that they would like to buy (+)-(S)-ketamine if it was available on the streets. Further, all indicated that it would be worth more than cocaine. All of the methadone patients stated that if there were any future experiments involving (+)-(S)-ketamine that they would “really like to” be volunteers again. None of the control subjects expressed any positive views about the drug experience; when asked directly about drug effects all control subjects stated that it was not a pleasant or particularly unpleasant experience, except for the pain caused by the nociceptive tests.

5.3.6.6 MBG scores

Mean ($\pm$ SEM) MBG scores (0 to 7 h) are outlined in Table 5.9, and are also graphically illustrated in Figure 5.15. Comparing MBG scores between methadone patient and control subjects in the (+)-(S)-ketamine only session, there was no main effect of group ($F(1,6)=3.2$; $p=0.126$). However, there was a main effect of time ($F(2.2,13.3)=5.1$; $p=0.021$), and a significant interaction between group and time ($F(2.2,13.3)=5.1$; $p=0.021$), with methadone patients' MBG scores increasing across time. However, compared with baseline scores, methadone patients' MBG scores were not significantly higher at any time point ($p>0.060$).

Comparing MBG scores between methadone patient and control subjects in the (+)-(S)-ketamine plus morphine session, there was no main effect of group ($F(1,6)=3.7$; $p=0.101$). However, there was a main effect of time ($F(2.6, 15.7)=16.5$; $p<0.0005$), and a significant interaction between group and time ($F(2.6, 15.7)=15.9$; $p<0.0005$), with methadone patients' MBG scores increasing across time. However, compared with baseline scores, methadone patients' MBG scores were not significantly higher at any time point ($p>0.005$).

Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) did not reveal any significant differences between the sessions for methadone patients ($p>0.187$) or control subjects ($p>0.390$) between the treatment sessions.

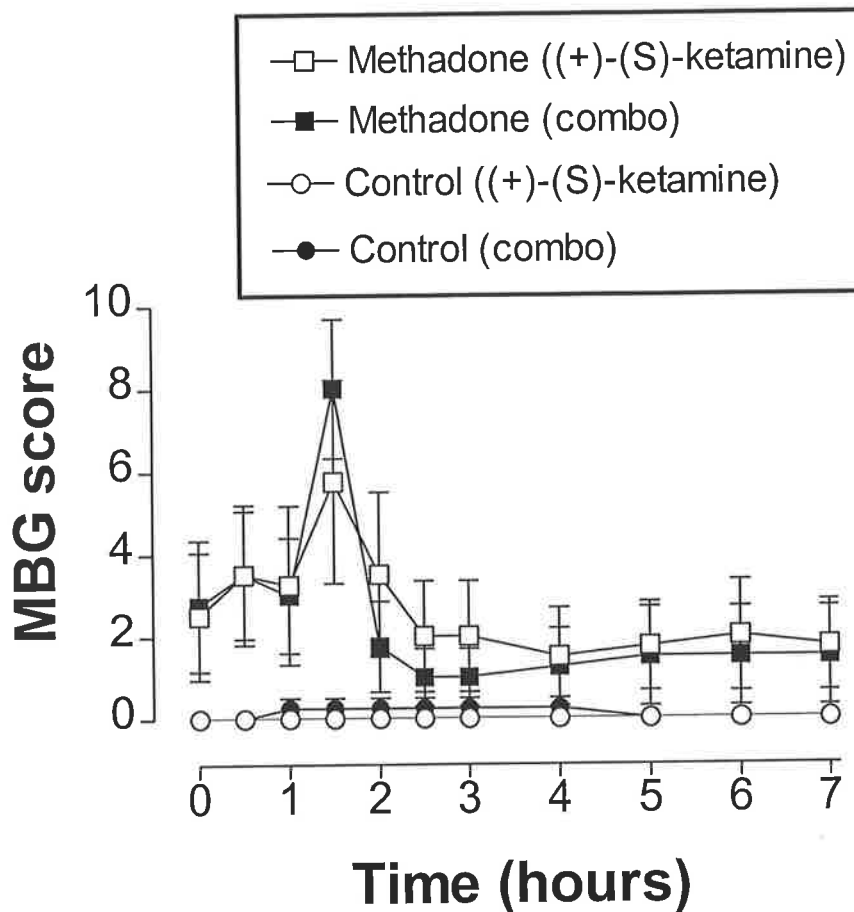
Table 5.9. Mean ($\pm$ SEM) MBG scores for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket denotes the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	2.5 (1.5)	2.75 (1.6)	0 (0)	0 (0)	*p=0.861, #p=0.206, +p=0.184, \$p=1.000
0.5 h	3.5 (1.5)	3.5 (1.7)	0 (0)	0 (0)	*p=1.000, #p=0.110, +p=0.133, \$p=1.000
1.0 h	3.25 (1.9)	3 (1.4)	0 (0)	0.25 (0.3)	*p=0.718, #p=0.191, +p=0.104, \$p=0.391
1.5 h	5.75 (2.5)	8.0 (1.7)	0 (0)	0.25 (0.3)	*p=0.299, #p=0.102, + p=0.004 , \$p=0.391
2.0 h	3.5 (2.0)	1.75 (1.0)	0 (0)	0.25 (0.3)	*p=0.188, #p=0.182, +p=0.235, \$p=0.391
2.5 h	2 (1.3)	1.0 (0.7)	0 (0)	0.25 (0.3)	*p=0.252, #p=0.236, +p=0.356, \$p=0.391
3.0 h	2 (1.3)	1.0 (0.7)	0 (0)	0.25 (0.3)	*p=0.252, #p=0.236, +p=0.378, \$p=0.391
4.0 h	1.5 (1.2)	1.25 (0.9)	0 (0)	0.25 (0.3)	*p=0.391, #p=0.297, +p=0.374, \$p=0.391
5.0 h	1.75 (1.0)	1.5 (1.2)	0 (0)	0 (0)	*p=0.391, #p=0.213, +p=0.297, \$p=1.000
6.0 h	2 (1.4)	1.5 (1.2)	0 (0)	0 (0)	*p=0.182, #p=0.236, +p=0.297, \$p=1.000
7.0 h	1.75 (1.0)	1.5 (1.2)	0 (0)	0 (0)	*p=0.391, #p=0.213, +p=0.297, \$p=1.000

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p < 0.0045$), this is highlighted in bold text.

Figure 5.15 Mean ($\pm$ SEM) MBG scores during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.7 MG scores

Mean ($\pm$ SEM) MG scores (0 to 7 h) are outlined in Table 5.10, and are also graphically illustrated in Figure 5.16. Comparing MG scores between methadone patients and control subjects in the (+)-(S)-ketamine only session, there was no main effect of group ($F(1,6)=4.4$; $p=0.082$). There was no main effect of time ($F(1.5, 8.9)=1$; $p=0.375$), and no significant interaction between group and time ($F(1.5, 8.9)=1$; $p=0.375$).

Similarly, comparing MG scores between methadone patients and control subjects in the (+)-(S)-ketamine plus morphine session, there was no main effect of group ($F(1,6)=0.01$; $p=0.909$). There was no main effect of time ($F(2.8, 16.8)=0.8$; $p=0.517$), and no significant interaction between group and time ($F(2.8, 16.8)=0.95$; $p=0.426$).

Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) did not reveal any significant differences for methadone patients ($p>0.057$) or control subjects ($p>0.181$) at any time point between the treatment sessions.

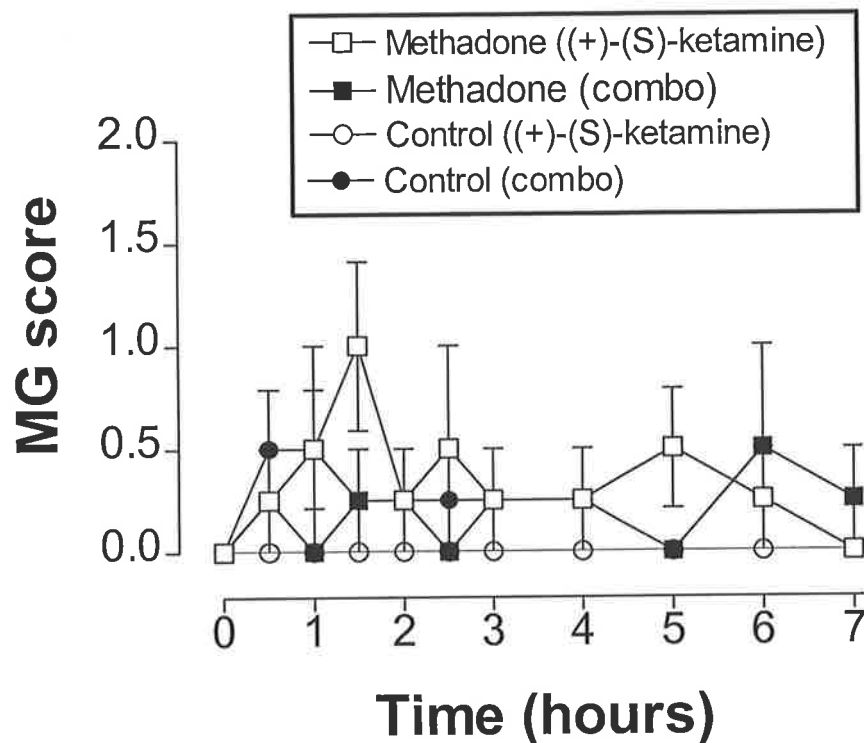
Table 5.10. Mean ($\pm$ SEM) MG scores for methadone (S-ket) patients, methadone (combo) patients, control (S-ket) and control (combo) subjects. Please note that the abbreviation S-ket means the (+)-(S)-ketamine only session, and combo means the (+)-(S)-ketamine plus morphine session.

Time (h)	MM (S-ket)	MM (Combo)	Control (S-ket)	Control (Combo)	
0 h	0 (0)	0 (0)	0 (0)	0 (0)	* $p=1.000$, $p=1.000$ + $p=1.000$, \$ $p=1.000$
0.5 h	0.25 (0.3)	0.25 (0.3)	0 (0)	0.5 (0.3)	* $p=1.000$, # $p=0.391$, + $p=0.537$, \$ $p=0.182$
1.0 h	0.5 (0.5)	0 (0)	0 (0)	0.5 (0.3)	* $p=0.391$, # $p=0.391$, + $p=0.134$, \$ $p=0.182$
1.5 h	1.0 (0.4)	0.25 (0.3)	0 (0)	0.25 (0.3)	* $p=0.058$, # $p=0.050$, + $p=1.000$, \$ $p=0.391$
2.0 h	0.25 (0.3)	0.25 (0.3)	0 (0)	0.25 (0.3)	* $p=1.000$, # $p=0.391$, + $p=1.000$, \$ $p=0.391$
2.5 h	0.5 (0.3)	0 (0)	0 (0)	0.25 (0.3)	* $p=0.391$, # $p=0.391$, + $p=0.356$, \$ $p=0.391$
3.0 h	0.25 (0.3)	0.25 (0.3)	0 (0)	0.25 (0.3)	* $p=1.000$, # $p=0.391$, + $p=1.000$, \$ $p=0.391$
4.0 h	0.25 (0.3)	0.25 (0.3)	0 (0)	0.25 (0.3)	* $p=1.000$, # $p=0.391$, + $p=1.000$, \$ $p=0.391$
5.0 h	0.5 (0.3)	0 (0)	0 (0)	0 (0)	* $p=0.182$, # $p=0.134$, + $p=1.000$, \$ $p=1.000$
6.0 h	0.25 (0.3)	0.5 (0.5)	0 (0)	0 (0)	* $p=0.718$, # $p=0.391$, + $p=0.356$, \$ $p=1.000$
7.0 h	0 (0)	0.25 (0.3)	0 (0)	0 (0)	* $p=0.391$, \$ $p=1.000$ + $p=0.356$, \$ $p=1.000$

* denotes MM (S-ket) vs. MM (Combo), # denotes MM (S-ket) vs. Control (S-ket)

+ denotes MM (Combo) vs. Control (combo), \$ denotes Control (S-ket) vs. Control (combo). Where there is statistical significance ($p<0.0045$), this is highlighted in bold text.

Figure 5.16. Mean ($\pm$ SEM) MG scores during the (+)-(S)-ketamine only session (methadone patients [open square] and controls [open circle]), and in the (+)-(S)-ketamine plus morphine session (methadone patients [filled square] and controls [filled circle]). Please note that the abbreviation “combo” denotes the (+)-(S)-ketamine plus morphine session.



5.3.6.8 Pulse oximetry

Mean SpO₂ levels of methadone patients during the (+)-(S)-ketamine only session (97.1 ± 0.2) were not different from those of controls (97.1 ± 0.2) at baseline ($p=1.000$). Similarly, mean SpO₂ levels of methadone patients (97.3 ± 0.2) in the period during and post-(+)-(S)-ketamine administration were not significantly different ($p=0.847$) from those of controls (97.3 ± 0.2). in that period. During the (+)-(S)-ketamine plus morphine session mean SpO₂ levels of methadone patients (96.8 ± 0.2) were not significantly different from those of controls (97.5 ± 0.4) at baseline ($p=0.132$). Furthermore, methadone patients' SpO₂ levels in the period during and post (+)-(S)-ketamine plus morphine administration (97 ± 0.1) were not significantly different ($p=0.885$) from those of controls (97.2 ± 0.2).

Within-group comparisons ((+)-(S)-ketamine only vs. (+)-(S)-ketamine plus morphine) revealed that for methadone patients, baseline SpO₂ levels in the (+)-(S)-ketamine plus

morphine session (96.8 ± 0.2) were significantly lower ($p=0.035$, [95%CI, -0.5,-0.04]) than those obtained at baseline in the (+)-(S)-ketamine only session (97.1 ± 0.1). However, there were no significant differences ($p=0.368$) in methadone patients' SpO₂ levels in the period during and post-infusion. For control subjects, there were no significant differences ($p=0.205$) in baseline SpO₂ levels between the sessions (97.1 ± 0.2 vs. 97.5 ± 0.4), or in the period during and post-infusion ($p=0.092$). With regard to SpO₂ levels at 95% and below, there were no significant differences between the sessions for methadone patients ($p>0.181$) or for control subjects ($p>0.213$).

5.4 Adverse events

During the (+)-(S)-ketamine plus morphine session one of the control subjects developed mild urticaria on the arm in which the drugs were intravenously administered; this commenced within 3 minutes of being given the initial bolus doses of these drugs. The rash did not require any treatment and was visible for approximately one hour. This reaction was probably due to morphine administration resulting in histamine release. The control subject was not distressed by this event. There was no nausea or vomiting.

5.5 Discussion

I sought to investigate the antinociceptive effects of (+)-(S)-ketamine, alone and in combination with morphine, at consecutive pseudo steady-state plasma concentrations in a sample of methadone maintenance patients and age and sex-matched control subjects. (+)-(S)-ketamine alone had no apparent antinociceptive effects in methadone patients or control subjects. Furthermore, the combination of (+)-(S)-ketamine plus morphine had no discernible antinociceptive effects in methadone patients. However, in control subjects this combination resulted in increases in nociceptive response values, although this was significantly different at one only time point compared with values in the (+)-(S)-ketamine only session. It is unclear whether this antinociception in control subjects was a direct result of the morphine, or possibly a synergistic or additive effect of (+)-(S)-ketamine and morphine. Despite an apparent lack of antinociceptive effects in the methadone patients, (+)-(S)-ketamine produced substantial subjective effects in this patient group. Surprisingly, the subjective effects of (+)-(S)-ketamine were markedly more pronounced, only during each C_{ss} period, in the methadone patients compared with the control subjects.

5.5.1 Antinociceptive effects

There were marked differences in responses between methadone patients and controls using the cold pressor test. The most pronounced difference was observed for pain tolerance, with methadone patients exhibiting hyperalgesic responses, as has been reported in chapters 2 and 3. Pain tolerance to detection ratios in the methadone patients, for the cold pressor test, were also markedly lower than the controls, as reported in chapters 2 and 3. The finding that methadone patients are hyperalgesic to pain induced by a cold pressor test but not electrical stimulation, is consistent with results reported previously in chapters 2 and 3.

I previously reported in chapters 2 and 3 that, for the cold pressor test, a low pain tolerance to detection ratio may be a marker of hyperalgesia in methadone patients. The results in this chapter confirm this ratio as being a sensitive marker of hyperalgesia in methadone maintenance patients. Once again, I would suggest that further research in populations maintained on opioids other than methadone is necessary to determine the validity of this ratio as a marker of opioid-induced hyperalgesia.

The dosing regimen was aimed to achieve plasma ketamine concentrations of 10ng/mL and 30ng/mL. These concentrations were chosen based on some evidence in the literature (Clements *et al.*, 1981; Tucker *et al.*, 1999). Tucker and colleagues (1999) derived plasma concentration-effect relationships for racemic ketamine and fentanyl, alone and in combination with each other. Their study was a randomised, placebo-controlled, double-blind laboratory experiment using 10 healthy human volunteers; on separate days, an increasing dose of ketamine (15, 30, 60 and 120 ng/mL), fentanyl (0.2, 0.4, 0.8 and 1.2 ng/mL) or fentanyl plus a sub-hypnotic dose of ketamine (30ng/mL) were given and compared with placebo in a cross-over design. Multiple measures of pain induction were used (electrical stimulation, mechanical pressure and radiant heat). Dose-dependent antinociceptive effects of ketamine and fentanyl were observed for electrical stimulation and mechanical pressure but not radiant heat. A dose-response curve for the antinociceptive effects of fentanyl in combination with ketamine showed an increase in pain threshold to electrical stimulation greater than that of either drug alone. Although they did not actually measure the plasma concentrations of the drugs, Tucker and colleagues concluded that a sub-hypnotic (30ng/mL) dose of ketamine causes potentiation of the antinociceptive effects of fentanyl. This finding supports the earlier results of Chia *et al* (1998), who in a prospective double blind clinical study, demonstrated that ketamine has an additive analgesic effect when given in combination with other analgesics, and that ketamine

decreases the consumption of these other analgesics. Further, there is clinical evidence that plasma ketamine concentrations of approximately 40 ng/mL produce significant analgesia (Clements *et al.*, 1981), and that plasma ketamine concentrations of 50ng/mL result in significant drowsiness (Bowdle *et al.*, 1998), the latter being an effect that I did not want to occur in my patients or control subjects. As discussed above, the dosing regimen aimed to achieve plasma (+)-(S)-ketamine concentrations of 10 and 30 ng/mL during C_{SS1} and C_{SS2} ; these precise concentrations were not achieved in either the methadone patients (7.6 and 21.6 ng/mL) or amongst the control subjects (5.1 and 16.5 ng/mL). Methadone patients achieved approximately 70-75% of target plasma (+)-(S)-ketamine concentrations, whereas controls achieved approximately 50-55% of the target concentrations. I am unable to definitively explain why there were differences in these concentrations between the respective groups; methadone could have reduced the clearance of ketamine, which resulted in greater plasma concentrations in the methadone patients.

Similarly, with regard to target plasma morphine concentrations there were differences between the groups; the target of 20ng/mL was achieved in the methadone patients (C_{SS} mean was 21.9ng/mL), whereas control subjects only achieved a mean C_{SS} of 10.8 ng/mL. I am unable to explain why control subjects had significantly lower plasma morphine concentrations than the methadone patients. As discussed in Chapter 3, perhaps further, and more detailed pharmacokinetic studies should be considered to investigate the effects of chronic methadone treatment on morphine metabolism and clearance.

Numerous animal studies performed at the level of the spinal cord have shown that NMDA receptor activation plays a role in the transmission of nociceptive information (Dickenson, 1995; Ren *et al.*, 1992; Yamamoto *et al.*, 1993; Kohrs & Duireux, 1999). NMDA receptor activation does not polarise dorsal horn neurones in the resting state, but prolongs action potentials if excitatory impulses have been initiated by neurokinins or non-NMDA excitatory amino acids (Dickenson, 1995). Consequently, blockade of the NMDA receptor produces only weak or no antinociception against acute thermal or mechanical stimuli in uninjured rats (Ahuja, 1983; Klimscha *et al.*, 1998), but elicits antinociception in various models of persistent pain (Ren *et al.*, 1992; Yamamoto *et al.*, 1993). The lack of antinociception following intravenous administration of (+)-(S)-ketamine in the nociceptive models of the present study seem to be consistent with those reported above (Ahuja, 1983; Klimscha *et al.*, 1998), as the models of nociceptive pain induction used in the present study do not cause persistent pain. Further, there is some recent evidence that plasma ketamine

concentrations of up to 150ng/mL did not have significant effects on the cold pain threshold of human subjects (Leung *et al.*, 2001).

It is likely that the doses of (+)-(S)-ketamine used in the present study were too small to result in the achievement of significant antinociception. Further studies using larger doses (and higher plasma concentrations) may need to be conducted to fully investigate the potential of this drug as an analgesic in combination with other opioids amongst methadone maintained patients. However, I would advise caution in using larger doses of (+)-(S)-ketamine in experiments involving methadone patients due to the extent of subjective effects experienced by patients in this study. Further experimentation using larger doses (and plasma concentrations) in this particular patient population could be deemed unethical in light of the pronounced subjective effects experienced by the sample of patients in the present study. All of the patients in the present study indicated that they would purchase (+)-(S)-ketamine if it was illicitly available. It is possible that if larger doses of (+)-(S)-ketamine are administered to methadone patients, the magnitude of subjective effects experienced by these patients may precipitate drug seeking behaviours. Hence, in light of the present data (albeit in a small sample of patients) I would suggest that (+)-(S)-ketamine is a drug of high abuse potential in this particular patient group. Furthermore, there is some animal evidence, which suggests that NMDA receptor antagonist-mediated modulation of opioid antinociceptive tolerance may be selective to morphine but not to fentanyl or to a δ (delta) selective agonist (Bilsky *et al.*, 1996). Perhaps, the intracellular mechanisms involved in methadone-induced tolerance are different to those in morphine tolerance. The plethora of available animal evidence all refer to a model of morphine tolerance (Elliot *et al.*, 1994; Kolesnikov *et al.*, 1993; Mao *et al.*, 1994, 1995a,b, 1996; Marek *et al.*, 1991; Mayer *et al.*, 1995; Tiseo & Inturrisi, 1993; Trujillo & Akil, 1991b). To the best of my knowledge no animal studies on the topic of opioid tolerance and hyperalgesia have used methadone. It would be valuable to conduct animal research using methadone in a similar manner to the well established and described morphine studies.

5.5.2 Physiological effects

The literature on respiratory effects of ketamine is somewhat confusing (Soliman *et al.*, 1975; Kochs *et al.*, 1996; Owen *et al.*, 1987; Bourke *et al.*, 1987; Mankikian *et al.*, 1986). Ventilatory stimulating (Soliman *et al.*, 1975) as well as depressing (Freye *et al.*, 1992) effects have been reported. There are several possible reasons for the apparent discrepancies including considerable variation in the doses used, modes of administration (bolus vs.

infusion) (Mildh *et al.*, 1998), rate of drug administration, spinal vs supra-spinal sites of action (Hartvig *et al.*, 1995; Sasao *et al.*, 1996), pharmacokinetic-pharmacodynamic differences between the enantiomers and dose-dependent interactions with different receptor systems (Bianchi *et al.*, 1995).

There is no apparent evidence to indicate that low-dose ketamine causes or contributes to respiratory depression (Madsuka & Hajghassemali, 1978; White *et al.*, 1982; Peat *et al.*, 1989; Edwards *et al.*, 1993; Bhattacharya *et al.*, 1994). Interestingly, ketamine has been shown to antagonise opioid-induced hypoventilation (Mildh *et al.*, 1998; Persson *et al.*, 1999). It has been suggested that plasma ketamine concentrations of less than 300ng/mL are likely to have antagonistic effects on opioid induced respiratory depression (Mildh *et al.*, 1998; Persson *et al.*, 1999). The results from the present study do not confirm or contradict this possible effect.

The mechanisms involved in the antagonistic effects of ketamine on opioid-induced respiratory depression are not clear. It has been suggested that the subjective side-effects of ketamine experienced by subjects may cause a general arousal, thereby stimulating respiration (Persson *et al.*, 1999). Evidence from animal studies indicates a direct involvement of NMDA receptors in the control of respiration. Furthermore, opioids depress ventilation by reducing glutaminergic transmission (Bianchi *et al.*, 1995; Pierrefiche *et al.*, 1990). The antagonistic effect is evident only when ketamine is administered in low doses such as those used in the present study. This effect could prove to be beneficial when managing pain in individuals who are already on large doses of opioids, ie reducing the risk of further respiratory depression. There is some evidence that low-dose ketamine may cause mild sedation (Sadove *et al.*, 1971) that is less than sedation seen with opioids (Bristow & Orlikowski, 1989; Bhattacharya *et al.*, 1994). When administered in combination with opioids, low-dose ketamine does not appear to enhance or add to opioid-induced sedation (Javery *et al.*, 1996; Stubhaug *et al.*, 1997). There was no evidence in the present study that low dose (+)-(S)-ketamine alone, or in combination with low dose morphine causes even very mild sedation.

As outlined in the preceding chapter, morphine-induced miosis has previously been shown in studies with healthy volunteers (Fraser & Isbell, 1952; Ghoniem *et al.*, 1984; Nicolodi & Sicuteri, 1992) and in opiate abusers (Fraser & Isbell, 1952; Jasinski & Mansky, 1972; Lamb *et al.*, 1991), and is a well known marker of opioid effect. In the present study morphine-induced miosis was most pronounced in control subjects but was much less

marked in the methadone maintenance patients; this is similar to the results reported in chapter 3. Furthermore, the miosis in the control group remained marked for at least 5 hours after morphine administration had ceased; this is also consistent with findings reported in chapter 3. These findings in the control subjects are in keeping with those observed in previous studies involving the administration of morphine to opioid naïve healthy volunteers. It has been reported that miosis was induced in a dose-dependent manner, and was still evident 5 hours post injection (Zacny *et al.*, 1994; Walker & Zacny, 1999). I am unaware of any studies reporting miosis related to ketamine or (+)-(S)-ketamine administration. Given that there was no observable miosis in the (+)-(S)-ketamine only session, I am confident that the miosis observed in control subjects during the (+)-(S)-ketamine plus morphine session was due to the opioid agonist effect of morphine. Interestingly, although the plasma morphine concentrations in the present study were somewhat lower than those reported in the preceding chapter, the miotic effect observed in the control subjects in the present study was very similar.

Studies examining cardiovascular response to low-dose ketamine report minimal changes in heart rate and blood pressure (Sadove *et al.*, 1971; Owen *et al.*, 1987; Dich-Nielsen *et al.*, 1992; Edwards *et al.*, 1993; Jahangir *et al.*, 1993). A few studies found a decrease in heart rate and blood pressure. However these were principally attributed to a decrease in pain (Joachimsson *et al.*, 1986; Royblat *et al.*, 1993), whereas others have reported that in an experimental situation, ketamine produces small but dose-related increases in systolic but not diastolic pressure (Krystal *et al.*, 1994). I am not aware of any other studies involving the use of (+)-(S)-ketamine in methadone maintained patients. The results of the present study are generally consistent with those reporting minimal cardiovascular effects related to ketamine administration. However, as a result of the small sample sizes, there may well have been a lack of power to detect possible changes. Further work with larger numbers of subjects should be considered.

Despite a lack of nausea or vomiting following administration of low-dose (+)-(S)-ketamine in the present study, others have reported that when low-dose racemic ketamine is administered to healthy volunteers, the incidence of nausea and vomiting appears to be greater than that reported in a clinical setting (Krystal *et al.*, 1998; Sethna *et al.*, 1998).

There were no significant effects of (+)-(S)-ketamine alone on arterial oxygenation as measured by non-invasive pulse oximetry. However, the combination of (+)-(S)-ketamine plus morphine, resulted in very small reductions in oxygen saturation levels amongst the

methadone patients; these changes were not deemed clinically significant as oxygenation levels remained within normal clinical parameters (96-99%).

5.5.3 Subjective effects

Disturbing emergence phenomena, such as bad dreams and hallucinations, have limited the clinical usefulness of racemic ketamine (Schmid *et al.*, 1999). Schmid *et al.* (1999) concluded there are several factors that appear to be associated with the occurrence of psychotomimetic effects; these include age, sex, previous psychopathology, high doses of ketamine (>2mg/kg i.v.) and rapid (>40mg/min) intravenous administration (White *et al.*, 1982). Evidence from earlier studies suggests that i.v low-dose ketamine given at an infusion rate <2.5mcg/kg per min (with estimated plasma ketamine concentrations of < 50ng/mL) does not cause hallucinations (Krystal *et al.*, 1994, 1998) or impairment of cognitive functioning (Krystal *et al.*, 1994; Sethna *et al.*, 1998). Others have suggested that at plasma ketamine concentrations of >200ng/mL the incidence of psychotomimetic effects, cognitive impairment, and other adverse events increases (Krystal *et al.*, 1994,1998; Adler *et al.*, 1998; Bowdle *et al.*, 1998; Sethna *et al.*, 1998). It has been reported that sub-anaesthetic doses (0.1mg/kg to 0.5mg/kg) of ketamine administered intravenously resulted in dose-dependent alterations in mood states of healthy volunteers (Krystal *et al.*, 1994). At the lowest dose in that particular study (0.1mg/kg) subjects reported feeling tingling sensations in their faces and extremities; this phenomenon also occurred in the present study. Control subjects in the present study likened the effect of ketamine to “having had one drink too many”. These reports are in agreement with laboratory data indicating that alcohol has NMDA receptor antagonist properties (Lovinger *et al.*, 1989), and that NMDA receptor antagonists have alcohol-like discriminative properties in rats (Colombo and Grant, 1992). The sense of ‘intoxication’ reported by control subjects in the present study is consistent with subjects in a previous study (Sethna *et al.*, 1998). It has been suggested that there are similarities between the ketamine “high” and alcohol intoxication (Øye *et al.*, 1992; Krystal *et al.*, 1994).

Krystal *et al.* (1994) provided some evidence that sub-anaesthetic doses of ketamine may be administered to healthy subjects in controlled laboratory settings without significant risk of untoward psychological consequences such as hallucinations and disordered thought content. Indeed, this is further supported by the lack of adverse psychological consequences in control subjects used in the present study. Findings from the present study are consistent with previous reports (Garfield *et al.*, 1972; Krystal *et al.*, 1994; Øye *et al.*, 1992) that at

low doses, ketamine distorts the perception of identifiable sensory stimuli, producing illusions rather than hallucinations.

Methadone patients in the present study seem to have enjoyed the subjective effects produced by (+)-(S)-ketamine; this is highlighted by comments such as “*this has to be the best ever drug experience*” and “*they’d charge a fortune for this on the streets*”. Indeed, all of the methadone patients indicated that they would use this drug if it was available illicitly. Such was their apparent enthusiasm for the subjective effects produced by this drug (in spite of the presence of repeated unpleasant nociceptive stimuli) that I would strongly advise caution in further use of (+)-(S)-ketamine in this patient population. Despite evidence of tachyphylaxis in relation to the subjective effects, I would caution that (+)-(S)-ketamine has high abuse potential in these patients.

Reports of ketamine abuse began to appear in the medical literature soon after its introduction into clinical practice (Siegel, 1978; Ahmed & Petchovsky, 1980). Ketamine has been reported to produce effects similar to phencyclidine (PCP), but with a much shorter duration of action (Jansen, 1993). There have even been reports of people requiring detoxification for dependent ketamine use (Hurt & Ritchie, 1994; Soyka *et al.*, 1993; Kamaya and Krishna, 1987). Dalgarno and Shewan (1996) reported the results of semi-structured interviews conducted in a sample of 20 illicit ketamine users in Scotland, where they suggest that ketamine abuse is increasing. Users’ experiences in the Dalgarno and Shewan study included: “a sensation of light through the body” “a sensation of floating” “radiantly colourful visions” “visual hallucinations”. None of the subjects in the Dalgarno study were currently dependent on opioids, although 2 of 3 subjects who had the heaviest ketamine use and for the longest periods had previously been dependent on opioids. Some of the subjective symptoms reported by subjects in the present study are consistent with those previously documented (Hansen *et al.*, 1988; Dalgarno & Shewan, 1996; Øye *et al.*, 1992).

There have also been reports of increasing ketamine abuse in the United States. The Drug Enforcement Agency warned in 1997 that ketamine abuse was increasing, and it has since become a controlled substance in seven states (US DEA, 1997). Weiner and colleagues (2000) reported substantially increasing numbers of ketamine abusers presenting to a hospital emergency department. Some recent evidence from New York City, where in at least 15 non-hospital deaths ketamine was detected in post-mortem blood sample analysis, suggests that the increased incidence of deaths involving ketamine (but not due to ketamine

alone) may be a reflection of increased ketamine use in the “club/rave scene” (Gill and Stajic, 2000). Ketamine seems to have gained increasing popularity in the “club” and “rave” scene (Jansen, 1993; Schwartz and Miller, 1997). In a study conducted in the United Kingdom, 32% of people interviewed at dance venues said that they had taken ketamine at least once (Release, 1997). This supports earlier suggestions by Jansen (1993) that ketamine was most commonly taken at “rave” parties and nightclubs. Dalgarno and Shewan (1996) also suggested that ketamine initially appeared as part of the “rave” scene as a contaminant in 3,4-methylenedioxymethamphetamine (“ecstasy”). Curran and Morgan (2000) reported that ketamine, also known as “Super K”, “vitamin K”, “Special K” (US DEA, 1997), is associated with “squat parties” where empty buildings are occupied for use as music venues. Overall there appear to be increasing numbers of people recreationally using ketamine (Curran & Morgan, 2000). In Australia, in the state of Victoria, ketamine was listed in Schedule II, in 1999, as a drug of dependence requiring a stricter enforcement regime, and penalties were also introduced for using, possessing and trafficking ketamine (Australian Bureau of Criminal Intelligence, 2000).

Grant and co-workers (1981) claimed that the frequency of psychic sequelae after ketamine is dose related and is markedly reduced with the use of the drug in sub-anaesthetic doses. Moreover, they suggested that if plasma ketamine concentrations are kept within the analgesia range, as after a 0.5mg/kg dose, these sequelae might be eliminated. However, others have concluded that the sequelae, after 0.5mg/kg, were not significantly lower than those after an anaesthetic dose of 2mg/kg (Dundee & Lilburn, 1978). The subjective responses outlined in the present study confirm the suggestion by Grant *et al.* (1981) that psychic sequelae of ketamine are dose related; all subjects, but particularly the methadone patients, in the present study reported significantly increased effects after the highest dose (plasma concentration) was administered/achieved. However, given that in the present study the doses administered and the plasma concentrations achieved are somewhat lower than the concentrations suggested by Grant and colleagues, I do not agree with their assertion that psychic sequelae can be eliminated by keeping plasma ketamine concentrations within the analgesic range.

Interestingly, Ghoniem *et al.* (1985) found that past experience with hallucinogenic drugs was associated with subjects in their study, who (after being given sub-anaesthetic doses of ketamine) reported it being a pleasant experience. I am unable to definitively explain why methadone patients seemed to experience more intense subjective effects related to (+)-(S)-

ketamine; I would speculate that because methadone acts as a weak NMDA receptor antagonist, perhaps long term methadone maintenance treatment may in some way cause up-regulation of that receptor complex resulting in increased sensitivity to the effects of additionally administered NMDA antagonist compounds. Another possible explanation is that the subjective effects experienced by the methadone patients may be additive effects of two NMDA antagonists, methadone and ketamine. Animal studies may need to be conducted to investigate the effects of methadone maintenance treatment on that particular receptor complex.

The lack of significant subjective effects (as measured by MBG scores) related to morphine administration in the present study was not unexpected, due to the frequency of pain induction throughout the testing sessions. There is some evidence that experimental pain attenuates subjective and behavioural effects of opioid drugs (Wolff *et al.*, 1940; Borgbjerg *et al.*, 1996; Walker & Zacny, 1998).

5.5.4 Conclusions

In summary, low dose (+)-(S)-ketamine alone, or in combination with low dose morphine is likely to be ineffective in managing episodes of acute pain in methadone maintenance patients. However, further studies using higher doses (and plasma concentrations) may need to be conducted to fully ascertain the analgesic efficacy of this drug combination amongst methadone maintenance patients. Despite a lack of antinociceptive effects, these findings show that even at very low doses (and plasma concentrations), (+)-(S)-ketamine produces pronounced subjective effects amongst methadone patients, and is likely to have high abuse potential in this patient group. Further research is urgently needed to determine whether other drugs such as gabapentin (Ekhardt *et al.*, 2000), tramadol (MacPherson, 2000), clonidine (Eisenach *et al.*, 1995; Tumber & Fitzgibbon, 1998), or non steroidal anti-inflammatory drugs (Maves *et al.*, 1994; Souter *et al.*, 1994; Christie *et al.*, 2000), alone or in combination with morphine, are effective in managing acute pain in this patient population.

GENERAL SUMMARY

6.1 Summary and Conclusions

This thesis had one broad aim, to produce data that would eventually help in the formulation of prescribing guidelines, improved policies, and more importantly help direct optimal acute pain management for methadone maintenance patients. To achieve this broad aim, specific objectives included:

- determining whether pain threshold and pain tolerance are similar in methadone maintenance compared to healthy volunteers;
- determining whether nociceptive responses are different at trough and peak plasma methadone concentrations;
- determining the antinociceptive effects of additionally administered morphine on pain sensitivity in methadone maintained patients;
- determining the physiological and subjective effects of additionally administered morphine in methadone maintenance patients;
- determining the antinociceptive effects of (+)-(S)-ketamine alone, and in combination with morphine, in methadone maintenance patients;
- determining the physiological and subjective effects of (+)-(S)-ketamine alone, and in combination with morphine, in methadone maintenance patients.

There were discrepancies in the literature about the pain sensitivity of methadone maintenance patients. It was possible that the contradictions in the literature may have been due to differences in the methods of experimental pain induction, and pain measurement indices; various methods of pain induction (cold pressor test, mechanical pressure, electrical stimulation) were used to determine pain sensitivity. Further, there was a lack of consistency in the measurement of pain thresholds ie. onset of pain measured in some studies, with pain tolerance and pain discomfort measured in others. In order to resolve this, it was necessary to use multiple pain induction and pain measurement methods, and to account for fluctuations in plasma methadone concentration, specifically at the two extremes of the inter-dosing interval: trough (23.5 hours after the dose) and peak (3 hours after the dose).

In the first study, I used two distinct methods of pain induction: (1) electrical stimulation, and (2) a cold pressor test; both have been shown to be reproducible and responsive to opioids, offer variety in pain stimulus (phasic pain vs. tonic pain), and both have been used in studies investigating the issue of pain sensitivity amongst opioid addicts (Inglis & Martin, 1964; Ho & Dole, 1979; Compton, 1994, 1998; Dyer *et al.*, 1999; Compton *et al.*, 2000). Further, I sought to determine the association between nociceptive responses and plasma methadone enantiomer concentrations. There were marked differences in pain tolerance responses between methadone maintenance patients and controls using the cold pressor test, with methadone patients exhibiting a hyperalgesic response. Using electrical stimulation, differences for pain tolerance between methadone patients and controls were much less marked, with methadone patients more pain tolerant than controls when their plasma methadone concentration was at the putative peak. Nociceptive responses of methadone maintenance patients were attenuated by the increase in plasma methadone concentration irrespective of the method of pain induction.

The data from this first study helped to reconcile the apparent discrepancies in the literature. They partly supported the findings of Ho and Dole (1979) who found that pain threshold (detection) values of methadone maintained patients were significantly lower than those of controls. However, with regard to pain tolerance values, these results are very different in that methadone maintained patients were substantially intolerant of cold pressor induced pain compared with control subjects, whereas Ho and Dole (1979) found no significant difference. The finding of pain intolerance, in methadone patients, is similar to that reported by Compton (1994), who also using a cold pressor model, found that methadone patients were pain intolerant compared with cocaine abusers. Further, these results are very different to those reported by Liebmann *et al.* (1994), who suggested that opioid addicts have higher pain thresholds than control subjects. Using electrical stimulation, these results concur with those of Dyer *et al.* (1999) who reported that at the time of trough plasma methadone concentrations patients had similar threshold (pain detection) values to controls, whereas at time of peak plasma methadone concentrations patients were less pain sensitive than controls.

In my analyses of data from the first study in this thesis, I used a pain tolerance to detection ratio. This ratio was used as a means of incorporating both ends of the pain continuum ie. when pain is first felt (detection) and the point when it becomes intolerable (tolerance); both indices are important factors in determining pain sensitivity. Thus this ratio incorporated

both ends of the pain continuum. Interestingly, the magnitude of differences between methadone patients and controls were significant only with the cold pressor test, with methadone patients' ratio being markedly lower than that of matched control subjects. To the best of my knowledge this is the first time that the pain tolerance to detection ratio has been used as a means of discriminating pain responses between methadone maintenance patients and controls.

Important differences in study procedures (eg., phasic versus tonic stimulation, and measuring thresholds for pain detection versus pain tolerance) may have contributed to the apparent discrepant results in the literature. Pain sensations produced by phasic stimuli, such as electrical stimulation, differ qualitatively, neurologically, and functionally from deep, prolonged sensations (eg., tonic pain induced by the cold pressor test) which are characteristic of many clinical pain syndromes (Beecher, 1966; Price, 1976; Chen *et al.*, 1989). Chen and colleagues (1989) postulated that phasic pain and tonic pain may well be subserved by different neurophysiological pathways as well as being differentially affected by opioids. This may explain the findings in my first study that methadone maintenance patients are considerably more intolerant of pain induced by the cold pressor test compared to electrical stimulation. Interestingly, cold hyperalgesia is a phenomenon that is present after chronic nerve injury (Fruhstorfer & Lindblom, 1984; Frost *et al.*, 1998; Ochoa & Yarnitsky, 1994), and is frequently encountered in central pain syndromes that follow thalamic infarction (Craig *et al.*, 1994; Vestergaard *et al.*, 1995). I would speculate that perhaps the central plasticity that occurs with chronic opioid treatment, such as those changes involved in opioid tolerance, may be responsible for methadone patients' hyperalgesic responses to pain induced by a cold pressor test. Further and more detailed animal research is necessary to shed scientific light on this theory. Interestingly, there is animal (Mao *et al.*, 1994, 1995a, 1995b; Laulin *et al.*, 1999) and human (de Leon-Casasola *et al.*, 1993; Rapp *et al.*, 1995) evidence of altered pain sensitivity related to chronic opioid exposure. Overall, these combined data suggest that, in general, chronic opioid exposure may result in altered pain sensitivity. However, it would be of value to investigate this in other groups of patients (eg. cancer and non-cancer pain patients) on chronic opioids.

Methadone maintenance patients are likely to experience acute and chronic pain to the same degree and frequency as the general population. It has been suggested that patients with current or past substance abuse are difficult to manage and should probably be excluded from treatment with opioid analgesics (Kennedy & Crowley, 1990). Unfortunately, there

are few and conflicting data on the antinociceptive effects of additional opioids in these patients. Indeed the literature was littered with anecdote and suggestion. To the best of my knowledge the only controlled scientific study was recently conducted by Compton *et al.* (2000). They investigated the analgesic effects of small oral doses of (1) hydromorphone, and (2) ketorolac, in 60 methadone maintained patients and 60 matched controls. They did not find any significant analgesic effects of either drug amongst methadone patients or control subjects. However, that study did not involve blood collection from any of the participants; there could possibly have been differences between the plasma concentrations of hydromorphone and/or ketorolac in either group (methadone patients or control subjects). This highlights the need to determine individual plasma drug concentrations in studies determining the analgesic effects of various drugs.

Potentially, methadone patients may require substantially higher doses of opioid for acute pain control because of, firstly, cross-tolerance to the effects of opioid agonists and secondly, their baseline hyperalgesia. I am unaware of any other controlled studies that have investigated the antinociceptive effects of morphine amongst methadone maintenance patients. Hence, in the second study, I sought to compare the intensity and duration of the antinociceptive effects of morphine at two target controlled plasma concentrations in a sample of methadone maintenance patients and matched controls. Furthermore, in methadone patients, I set out to determine if the antinociceptive effects of morphine are affected by changes in plasma methadone concentrations that occur during an inter-dosing interval.

Despite significantly greater plasma morphine concentrations, methadone patients experienced minimal if any antinociception in comparison with control subjects in relation to the cold pressor test. Furthermore, in methadone (peak session) patients the antinociception ceased when the infusion ended, but in methadone (trough session) patients the small degree of post-infusion antinociception was due to increasing plasma (-)-(R)-methadone concentrations. In comparison, the duration of effect in all of the control subjects was 3 hours.

As in the first study, there were marked differences in responses between methadone patients and controls using the cold pressor test but not with electrical stimulation; the most pronounced difference was observed for pain tolerance, with methadone patients exhibiting hyperalgesic responses. Furthermore, also consistent with the results of the first study, pain tolerance to pain detection ratios in the methadone patients, for the cold pressor test, were

markedly lower than the controls.

The plasma morphine concentrations were chosen based on evidence that a plasma morphine concentration of approximately 15ng/mL is adequate for minimum effective post-surgical analgesia (Dahlström *et al.*, 1982; Gourlay *et al.*, 1986) and that plasma morphine concentrations in the region of 50ng/mL provide analgesia for moderate to severe post-surgical pain (Berkowitz *et al.*, 1975). However, at these and higher plasma morphine concentrations, morphine was ineffective in altering the response to the cold pressor test in methadone patients. This indicates that methadone patients are cross-tolerant to the antinociceptive effects of plasma morphine concentrations which are effective in opioid-naïve patients. To my knowledge, this is the first such report involving humans. Similar results, as reflected by flat log dose-response curves, were reported in rats receiving chronic high dose morphine administration (Mucha *et al.*, 1978; Mucha *et al.*, 1979; Mucha & Kalant, 1980).

In the context of acute pain management of methadone maintenance patients, it is important to remember that when administering additional opioids such as morphine, antinociception is not the only pharmacodynamic effect that occurs. There are a number of other side effects that need to be monitored (as outlined previously in detail in section 1.17). These include respiratory depression (Reisine & Pasternak, 1995), cardiovascular changes pressure (Gritz *et al.*, 1975; Platt, 1988; Rogers & Spector, 1980; Martin, 1984), miosis (Jaffe & Martin, 1992; Reisine & Pasternak, 1995), nausea and vomiting (Foley, 1993; Reisine & Pasternak, 1995), and sedation (Foley, 1993; Macintyre & Ready, 2000).

Little is known about methadone maintenance patients' physiological and subjective responses to additionally administered morphine. Hence, it is of clinical importance to investigate the non-antinociceptive pharmacodynamic effects in this patient group. Furthermore, given that physicians may have fears about the abuse potential of prescribing such drugs to this patient group, it is of interest to investigate the subjective effects of additionally administered morphine amongst these patients. The results from my third study, investigating the physiological and subjective effects of additionally administered morphine, indicate that methadone patients have a significantly lower respiratory rate compared with healthy control subjects; the difference in respiratory rate is most pronounced when methadone patients' plasma methadone concentrations are at the putative peak. Plasma morphine concentrations known to produce analgesia in opioid-naïve patients

had little effect on the respiratory rate of methadone patients, but had a marked depressant effect among the control group. These results suggest that in methadone maintenance patients, methadone may be a more potent respiratory depressant than morphine; further studies are needed to determine the relative respiratory depressant potencies of these drugs.

With regard to miosis, methadone had a significant effect on patients' pupil sizes within the inter-dosing period; miosis was most pronounced at the time of peak plasma methadone concentrations. The administration of morphine resulted in marked reductions in the pupil sizes of control subjects, but only very small reductions in the methadone patients; this suggests that methadone patients have partial tolerance to the effects of opioid drugs. There were no significant cardiovascular effects (heart rate and/or blood pressure) in relation to additionally administered morphine.

Overall, the results from the third experiment suggest that conventional doses of morphine have only minor physiological effects amongst methadone maintenance patients. Furthermore, there were no significant changes as measured by MBG and MG scales; this suggests that in the context of acute pain management, methadone patients are unlikely to experience a classic "high" from the administration of additional opioids. Further studies using substantially larger doses (and plasma concentrations) of morphine in a larger sample of methadone maintenance patients would be of value.

The NMDA ion channel receptor is regarded as being principally responsible for the induction and maintenance of hyperalgesia (Dickenson, 1994). Mao and colleagues (1995b) suggested that both hyperalgesia and the development of opioid tolerance involve activation of the NMDA receptor and subsequent biochemical processes. Others have proposed that activation of NMDA ion channel receptor following chronic opioid treatment may reduce the magnitude and duration of opioid-induced antinociception (Wiesenfeld-Hallin, 1998). Chronic opioid treatment could be indirectly activating this receptor via an increase in protein kinase C which removes the Mg^{2+} blockade of the NMDA receptor (Chen & Huang, 1992; Mayer & Mao, 1999). Dickenson (1997) proposed that this activation will itself contribute to poor opioid sensitivity because it will increase excitation in the pain transmitting systems. Interestingly, the co-administration of NMDA receptor antagonists with opioids has been shown to reduce and/or reverse the development of tolerance to opioids in rats (Trujillo & Akil, 1991 & 1994; Tiseo & Inturrisi, 1993; Elliott *et al.*, 1994; Mao *et al.*, 1996; Shimoyama *et al.*, 1996). Whilst methadone itself is a weak non-competitive NMDA receptor antagonist (Gorman *et al.*, 1997; Ebert *et al.*, 1998) the clinical

implications of this for humans chronically administered methadone are unknown. In particular, the magnitude of NMDA antagonist activity achieved at normal therapeutic concentrations is unknown. Further, I am unaware of any methods that can measure the physiological effects of NMDA antagonist inhibition.

Clinically, there is considerable evidence that NMDA receptor antagonists are effective adjuncts to opioids for the relief of pain. There are indications that a ketamine-opioid combination could provide superior analgesia compared to an opioid alone (Parkhouse & Marriott, 1977; Bristow & Orlikowski, 1989; Javery *et al.*, 1996; Stubhaug *et al.*, 1997; Suzuki *et al.*, 1999), and that such a combination will reduce opioid tolerance, further enhancing treatment efficacy (Bell, 1999). Furthermore, there is evidence that these combinations result in a significant reduction in opioid consumption (Cherry *et al.*, 1995; Chia *et al.*, 1998). Indeed, it has even been suggested that NMDA receptor antagonists such as ketamine may be effective in improving opioid analgesia in difficult pain syndromes, such as neuropathic pain (Mercadante *et al.*, 2000).

The aims of the fourth experiment were (1) to investigate the antinociceptive effects, and (2) the physiological and subjective effects, of low dose (+)-(S)-ketamine alone and in combination with morphine, at consecutive pseudo steady-state plasma concentrations in a sample of methadone maintenance patients and age- and sex-matched control subjects. (+)-(S)-ketamine alone had no apparent antinociceptive effects in methadone patients or control subjects. Furthermore, the combination of (+)-(S)-ketamine plus morphine had no discernible antinociceptive effects in methadone patients. However, in control subjects this combination, (+)-(S)-ketamine plus morphine, resulted in significant increases in nociceptive response values. It is unclear whether this antinociception in control subjects was a direct result of the morphine, or possibly a synergistic or additive effect of (+)-(S)-ketamine and morphine. Consistent with my previous experiments, methadone patients were hyperalgesic to pain induced by the cold pressor test but not electrical stimulation, thus further confirming their sensitivity to this method of pain induction. Furthermore, as in my second and third experiments, methadone patients' pain tolerance to detection ratios were markedly lower than those of control subjects only for the cold pressor test; this confirms this ratio as a sensitive marker of hyperalgesia in this patient population.

Despite an apparent lack of antinociceptive effects in the methadone patients, (+)-(S)-ketamine produced substantial subjective effects in the methadone patients. Surprisingly, the subjective effects of (+)-(S)-ketamine were markedly more pronounced in the methadone

patients compared with the control subjects. These results indicate that (+)-(S)-ketamine is likely to have high abuse potential in this patient group. Further studies using higher doses (and plasma concentrations) may need to be conducted to fully ascertain the analgesic efficacy of this drug combination amongst methadone maintenance patients. However, I would urge caution in using larger doses of (+)-(S)-ketamine amongst this patient group, given the nature of the subjective effects and apparent drug liking experienced by the sample of patients in this thesis. In addition, there is evidence from animal studies, which suggests that NMDA receptor antagonist-mediated modulation of opioid antinociceptive tolerance may be selective to morphine but not to fentanyl or to δ (delta) selective agonists (Bilsky *et al.*, 1996). Perhaps, the intracellular mechanisms involved in methadone-induced tolerance are different to those in morphine tolerance? The plethora of available animal evidence all refer to a model of morphine tolerance (Elliot *et al.*, 1994; Kolesnikov *et al.*, 1993; Mao *et al.*, 1994, 1995a,b, 1996; Marek *et al.*, 1991; Mayer *et al.*, 1995; Tiseo & Inturrisi, 1993; Trujillo & Akil, 1991b). To the best of my knowledge no animal studies on the topic of opioid tolerance and hyperalgesia have used methadone. It would be valuable to conduct animal research using methadone in a similar manner as the well established and described morphine studies.

6.2 Clinical and Research Implications

Overall, the results from this thesis consistently show that methadone maintenance patients are hyperalgesic to pain induced by a cold pressor test but not electrical stimulation. Furthermore, methadone maintenance patients are cross-tolerant to the antinociceptive effects of conventional doses of morphine. In addition, low dose (+)-(S)-ketamine, alone, or in combination with low dose morphine, did not produce any significant antinociceptive effects amongst this patient group. Plasma morphine concentrations known to produce analgesia in opioid-naïve patients only had minor physiological effects amongst methadone maintenance patients. Similarly, (+)-(S)-ketamine alone, and in combination with morphine, did not produce any significant physiological effects amongst these patients. Finally, with regard to subjective effects, additionally administered morphine did not produce any significant effects as measured by the MBG scale. However, (+)-(S)-ketamine alone, and in combination with morphine, produced marked psychotomimetic effects (as measured by the LSD scale and verbal descriptions of effects) amongst methadone maintenance patients. Furthermore, the methadone patients indicated that they would abuse this drug if it was available illicitly. Hence, it is likely that (+)-(S)-ketamine has very high abuse potential amongst this patient group. Overall, whilst these results have undoubtedly

helped to clarify some previous discrepancies in the literature, and have established some controlled evidence about methadone maintenance patients' response to additionally administered morphine, and (+)-(S)-ketamine, a number of issues need to be resolved.

Is the hyperalgesia to pain induced by the cold pressor test a bi-product of opioid maintenance therapy? Are methadone maintenance patients hyperalgesic to other methods of experimental pain induction (eg. radiant heat, mechanical pressure, and ischaemic tourniquet)? To help answer this specific question further studies involving the use of these other types of experimental pain induction should be considered. Does hyperalgesia to pain induced by the cold pressor test vary amongst the different opioid drugs used as treatments for opioid addiction (eg. LAAM and buprenorphine)? It would be of value and interest to determine whether or not heroin addicts have hyperalgesic responses. Further research in patients maintained on these different opioid pharmacotherapies (and heroin addicts pre-treatment) is obviously needed to answer these two questions.

Another question concerns the duration of hyperalgesia. There is some evidence, albeit not a strictly controlled study, that ex-addicts (ie. 24 formerly opioid addicted prisoners) were much less pain tolerant to pain induced by the cold pressor test (Martin & Inglis, 1965). Does pain sensitivity of methadone maintenance patients return to normal after 1 month, 3 months, 6 months, 12 months or longer, after the patient becomes completely drug-free? It would be of clinical importance to ascertain the pain sensitivity in a sample of ex-addicts perhaps after a drug free period (possibly post-rehabilitation). Another interesting research avenue involves the use of the opioid antagonist naltrexone to improve the pain tolerance of former methadone maintenance patients. Indeed, there are some pilot data (Compton, 1998) which suggest that treatment with naltrexone may lead to an improvement in cold pressor test pain tolerance levels in ex-opioid addicts; intra-subject comparison of cold pressor test pain tolerance values revealed that the majority of patients (8 out of 10) were more tolerant of pain whilst on naltrexone. Hence, I would pose the question; does treatment with naltrexone alter (1) pain sensitivity of ex-methadone maintenance patients, and (2) what is the time course of returning pain sensitivity to normal levels (as observed amongst control subjects in this thesis)? It would be of interest to extend the work of Compton (1998) to address this question.

Finally, is hyperalgesia caused by the plasticity (central changes) associated with opioid tolerance? Are there intracellular differences involved in tolerance to various opioid agonists? Is the cold hyperalgesia observed in methadone maintenance patients, in patients

with chronic nerve injury (Fruhstorfer & Lindblom, 1984; Frost *et al.*, 1998; Ochoa & Yarnitsky, 1994), and in patients with other central pain syndromes eg. following thalamic infarction (Craig *et al.*, 1994; Vestergaard *et al.*, 1995), caused by the same (or similar) cellular changes? Animal studies using different opioid drugs should be conducted to answer these crucial questions. There is evidence that the C-fibres mediate cold hyperalgesia, a process involving adaptive changes integrated at the level of the thalamus (Craig, 1995). Nociceptive information concerning cutaneous cold stimuli (originating in lamina I of the dorsal horn) is transmitted to the thalamus via the dorsal spinothalamic tract (Dostrovsky & Craig, 1996; Millan, 1999). Millan (1999) proposed that over-activation of the thalamo-cingulate pathway in cold allodynia and cold hyperalgesia involves the disabling of GABAergic or other types of inhibitory interneurons interconnecting with the ventromedial and medial thalamus. In this light, it is of interest to note that Eckhardt *et al.* (2000) suggested that gabapentin, a GABA analogue whose mechanism of action as an anticonvulsant is not fully understood (Taylor *et al.*, 1998), in combination with morphine may be an effective treatment for neuropathic pain. Eckhardt and colleagues in a randomised, placebo-controlled, double-blind study investigated the pharmacodynamic and pharmacokinetic interaction of gabapentin and morphine in 12 healthy volunteers. They found gabapentin enhanced the antinociceptive effects of morphine as measured by increased cold pressor pain tolerance. Field *et al.* (1997) reported that gabapentin binds to the $\alpha_2 \delta$ -subunit of the voltage-dependent Ca^{++} channel. Hence, it may also interfere with spinal Ca^{++} flux, which plays a role in neuropathic pain (Taylor *et al.*, 1998). Millan (1999) proposed that the likely effects of drugs such as gabapentin may involve an indirect potentiation of GABAergic transmission. However, Millan also added, that other actions such as the inhibition of glutamate release and the blockade of Ca^{++} channels may be involved. This suggestion has yet to be proven with specific evidence.

This thesis has not produced data that definitively show how to successfully treat acute pain in methadone patients, but this was not the precise intention of the thesis. However, my thesis has provided a base from which future research should be built upon. A possible criticism of the experiments in this thesis is that the doses (plasma concentrations) used in these pilot studies were small; it would be of scientific value to replicate and extend my experiments using larger doses (plasma drug concentrations), involving larger numbers of methadone maintenance patients. Further research is urgently needed to determine whether other drugs such as gabapentin (Eckhardt *et al.*, 2000), tramadol (MacPherson, 2000), clonidine (Eisenach *et al.*, 1995; Tumber & Fitzgibbon, 1998), or non steroidal anti-

inflammatory drugs (Maves *et al.*, 1994; Souter *et al.*, 1994; Christie *et al.*, 2000), alone or in combination with morphine, are effective in managing acute pain in this patient population. Future research should also consider the use of substantially increased doses of methadone (administered 3-4 times per day) itself in the treatment of pain in this patient population, as there is some evidence to suggest that this may be a successful way of managing pain in these patients (Manfredi *et al.*, 2001).

Portenoy and colleagues (1997) suggested that ignorance and stigma compromise the management of pain amongst patients receiving methadone maintenance therapy. We are now in an era where we are guided, in most clinical arenas, by the paradigm of evidence-based-medicine. Hopefully the published evidence from this thesis will help inform clinicians that methadone maintenance patients have distinct needs with regard to the management of acute pain. I would suggest that fear and prejudices be cast aside, and that in light of these findings, albeit in a clinical laboratory setting, clinicians should aggressively treat complaints of pain amongst patients in this population, remembering importantly to treat the pain not the addiction.

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APPENDIX 1

Combined MBG and MG scales

Please put a $\checkmark$ in the appropriate box for each of these feelings.

	TRUE	FALSE
I would be happy all the time if I felt as I feel now		
I am in the mood to talk about the feeling I have		
I am full of energy		
Things around me seem more pleasing than usual		
I feel less discouraged than usual		
I fear that I will lose the contentment that I have now		
I feel as if something pleasant just happened to me		
Today I say things in the easiest possible way		
I feel so good that I know other people can tell it		
I feel very more-headed than dreamy		
I can completely appreciate what others are saying when I am in this mood		
I feel as if I would be more popular with people today		
I feel a very pleasant emptiness		
I feel in complete harmony with the world and those about me		
I have a pleasant feeling in my stomach		
I feel high		
My nose itches		
I have had some pins and needles sensations		
I have a sentimental feeling		
I would like to sit and think		
I have a peculiar craving for ice cream or something cold		
I have been scratching myself		
My speech is not as loud as usual		
I have been dosing occasionally for seconds or minutes		

APPENDIX 2

LSD scale

Please put a $\sqrt$ in the appropriate box for each of these feelings.

	TRUE	FALSE
My hands feel clumsy		
I would be happy all the time if I felt as I do now		
I have an unusual weakness of my muscles		
I notice my hand shakes when I try to write		
I feel anxious and upset		
My movements are free, relaxed, and pleasurable		
Some parts of my body are tingling		
I have a weird feeling		
It seems I'm spending longer than I should on each of these questions		
I feel very patient		
I feel an increasing awareness of my bodily sensations		
A thrill has gone through me one or more times since I started the test		
I feel drowsy		
I have a disturbance in my stomach		