Volume 1

An Investigation into the effects of Methadone on cognitive and psychomotor function, mood, concentration and craving.

Julia Kleckham

D.Clin. Psy. 1999

University College London

Contents

Tables and Figures:

Abstract

Methadone is a synthetic opioid that produces cross-tolerance with opiate drugs and can therefore be used to suppress withdrawal symptoms in opiate dependent patients. Methadone is the main treatment offered by the NHS in the UK for opiate dependence. Methadone can be used for both detoxification (if the primary treatment aim is abstinence from opiates), or as a maintenance dose (if the primary treatment aim is harm reduction until the patient is ready to detoxify).

In the UK the number of deaths from methadone exceeds the number of deaths from heroin and numbers have increased over the last ten years.(ONS England and Wales: 1993-1997, 220 to 368 deaths from methadone, 55 to 169 deaths from heroin. Curran et.al. (1999) found no sedative, cognitive or psychomotor effects but an increase in craving for opiates in methadone maintenance outpatients, with a 33% increase in their prescribed maintenance dose of methadone. Previous studies have methodological limitations (Zacny, 1995, Weinreib et al, 1993) and inconclusive results. The aim of this study is to investigate the cognitive, psychomotor and mood effects of a 100% increase in methadone dose for opiate dependent in-patients, using a double blind, placebo controlled design, with urinalysis to address some limitations of previous research. A range of measures was used to assess the effects of this increase on cognitive and psychomotor functioning, mood and craving.

On admission, participants were stabilised on methadone for 5 days, before the dose is reduced for detoxification in the usual way. Participants were assessed on day 3 and day 5. All participants received their complete dose each day, half the participants

received methadone as one whole dose. The others received methadone in a divided dose (50% in the morning, 50% in the evening). The design was balanced for treatment order. Methadone vehicle (linctus) was used as a placebo to maintain double-blind conditions, resulting in the same quantity of linctus administered on each occasion. Both placebo and methadone were flavoured with peppermint so appeared, tasted and smelled the same. Participants were unable to distinguish methadone from placebo. There was no evidence of illicit drug use detected by urinalysis. Results suggest that Methadone has no effect on craving for heroin or mood, but significantly affects delayed recall. The implications of these findings for the treatment of opiate dependency are discussed.

Acknowledgements

I would like to extend my grateful thanks to all the participants for their time and effort, and for being so honest about their experiences. Thanks also to the Staff at Wickham Park House for their part in the successful completion of this project. I am especially grateful to my supervisors, Dr. Val Curran and Dr. Shamil Wanigaratne, for their help and guidance through the whole research process. A big thank-you to Lucy Reeves for sorting the drugs side, to Colin Taylor for the statistical support, and to Katy Rees for interviewing when I couldn't. Most importantly, thanks to my family and friends for their unending support through the whole thing, I am indebted to you all. Finally, I dedicate this to Niall, Linda and Emma.

1.0 Introduction

This chapter presents a review of the literature on methadone and focuses particularly upon the effects of opiate drugs, on cognitive function, craving, psychomotor performance, self-efficacy, mood and drug use.

1.1 History: The discovery of Methadone

In 1939 Scientists working for the Chemicals Company Hoechst-Am-Main in Germany, discovered an effective opioid analgesic drug which they called Dolatin. (Pethidine). Brockmuhl & Ehrhart were working on compounds with a similar structure to Dolatin. Their aim was to find water soluble, hypnotic (sleep inducing) substances, effective drugs to slow the gastrointestinal tract for surgery, and effective analgesics, which were structurally different to morphine in the hope that they would be non-addictive. During 1937 and early 1938, Brockmuhl & Ehrhart created another substance which they called Hoescht 10820 or polamidon. Partly because the two-dimensional structure of the new compound did not resemble morphine, its pain-killing properties were not recognised until after the war had ended. The patent for Hoescht 10820 was filed in 1941 and Brockmuhl & Ehrhart (1949) were formally credited with the discovery of what is now known as methadone.

The commercial name of methadone was 'Dolphine'. Some in the US and UK believed that the drug reflected an attempt directed by Hitler, to replace opium supplies cut off during the war. It is thought that this belief is attributed to the trade name of the drug, Dolophine, bearing similarities to Adolph. However, the name is most probably derived from the French

dolor (pain) and Fin (end).

1.2 Use in the UK

The earliest accounts of the use of methadone in the UK were published in The Lancet in 1947. It was described as "at least as powerful as morphine, and 10 times more powerful than pethidine". It was subsequently used as an obstetric anaesthetic at University College Hospital, London. However its use was discontinued because methadone caused respiratory depression in newborn babies.

Early advertisements from Wellcome pharmaceutical company claimed that methadone carried "little risk of addiction". However; in 1955 there were 21 methadone addicts notified to the Home Office, rising to 60 in 1960 (Spear, 1969). The Home Office notification system was set up in 1968 with two new notifications. By the end of 1968, the number of people notified as addicted to methadone had risen to 297. In 1965, a change in policy and the law meant the prescription of controlled drugs for the treatment of addiction was restricted to doctors with a Home Office licence. Doctors were legally required to notify the Home Office of addicts and drug clinics were proposed for the specialist treatment of addiction. By 1969 the number of patients notified with a methadone addiction had risen to 1687.

Heroin first overtook morphine as the most notified drug of addiction in 1962. In 1966, the number of notified heroin addicts was 6 times greater than morphine addicts (Stimson & Oppenheimer, 1982). The new drug clinics opened in 1968 with the aim of providing a legal supply of drugs, attracting addicts to services, preventing the illicit market in drugs and

associated crime and helping people to abstain from drug taking. At this time there were 2881 addicts, 2240 addicted to heroin (Methadone Briefing , Preston, 1996).

1.3 The origin of legal control

In 1924, the Dangerous Drugs Act was amended to include opium and opium derivatives, which led to concern from doctors as to whether this affected the legality of the prescribing of such drugs. In 1924, The Ministry of Health set up a committee, chaired by Sir Henry Rolleston, which published The Rolleston Report in 1926. This accepted the principle that doctors could legitimately prescribe addictive drugs as part of the treatment of dependence. Abstinence was seen as the ultimate treatment goal, but the report accepted that long term prescribing was a legitimate way of treating those who were unable to achieve abstinence.

In the 1970's in the UK, the incidence of heroin use continued to rise and doctors started to question the efficacy of prescribing the client's drug of choice as a treatment. Prescribing practice moved away from injectable heroin to oral methadone. The rationale for this change in policy was: i) it was safer to prescribe a non-injectable drug and ii) because methadone has a longer half life than heroin, it can be taken once a day rather than every few hours. Hartnoll et al, (1980) reported that providing heroin maintained the status quo but reduced the associated problems with acquisition of the drug. In contrast, methadone meant that people were more likely to leave treatment but also more likely to achieve abstinence. From this study arose the question of maintenance prescribing of methadone. By the late 1970's, studies such as Paxton et al (1978) led to the questioning of the value of prescribing methadone in

maintenance doses, or indeed prescribing at all.

In the 1980's, there was another dramatic increase in the prevalence of heroin use. The number of notified addicts had doubled during the 1970's from 509 in 1973 to 1110 in 1979. This number doubled again between 1979 and 1982 and yet again between 1982 and 1984. (Home Office statistics, 1986).

The emergence of HIV and its rapid transmission through the drug taking population in the UK prompted another revaluation of addiction treatment and prescribing policy. The 1988 report of The Advisory Council on the Misuse of Drugs led to the development of community based needle exchange schemes all over the UK. Treatment was directed towards abstinence by achieving goals such as stopping unsafe injecting, taking drugs by other routes, e.g. orally or by inhalation, and taking prescribed rather than illicit drugs.

1.4 Methadone use in the U.S.A.

In the USA, the Harrison Act in 1914 controlled the sale and possession of drugs. In 1922, a ruling determined that it was a crime for any doctor to prescribe narcotic drugs to an addict. The first reported use of methadone to treat opiate addicts in the USA was in 1989 (Payte, 1991). In 1960, Dole & Nyswander found that they could not stabilise opiate users on morphine unless they continually increased the dose. They realised that by prescribing methadone instead of morphine, that they could maintain patients on a stable dose for long periods.

Within a year, they had developed 'methadone maintenance treatment'. This innovative treatment was offered to patients who had a long history of opiate abuse and who had failed in previous treatment. The numbers of patients receiving methadone maintenance continued to rise steadily, and by 1992, there were about 120, 000 patients served by 800 treatment programmes. Over half of patients receive less than 60mg daily, the minimum therapeutic dose accepted in the USA, and well below the 80-150mg recommended by Dole & Nyswander.

1.5 Epidemiology: Prescribing in the UK today

Methadone prescribing services in the UK are variable. There are three main types of community service: street agencies, community drug teams and drug clinics. Also available are prescriptions from private doctors. General Practitioners are also able to prescribe methadone, although attitudes and practice in treating drug problems vary widely. Methadone is currently the main treatment in the UK for heroin dependence (Gossop & Grant, 1991). The criteria for dependence are categorised in DSM IV and a distinction is made between dependence and misuse. Treatment involves substituting heroin with methadone, which is longer acting therefore needs to be taken less often. Reasons for prescribing methadone include: i) stopping intravenous drug use thus minimising risks associated with IV drug use, (e.g. HIV, Hepatitis, abscess or blood poisoning); ii) reducing criminal activity; iii) increasing stability of lifestyle to allow employment and iv) eventual detoxification and abstinence.

1.6 Pharmacology

Opiates appear to mimic the action of naturally occurring chemicals in the body, in particular, endorphins, enkephalins and dynorphins. There may be as many as eight different opiate receptors in the brain. Opiates directly cause a number of actions: including effects on the central and peripheral nervous system, histamine related effects, and effects for which there is no identified and/or causal link. Physiologists have identified three types of opiate receptors in the brain (μ,κ,δ) (mu, kappa and delta). This has led to the classification of the drugs acting on those receptors. Opiate agonists are classified in two ways: first, morphine-like agonists (act as agonists primarily at mu receptors and perhaps kappa and delta receptors, Koob, 1992). The second classification is opioids producing mixed actions which are sub divided into: mixed agonist-antagonists (opioids which act as agonists at some receptors and antagonists or very weak agonists at others) and partial agonists (agonists of weak efficacy that are not thought to have antagonist properties) Koob (1992).

The half-life of a drug is the time it takes for the blood levels of the drug to reduce to 50% of peak concentration. The half -life of diamorhine (heroin) is very short as it is rapidly metabolised (within minutes) into its active metabolite morphine. The duration of action of morphine is 3-4 hours. Methadone has a more variable half -life, dependent in part on whether it is taken as a maintenance dose or if it is the first dose. Methadone mixture is prescribed for opiate users in 1mg/1ml or 1mg/5ml or 10mg/1ml.

1.7 Cognitive and psychomotor effects of methadone

Methadone is the most widely used pharmacological treatment for people dependent on opioids (Gossop & Grant 1991). Despite its widespread use, relatively little is known of the acute or chronic effects of methadone on drug craving, cognitive functioning and mood. Its plasma elimination half-life is 16-24 hours in opiate naive people, but in chronic users this may extend to 24-48 hours, showing considerable variation (Tenant, 1987). This variation in how individuals metabolise the drug may contribute to differences in self- report of withdrawal symptoms reported by methadone maintenance patients (Dyer & White, 1997). After three days off a stable daily dose, the half life is extended to between 13 and 47 hours with a mean average of 25 hours (Tenant, 1987). Methadone takes around 30 minutes to start being absorbed, and peak blood levels are reached between 2 and 4 hours after oral administration (Dyer & White, 1997)

Research into the cognitive, psychomotor and mood effects of methadone has, to date, been limited and many studies have methodological problems. A summary of these problems is in Weinreib & O'Brien (1993), who conclude: "The information about the long-term consequences of opiate use remains unclear. In fact, an overall summary of the persistent cognitive effects of long term drug use yields vague and tentative information". In this literature, there has been relatively little research into the effects of opioid drugs on cognitive functioning, compared with that which is concerned with the effects of other classes such as benzodiazepines. It is possible that this is because there is a belief that opioids "do not produce robust impairment of human performance" (Roache, 1991).

Zacny, (1995) reviewed research between 1966-1995, on the effects of opiates on cognitive and psychomotor functioning. Of the studies that have evaluated the effects of methadone, Zacny reports that for most of the measures used there was no effect or inconsistent effects in methadone maintenance patients. The studies are summarised below.

1.7.1 Motor performance

Methadone impaired reaction times in healthy control subjects but not in methadone maintenance subjects (Rothenberg et al 1977). In similar studies looking at the effects of morphine, Christie (1958) found no difference in performance between participants who received 16mg morphine or a placebo, using the formboard test which times how long the subject takes on a task to place blocks into holes on a board. In two of three studies using healthy volunteers, morphine did not affect tapping rate. In the third study, performance was affected on one of three measures (Kerr et al, 1991). Morphine appears to have an effect on motor performance in that many studies reported a decrease in the speed at which tasks were performed. However, the research suggests that tolerance develops so that after repeated use of morphine at a fixed dose, the deleterious effect on motor performance disappears. Morphine also impairs sustained attention in both patients and healthy volunteers (Zacny, 1995). Studies into the effects on cognitive and psychomotor functioning of heroin found no effect of the drug on performance in opiate dependent patients, but impaired accuracy and speed of processing in healthy volunteers (Zacny, 1995).

1.7.2 Information Processing

Isbell et al (1948) tested the speed and accuracy of symbol copying and performance of arithmetic tasks in former opiate abusers who were give increasing methadone doses that eventually produced dependence. The rate at which the tests were completed did not decrease with higher doses of methadone, but the number of mistakes relative to that occurring before dependence did increase slightly. In addition to the ethical issue of producing dependence in former opiate users, these results must be interpreted carefully because of the small numbers and the lack of any statistical analysis.

Gritz et al (1975) compared patients on methadone maintenance with former opioid users. No difference was found on the performance on a number cancellation test. There was a difference in the performance on a hidden word test, the methadone maintenance patients performed less well, although without a non- opiate user control group the results are inconclusive. Using a matched set of non-opioid users and opioid dependent patients, no difference in performance was found (Appel & Gordon 1976). Using the digit symbol substitution test (DSST) (Weschler, 1958) studies have reported mixed results. Zacny et al (1994a) found mild impairment in morphine dependent participants. Other studies have reported no effects (Jarvick, 1981; Zacny et al 1994b; Oliveto et al, 1994). Using healthy, nondependent participants, other studies have similarly found no difference in performance between those receiving 30mg morphine or placebo (Higgins, 1992; Preston 1992).

1.7.3 Sustained attention

Kelly et al (1978) found that methadone did not to substantially impair sustained attention or short-term memory in methadone maintenance subjects. Other studies have similarly found no difference in continuous performance tasks between methadone maintained and non-opioid users (Appel, 1976; Rothenberg et al, 1977). Studies of the effects of morphine on reaction time, which are of at least 5 minutes duration, also measure sustained attention. Westerling et al (1993) examined different dose and administration (IV infusion, oral or controlled release) effects of morphine on an auditory simple reaction test lasting 10 minutes in healthy volunteers. Sustained attention was impaired only in healthy volunteers who received morphine by IV infusion.

1.7.4 Memory, Learning and Comprehension

Two studies tested short-term memory in methadone maintenance patients: Gritz et al (1975) and Kelley et al (1978). Neither study found any impairment of function. Saddler et al (1985) also found no effect on immediate recall in healthy volunteers given morphine.

In the unethical 1948 study by Isbell in which physical dependence on methadone was induced in former opioid users, participants were given an IQ test before and during the period of physical dependence. IQ did not decrease, but no comparison group was tested and no statistical analysis was performed.

Lombardo et al, (1976) used the WAIS (Weschler, 1958) to test the effects of a) different

doses of methadone and b) reducing doses of methadone in methadone dependent patients. No difference in performance was detected between doses of 50mg compared with 80mg. Gritz et al (1975) measured learning ability between methadone maintenance patients and former opiate addicts. When no cues were present, methadone maintenance patients had impaired ability to comprehend a story. They also had impairment on a nonsense syllables (recall of a list of syllables which have no literal meaning) and of a non-paired associates task involving the recall of pairs of words which are not logically related.

The negative effects of opiate withdrawal on performance have also been studied. Folli, (1992), found no difference in the performance of healthy volunteers and opiate dependent patients assumed, from the extent of their use and the time of their last dose (at least 12 hours), to be in withdrawal. Some studies have looked at the effects of administering naloxone, to precipitate withdrawal. Lamas et al (1994) found no effect on motor performance. Other studies have found no effect on the Stroop test or an immediate recall test (Kanof, 1992). Studies of performance on the digit symbol substitution test (DSST) (Weschler, 1955) similarly found no impairment (Preston et al, 1988, 1989; Strain et al, 1992,1993). Results from these studies suggest that methadone detoxification has no acute effect on psychomotor and cognitive functioning. Two studies measured the speed at which a passage was read and the comprehension of the passage by questions about the content. In both studies, morphine decreased the speed at which participants read the passage, but it did not adversely affect comprehension (Coda et al, 1994; Kerr et al, 1991).

Grant et al (1979) reported that 50% of polydrug users and 20% of alcoholics showed impairment using the Halstead-Reiten battery. Reports suggest that 40-50% polydrug users

will show cognitive deficits several weeks after detoxification (Grant & Adams et al 1978). Some studies report a correlation between these deficits and the use of certain classes of drugs, notably opiates and alcohol (Adams et al, 1975; Grant et al 1978). These studies used polydrug users compared with those previously cited, which focus on opiate dependent users. Therefore it could be that there is no explanation for the differences reported, beyond a history of heavy multiple drug use.

Hill & Mikhael (1979) looked at cognitive performance in a mixed group of heroin dependent and nonuser participants. However, the only measure of drug use was from history and so was unreliable and it was difficult to differentiate chronic and recent use and the results therefore were uninterpretable. Rounsville & Novelly (1980) compared differences in cognitive functioning in epileptic and heroin dependent participants. However, 46% of the heroin dependent sample were found to have used significant amounts of other drugs and that a majority of them was not drug free at the time of testing. Similarly, it is not possible to interpret the data. These studies, with others reported, highlight one difficulty with research in this area, that of obtaining a sample which fulfils criteria for opiate dependence, but which is not polydrug dependent.

1.8 Craving and drug use

Tiffany (1992) reviews contemporary urge and craving research, with reference to methodological, psychometric and theoretical issues. Compulsion may be regarded as a central and necessary feature of drug dependence (Gossop et al, 1989). Craving as a construct is an important component in the conceptualisation of addictive behaviour

sometimes termed compulsive drug use. Beginning with Jellinek (1955), writing about the causes of alcoholism, the idea was proposed that urges arise from conditioned or unconditioned drug withdrawal. More recent accounts describe the positively reinforcing effects of a drug as the basis of craving (Marlatt & Gordon, 1985). Other research suggests that there is a physiological component to craving, and that the urge state is determined by a pattern of physiological responses. Reports are divided, with some reporting the physiology of urges appears the same as the physiology of withdrawal (e.g. Poulos et al, 1981). Alternatively, others suggest that urges are similar to the excitatory effects of the drug (e.g. Baker et al, 1987).

Compulsion was included in the 1969 World Health Organisation's definition of drug dependence:

"...a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterised by behavioural and other responses that always includes a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of abstinence".

Rankin et al (1979) discussed the part compulsion had in understanding models of change. It was proposed that an individual's degree of dependence was associated with the frequency and intensity with which cues triggered behaviour. Russell (1976) states that the notion of dependence is associated with negative affect experienced in the absence of the drug, and the degree of dependence can be equated with the amount of this negative affect. His view was that in dependence, as with craving, the crucial feature is the strength of the underlying urge.

Kozlowski & Wilkinson (1987) argue that craving has been conceptualised in many ways and that each different conceptualisation has different implications for research and treatment. There remains considerable debate about how to best define craving: in terms of overt drug seeking behaviour (as proposed by Schuster & Thompson, 1969), to discard the concept altogether; or to conceptualise craving as having components e.g. physiological, pharmacological, behavioural, cognitive. Schuster & Thompson suggest that the incongruity between the current technical use of the term and its use in ordinary language may be problematic and misleading. In particular they suggest it is unacceptable to attribute craving as a cause of relapse or loss of control in drug taking or drinking. In this paper, Schuster & Thompson stimulated debate about the weaknesses surrounding the use of the term 'craving'. Marlatt, (1987) suggested a further distinction, between 'cravings' and 'urges': " It is possible to conceptualise craving as a motivational state (often in response to external CS cues), and to define an urge as the behavioural intention". Further, he highlighted the importance of viewing craving as " a subjective state that is mediated by the incentive properties of positive outcome expectancies".

The problem with defining craving as "overt drug seeking behaviour" (Schuster & Thompson, 1969) is that it prevents consideration of the competing motivational forces, (of which craving is one), which contribute to drug seeking behaviour and to relapse. (West and Kranzler, 1990). It also ignores the part played by factors in dependence and relapse such as 'will power' or coping strategies. To view craving as a subjective, unidimensional phenomenon allows a dissociation between craving and drug seeking behaviour, and between craving and interoceptive cues and their physiological bases. Considering craving in this way also permits theories of craving which incorporate cognitive processes. Tiffany, (1990) challenges the

assumptions that urge report and drug use behaviour are strongly linked, that urges are necessary for relapse or that urges are direct manifestations of the motivational processes underlying drug using behaviour.

Tiffany et al (1998) has further investigated the role that craving has in compulsive drug use. He reports that craving and drug use are not interdependent to the degree required by the hypothesis that craving is the source of all drug use in the addict. An alternative to the widely accepted craving based view is given - that drug taking can be characterised as automated behaviour. Tiffany describes compulsive drug use as similar to any other automated behaviour in that it is stimulus-bound, stereotyped, effortless, difficult to control and regulated mostly unconsciously, in a similar way to other over-learned behaviours such as driving a car, reading or dialling a telephone. Tiffany's (1990) cognitive model of drug urges and drug use behaviour thus proposes that drug use behaviour is an activity controlled by automatic processes. The model also assumes that non-automatic processes determine responses to urges, contrary to the previously held assumption that craving is the source of compulsive drug use.

The assumption that craving is responsible for compulsive drug use is widely accepted but Tiffany (1998) again reviews the evidence for and the limitations of such a view. Craving is reported by addicts when they are using drugs and trying to abstain. During attempts at abstinence, craving report and drug use may change in parallel. Furthermore, levels of craving may predict propensity for relapse. Finally, craving, like drug use, may display a high degree of stimulus specificity. This is all evidence consistent with the proposal that craving is central to compulsive drug use, but is not sufficient to explain it. Tiffany criticises many studies that

report correlations, in that it cannot demonstrate that craving causes drug use.

Reviews of literature investigating relapse have suggested that craving is not strongly linked to drug use (Tiffany, 1990, 1992, 1997). These studies have used laboratory based research, using the cue reactivity paradigm (Niaura et al 1988). This is based on the notion that urge responses (measured by verbal report and physiological changes) can be triggered by the presentation of a stimulus object, which has become strongly associated with drug administration. The results are questionably relevant to actual drug use in the real world. Research that has explicitly asked addicts about their craving before relapse also, suggests that craving in itself is not the cause of drug taking behaviour. For example, Miller & Gold (1994) found in a survey of 300, that only 7% of addicts identified craving as a primary reason for their relapse.

In an attempt to improve research, Tiffany and colleagues devised a number of multi item craving scales. These are for the assessment of cigarette, cocaine, heroin and alcohol craving (Tiffany et al, 1991, 1993, 1996; Singleton et al 1994). The use of multi items produces an increase in the reliability of the craving factors.

Heather et al (1991) suggested that studies examining the variables associated with relapse might use methods which do not allow the detection of urges or cravings as a major relapse factor. Results show that a sample of addicts who did not identify craving as central to their relapse in a structured interview, later reported craving as the most important factor in relapse when rating the importance of possible reasons for relapse.

The question of whether craving is a conscious or unconscious process is another impediment to conclusive evidence to support the craving hypothesis. The possibility that craving is an unconscious process is used as a reason for dissociations found between craving and drug use by Miller & Gold 1984. The proposal that craving operates on both a conscious and unconscious level poses problems for addictions research. If craving is an unconscious process it is almost impossible to measure and research quantitatively. Tiffany (1993) proposes that craving is conscious, based on results of studies measuring cue specific increases in craving.

1.9 Self-efficacy and drug use

Self-efficacy (Bandura, 1986) is a concept particularly relevant to compulsive drug taking. Efficacy is coping with one's environment, and involves a number of behavioural, cognitive and social skills. Self-perception of efficacy is seen as important determinant of how people behave, think and respond emotionally.

Marlatt & Gordon (1985) propose that self efficacy is an important determinant of relapse. He describes "high-risk situations": those that threaten an individuals' sense of control and increase the risk of potential relapse. Marlatt views the expectancy of coping with high-risk situations as similar to Bandura's (1977) notion of self-efficacy. This is defined as the individual's expectation of capacity to cope with an impending situation or task. A feeling of confidence about the ability to cope effectively with high-risk situations is associated with increased self-efficacy. As the duration of abstinence (or controlled use) increases, and the individual is increasingly able to cope effectively with high-risk situations, so the probability of

relapse decreases accordingly.

Gossop (1987) found that deliberate decision making processes were commonly given reasons for returning to opiate use in addicts. Self efficacy theory predicts that if a treatment is to be successful, it will exert an influence on the person by enhancing the efficacy expectation; the person's own belief in their ability to behave in a certain way (Annis & Davis 1986). Efficacy expectations will influence initiation, generalisation and maintenance of coping behaviours. The strength of the efficacy beliefs will determine how the coping behaviours are maintained under stress. The disease model of addiction and total abstinence as a treatment goal are considered to be counterproductive in that they minimise the individual's efficacy expectations. Annis recommends systematic teaching of self-regulatory and social skills to best equip the individual to cope with lapses to prevent them becoming catastrophic and reflecting the abstinence violation effect; an attempt by Marlatt & Gordon (1985) to explain the effects of an initial lapse on someone who is trying to abstain from drug taking. It is based on the assumption that most people view abstaining as an 'all or nothing' act, that on slip is sufficient to violate the rule of abstinence.

Niaura (1988) integrated classical conditioning, affect regulation and social learning concepts within the 'Dynamic Regulatory Model of Cue Reactivity'. Self -efficacy is identified as one of the cognitive cues central to the model. Reactions to affective states and drug cues have inhibitory effects on cognitive processes which might protect the individual from relapse. Urges, physiological activation and positive outcome expectancies also contribute, with negative attributions that these states are uncontrollable and due to personal weakness. They will also inhibit cognitive or behavioural attempts to avoid drug use, and decrease self-efficacy

beliefs. Tiffany (1995) describes this model (Niaura, 1988), as an ambitious attempt to integrate a variety of social, cognitive, conditioning and physiological and affective concepts into a comprehensive account of the influence of drug cues and mood states on drug use behaviour. Thus, the model describes how self-efficacy beliefs operate to inhibit drug use in a high-risk situation. However, there is nothing in this model that describes how drug use behaviours might be activated in the first place. Tiffany states this is a shortcoming of the model, that despite its complexity, there is a critical omission in the sequence of events from drug cues through mood states to actual drug use; within this model there is no positive input to drug using behaviour.

1.10 Mood and drug use

The reported prevalence of psychiatric comorbidity in drug users is high (Milby, 1996). The prevalence of anxiety disorders have been reported as high as 55%, and affective disorders have been reported as being as high as 36%. There is debate about whether opiate dependency produces secondary anxiety and dysthymic syndromes in otherwise healthy people, or if the opiate misuse by patients is an attempt to self-medicate pre-existing psychopathology. Research by Musselman & Kell (1995) concludes that patients are self-medicating themselves. They report that improvement occurred when patients were in methadone programmes, attributed to the mood stabilising properties of methadone in disorders that are believed to be moderated or mediated by endogenous endorphins. However, it is not clear if the patients were also using additional drugs. Hiltuen et al (1995) found that methadone plasma levels correlated with self-ratings of levels of anxiety and

irritability, although there were no placebo controls which limits the interpretation of the self-report data. In another study, Dawe & Gray, (1995) found no significant difference, in terms of reported desire to use heroin for its pleasant effect or to alleviate negative mood states or feelings, in detoxifying opiate addicts receiving either methadone or clonidine (an α-2-adrenergic agonist which alleviates opiate withdrawal symptoms by decreasing central nervous system noradrenergic activity (Gossop, 1989); without activating the pathways involved in positive reinforcement. There was no evidence to suggest that methadone had any effects on craving, although baseline rates of craving were higher in the methadone group than the clonidine group.

1.11 Methadone and craving

Kreek's (1992) review of methadone maintenance treatment comments

"It is known that methadone prevents abstinence symptoms, prevents drug hunger or craving ... and prevents relapse to illicit use of opiates"

In contrast to this claim is the reports of craving in methadone patients who are receiving high doses. de Vos et al's (1996) single case study reported increases in the self-reported craving of a patient taking up to 700mg methadone daily. There were large increases in self-reported craving around the time of methadone administration (highest levels were two hours before and two hours after), despite extremely high methadone plasma concentration. Other studies have described similar increases in craving or in withdrawal symptoms, despite high methadone plasma concentrations (Horns et al, 1975, Bell et al, 1990, Lorimer & Schmidt, 1992). de Vos suggests that a sensitisation influence of repeated use of drugs on the nervous system may account for this finding. Robinson & Berridge (1993), describe sensitisation in

terms of addictive behaviour. The result of repeated drug use is progressive and persistent neuroadaptations. These changes are manifest neurochemically and behaviourally by 'sensitisation' which refers to a progressive increase in a drug effect with repeated treatment. Drug associated stimuli become more able to control behaviour, because the neural system that mediates 'wanting' becomes progressively sensitised.

Curran et al (1999) carried out a preliminary outpatient study which suggests that methadone actually increases both positive and negative craving in methadone maintenance outpatients, but no difference in cognitive or psychomotor function or mood. In that study, 18 people who had been taking prescribed methadone for a minimum of 6 months, in doses between 20-100mg per day for the previous 4 weeks. A double-blind placebo controlled cross-over design was used. Participants were assigned randomly to treatment order (methadone or placebo on the first testing day). Participants were tested pre drug and 3 hours post drug on each test day. Participants attended two separate sessions with one week in between. The average daily dose of the participants was 43.5 ml ± 16.2ml (range 20-100ml). The doses given represented a 33% increase in normal daily dose(average increase 14.5 ml range 6-26ml). The results draw comparisons with the findings reported in Hodgson et al (1979) in which a very small amount of alcohol is sufficient to 'prime' craving for more alcohol in an abstinent alcoholic. Tiffany (1997) found that alcohol also acts as a 'primer' for cigarettes and as such alcohol can lead to relapse in people trying to give up smoking. In a similar way, methadone can be viewed as a 'primer' for craving for heroin.

Limitations of this study are that the sample was outpatients so it was not possible to control for other drug use additional to methadone. Also, only one dose of methadone was given and

this was only 33% increase on normal daily dose. An inpatient study can control these problems. In the current study, it was possible to give participants a 50% increase in daily dose because of 24 hour medical cover. There is routine urine screening of all patients, so it is possible to control for drug use additional to prescribed methadone.

1.12 Research questions

i) Does methadone increase craving for heroin in opiate users?

ii) Does increased methadone prime craving for heroin in opiate users?

iii) What are the cognitive and psychomotor effects of differing doses of methadone

iv) What are the effects of methadone on ratings of mood and mental state?

v) Generalised self -efficacy scores will be lower in participants than standardised population.

1.13 Rationale for study

British statistics show that deaths from heroin in the period between 1993-1997 increased from 55 to 169, but those for methadone increased from 220 to 368 in the same period. These figures reflect the toxicity of methadone relative to heroin, a typical daily dose of 60mg can kill a non-tolerant person, much less a child. However, methadone is still the main treatment for opiate dependency in the U.K. (DoH 1996). This, together with the finding that methadone significantly increased positive and negative craving scores in a methadone maintenance out patient population suggested a need to investigate the effects of methadone further.

There is a lack of clarity about the effects of methadone and other opiates as reported earlier. This was an important fact to consider when this study was designed. Inpatients at a detoxification unit are theoretically free of other drugs and it is therefore possible to measure cognitive, psychomotor and mood effects of methadone in isolation. Using this population, the present study aimed to address some of the methodological difficulties encountered in previous studies.

1) In the UK the number of deaths from Methadone exceeds the number of deaths from heroin and numbers have increased over the past ten years (ONS England & Wales: 1993-1997, 220 to 368 from methadone, 55 to 169 from heroin)

2) Curran et al (1999) Found no cognitive, psychomotor or mood effects when a sample of 18 methadone maintenance patients were given a 33% increase in their methadone dose.

However, there was a significant increase in both positive and negative craving scores.

3) This study replicated the previous research using an inpatient population in a detoxification Unit, thus there is more control over other drug use, including the amount of methadone used. (50% of previous sample had used other opiates additional to methadone).

4) The design is double-blind , placebo controlled so only drug effects will be detected.

5) The dose of methadone given is a 50% increase (compared with a 33% increase in the previous sample)

2.0 Research Setting

The study was undertaken at Wickham Park house, an in-patient service within the Addictions Directorate at the Bethlem Royal Hospital, part of the Bethlem and Maudsley NHS Trust. The unit has 20 beds and serves men and women from Lewisham and Southwark, Croydon, Greenwich and Bexley. In addition there are National extra contractual referrals. The majority of referrals are for opiate and polydrug dependent patients. The treatment programme is 4 weeks long. During the 3 day assessment period after admission, opiate dependent patients are stabilised on methadone. There is a choice of 3 different detoxification treatments, which use i) Methadone, ii) Lofexidine (a non-opiate used to manage opiate withdrawals, without the risk of dependency) and iii) Lofexidine with Naloxone (an opioid antagonist used to accelerate withdrawals).

Of 167 approached, 24 patients agreed to participate and of those, 20 completed both testing sessions. Thus the sample size was 20. Participants in the study were free to choose any of the three available detoxification treatments, as were those who had not agreed to take part. In addition to the detoxification treatment, there is a compulsory full time therapeutic group programme focussing on Relapse Prevention, health education and personal awareness. In addition to the group programme, residents have a key worker with whom they are encouraged to have individual counselling sessions.

The staff team is multidisciplinary, comprising nurses, drug workers, clinical psychologists,

psychiatrists and an occupational therapy technician. (An occupational therapist post is currently vacant). Weekly consultation is provided to the team by a consultant clinical psychologist.

2.1 Inclusion criteria

1. Addicted to opiates at least 6 months.
2. Between 18-55 years of age
3. Without major psychiatric or physical illness
4. With basic literary skills and be able to give informed consent

2.2 Exclusion Criteria

1. Pregnancy
2. Any past history of severe head injury

2.3 Design

The design of the study is depicted in Table 1a and Table 1b. There were two main parallel groups: Group 1 and Group 2. Within each group, a balanced cross-over design was used. In Group 1, the effects of receiving 100% of their daily dose (DD) were compared with then effects of placebo (0% of their daily dose). Thus half of the subjects in Group 1 were

allocated to receiving 100% DD on the morning of day 3 and 0%DD on the morning of day 5. The other half of the subjects in Group 1 received these treatments in the opposite order (i.e. 0% DD a.m. day 3; 100%DD a.m. day 5).

Similarly, in Group 2, half the subjects received 50% DD in the morning of day 3 and 0%DD in the morning of day 5. The other half of the subjects in Group 2 received these treatments in the opposite order (i.e. 0% DD a.m. day 3; 50% DD a.m. day 5).
The evening dose of methadone was such that it ensured the patient received a full 100% during that day. Thus when patients received 0% in the morning, they received 100% in the evening. When 50% was given in the morning, they received 50% again in the evening. When 100% was given in the morning, 0% was administered in the evening.

All participants were randomly allocated to Group 1 or 2 and to treatment order within these groups (i.e. allocation to groups 1a,1b,2a,2b was random). Testing took place before (pre) and beginning 3 hours after (post) the morning dose on each day for all participants. Thus post-drug testing occurred during the peak action of methadone (3-4 hours).

Double-blind procedures were used throughout such that neither the participants nor the researcher knew which treatment they would receive on each of the two days. Participants were informed that they would receive their whole DD of methadone at some point during each day. After participation in the study, participants went on (day 6) to commence the detoxification treatment of choice.

Table 1a: Group design of the study showing percentage of daily dose given in the morning and evening on day 3 and 5

	DAY 3		DAY 5	
	a.m.	p.m.	a.m.	p.m.
GROUP 1a	100%	0%	0%	100%
GROUP 1b	0%	100%	100%	0%
GROUP 2a	50%	50%	0%	100%
GROUP 2b	0%	100%	50%	50%

Table 1b: Group design of the study showing % of daily dose given between pre and post assessments on day 3 and 5.

	DAY 3 a.m.			DAY 5 a.m.		
GROUP 1a	PRE	100%	POST	PRE	0%	POST
GROUP 1b	PRE	0%	POST	PRE	100%	POST
GROUP 2a	PRE	50%	POST	PRE	0%	POST
GROUP 2b	PRE	0%	POST	PRE	50%	POST

2.4 Ethical Approval

Ethical approval was granted from the Bethlem and Maudsley NHS Trust/ Institute of Psychiatry Ethical Committee in July 1998, (for approval letters see Appendix 1).

Recruitment of participants began in December 1998 and testing participants continued until March 1999.

2.5 Drugs

Methadone syrup (1mg methadone in 1 ml vehicle) and placebo (the same vehicle on its own) was obtained from Martindale Pharmaceutical Company. To mask the taste of methadone, both the methadone and placebo syrup were supplemented by ten drops of peppermint essence. Thus both treatments had the same appearance, smell and taste. Nurses administered the methadone or placebo syrup as prescribed by the Doctor, in accordance with randomisation codes (see Appendix 4 for randomisation codes).

2.6 Measures

A range of tests were used to determine the effects of methadone on cognitive and psychomotor functioning, mood, self-efficacy and craving. An opiate withdrawal scale was used to assess subjective ratings of physical symptoms and a sleep scale was used to determine effects on sleep pattern.

Versions of the psychological tests were counterbalanced across subjects and design, ensuring that the four versions of each test were used equally often at each of the four testing times. (see Appendix 4 for randomisation codes). The order in which tests were administered is given in Table 2.

Table 2: Order of administration of measures:

Pre drug (time 1)	Post drug (time 2)	Measures used once only
RBMT- immediate recall	RBMT – immediate recall	National adult reading test-NART
Mood rating scale	Mood rating scale	Hospital Anxiety and Depression Scale- HADS
Heroin Craving Questionnaire	Heroin Craving Questionnaire	Drug use questionnaire
Tapper	Tapper	Generalised Self-efficacy Scale
Simple Reaction Time Test (SKRT)	Simple Reaction Time Test (SKRT)	Urine analysis after each testing occasion
Digit cancellation	Digit cancellation	
Present words	Word stem completion	
Digit Symbol Substitution	Digit Symbol Substitution	
Opiate Withdrawal Scale	Opiate Withdrawal Scale	
Sleep Questionnaire	Sleep Questionnaire	
RBMT-delayed recall	RBMT-delayed recall	
	Guess on Treatment	

2.7 Cognitive Assessments

1. *Rivermead Behavioural Memory Test (Cockburn, J & Smith P.T. (1989)*

The Rivermead behavioural memory test (RBMT) is a test specifically of everyday memory'. Within the battery, there are 11 items. This research used the prose recall which is a short story comprising between 54 to 65 word in each story. Participants are asked to listen to the story and to recall as much as they are able immediately and after a 20 minute delay. Scoring is based upon the 21 separate 'ideas' for which the participant receives 1 point for an exact synonym, half a point for partial recall or synonym of each. There are 4 versions of the story so that practice effects using the same test can be avoided. Norms are given which indicate that a minimum score of 6 on the immediate recall and 4 on the delayed recall must be obtained.

2. *Digit cancellation test*

This is a paper and pencil test that requires visual selectivity at fast speed on a repetitive motor response task. With the addition of a motor component this is a complex test of attention. Rows of 400 digits from 1-9 in random order are presented with an identified target number. The patient is required to cross out all of the target numbers from the rows.
The score is the number of errors and the time taken to complete the task. A number of versions of this test are available (Bond and Lader, 1974) and a single and a double digit version were used in this study.

4. Digit Symbol Substitution Test (WAIS-R)

From the Wechsler Adult Intelligence Scale (Wechsler, 1944, 1981). Digit Symbol substitution is a test of psychomotor performance that is little affected by overall intellectual ability, memory or learning. It consists of four rows of 100 squares, each paired with a randomly assigned number from 1 to 9. Above the rows of blank squares, there is a key wherein numbers from 1 to 9 are paired with a nonsense symbol. The task is to complete a practice trial and then to pair as many of the numbers with the correct corresponding symbol from the key within a 90 second time limit. The importance of speed and working in sequence is stressed at the outset of the test procedure. The score is the number of squares filled in correctly.

2.8 Psychomotor Assessments

1. Finger tapping speed

Tapping rate is used as a measure of motor sedation (Frith, 1967). In the test, participants are required to repeatedly tap with the preferred hand a computer key, as many times as possible in 60 seconds.

2. Simple Reaction Time Test

This comprises 24 trials with a random interval between the trials. The participant is required to press a computer key immediately the stimulus object (a flower) appears on the screen. It is used in experimental drug trials as a within subject measure of any sedative effects, indicated by response latency.

2.9 Self-ratings

1. *Heroin Craving Questionnaire (Tiffany 1997)*

The Heroin Craving Questionnaire is a 45 item self report questionnaire designed to measure craving for heroin. Scores yield five components of craving: 1) desire to use heroin; 2) intention to use heroin; 3) anticipation of positive outcome from using heroin 4) relief from withdrawal and dysphoria and 5) lack of control over use. The participant has to rate each item according to a 7 point Likert scale, from strongly agree to strongly disagree. (See Appendix 5 for examples of non-standardised measures)

2. *Generalised Self Efficacy Scale (GSES) (Schwarzer& Jerusalem, 1993)*

Specific self efficacy beliefs, proposed by Bandura (1977) is a concept used to measure situation specific self efficacy beliefs, i.e. the belief in one's ability to perform a specific action. More generalised self efficacy beliefs are in one's ability to respond to and control environmental demands and changes. The Generalised Self Efficacy Scale (GSES, is a 10 item scale which assesses the individuals belief in their ability to respond to novel or difficult situations and to cope with and associated difficulties. There are 10 items, each scoring between 1 and 4. The higher the score, the stronger the generalised self-efficacy beliefs. Self efficacy is an integral part of the Relapse Prevention model (Marlatt and Gordon, 1985) seen as central to predicting relapse and coping strategies in a recovering addict. As such it was considered important to measure the self-efficacy beliefs of this population in order to establish any difference to the general population. If difference is found, implications for treatment include the enhancement of self efficacy beliefs in terms of recovery as an important treatment aim. (see appendix 5 for copy of GSES).

3. *Opiate Withdrawal Scale*

(St. George's School medicine. In Ghodse, 1995).

This is an 18 item self report scale of the physical symptoms of withdrawal from opiates. Patients are asked to rate each symptom as present or absent over the previous 24 hours. The severity of symptoms is rated on a scale of 0-3, not at all to continuously.

4. *Mood Rating Scale (Bond and Lader, 1974)*

A 17 item visual analogue mood rating scale was used to assess subjective feelings at the present time. The scale yields 3 mood factors: 'alertness' 'content' and 'calm'

5. *Sleep Questionnaire*

This is a visual analogue scale which asks participants to rate the quality of their sleep, onset of sleep, speed of awakening, feeling on awakening and dreaming. It was included on suggestion of nursing staff in response to the most common complaint from patients about poor sleep during detoxification treatment. Nurses considered it important to obtain some measure of sleep quality and this scale was included in the test battery. The data obtained from the sleep questionnaire was not analysed since there was no difference in the ratings given by participants at different times: the results reported bad sleep exclusively.

2.10 Additional measures

1 *Drug use questionnaire*

(Maudsley Addiction Profile Marsden et al 1998)

This includes a drug taking history, and alcohol history, amounts and methods of using, drug use over the previous 48 hours prior to admission.

2. ***National Adult Reading Test (NART) Nelson, H.E. (1991)***

The NART is a list of 50 phonetically irregular words which the participant is required to read aloud. The test is scored by counting the number of words pronounced correctly then subtracting this from the total number of words on the list. This error score can then be converted to an IQ score (Nelson and O'Connell, 1978) as in the current study. NART scores

are relatively resistant to cognitive deterioration and are thus widely used as an index of premorbid IQ. (Crawford, Moore and Campbell, 1992)

3. *Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983)*

The Hospital Anxiety and depression scale is a questionnaire designed to detect anxiety and depression in hospital patients. Participants are required to rate how they have been feeling in the past week. The HAD comprises 7 anxiety items and 7 depression items, which are scored between 0 and 3. Scores of between 11 and 21 on the HADS indicate clinical levels of anxiety and depression.

2.11 Development of protocol and communication with staff team

The staff team was approached about the study at a research meeting in September where they were able to ask any questions and there was opportunity to discuss any potential operational difficulties which they could foresee.

All patients who were admitted from December were approached during the first two days of their admission and asked if they were willing to participate in the study. The procedure was explained and questions answered about the study. In addition a written information sheet (see Appendix 2) was given. Those who agreed were then asked to give their written consent by signing the consent form (see Appendix 3).

Of 167 approached, 24 patients agreed to participate and of those, 20 completed both testing

sessions. Thus the sample size was 20.

2.12 Procedure

The collection of four sets of data was done on day 3 and day 5 after admission to the unit. Testing was carried out on day 3 before medication (methadone or placebo) (time 1) and 3 hours after medication (methadone or placebo) (time 2). On day 5 pre medication is time 3, post medication is time 4 (see table 3). All participants were tested four times.

The participants were requested to guess at the dose they had received, and on a visual analogue scale were asked to rate how sure they were of the treatment they had received

Table 3: Research procedure step-wise.

	Pre-drug	**Post-drug**
Day3	Time1	Time2
Day5	Time3	Time4

2.13 Statistical analyses

A statistician expert in repeated measures designs was consulted as to the most parsimonious

analyses of the data which had both within and between subjects dose factors. The analyses used the statistical package Stata which provides a maximum likelihood random effects regression routine 'xtreg' for analysing repeated measures data. Estimating parameters of interest in a random effects regression model can reproduce all the calculations other older methods use in the least squares analysis of variance of repeated measures - which are implicitly based on random effects models - and furthermore extends the range of such models that can be used. For example, within subject effects and between subject effects can be estimated for specific contrasts of interest, and so can effects for contrasts that are represented in the experimental design as a mix of these two types.

In this approach the simplicity of formulation is achieved by treating all measures across subjects, time and dose as separate datum points rather than as a multivariate response for each subject and using the random effect error terms to represent the correlations induced by multiple measures on the same subject - that is, using a random effect for subjects as well as a random experimental error term. Standard errors, confidence intervals and significance tests for the analysis of variance are calculated automatically from the formulae for a General Linear Model, as are the separate variances between subjects and between measurements within subject.

The analyses carried out therefore fit the simplest dose-response model of a linear effect of dose across the three levels 0%, 50% 100% of the dose factor. Thus a single parameter representing 1 df is estimated from the 2 df available between the three levels of thefactor. Linearity of response implies that that the increase in response from 0% to 50% dose must be doubled to give the increase from 0% to 100% and these increases are represented by once

and twice the parameter value respectively. The linear dose contrast has been used in the model to apply to the change from pre- to post-response (base-line to experimental response) by using a linear*pre/post interaction term in addition to the main effect terms for linear dose and pre/post change. Analyses were also carried out using the base-line response as a covariate.

Correlations were computed using Spearman's rank correlations. Non-parametric data was analysed using chi-squares.

3.0 Results

3.1 Demographic information about participants.

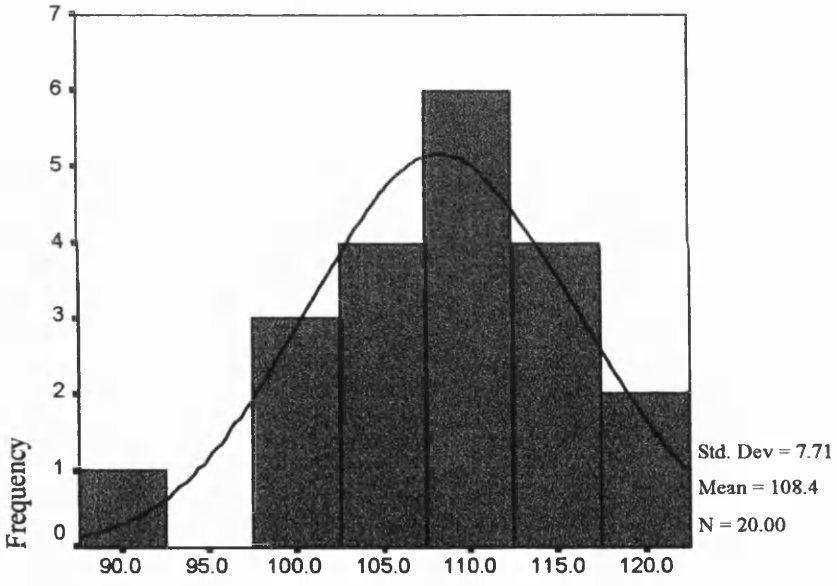
The total number of participants who completed the study was twenty. All new admissions to the unit between December 1998 and March 1999, fulfilling the inclusion criteria were approached and asked to participate. Of 167 approached, 24 agreed and of those, 20 completed testing on both day 3 and day 5. Table 4 gives a summary of the demographic details of the sample. The participants are broadly representative of opiate users in treatment, with a mean age of 33.

Table 4: Demographic details of participants

Age (years)	Mean	33.3 (±8.1)
	Range	19-51
Gender (%)	Male	80
	Female	20
Employment (%)	Unemployed	85
	Unskilled	5
	Skilled	10
Education (%)	No qualifications	25
	'O' level	45
	'A' level	5
	vocational qualification	25
Been in prison (%)	Yes	55
	No	45
Years of opiate use	Mean	10.35 (±6.7)
	Range	2-30

Two thirds of opiate users in treatment are male, as reflected in this sample. However, the sample is not a true reflection of the proportion of males and females in the treatment centre at this time, since most of the women were pregnant, and thus excluded from this study. The employment status of the participants is similar to most treatment populations, as is their educational qualifications. The NART test results show the mean IQ of the sample to be 108.4, (± 7.71)(Figure 1). The general population mean is 100, (±15).

Figure1: Histogram to show NART I.Q. scores



The years of opiate use of the participants varied widely, the range of years of use being 2-30, with a mean of 10.4 (±6.7). For 40% of the participants, this admission was their 2nd detoxification. As seen in table 5 , over half the participants had been admitted for

detoxification 3 or more times. 55% of the participants had been in prison, and the other 45% had never received a custodial sentence.

Table 5: Number of times in detoxification(including present admission)

Number of times in detoxification (including present admission) Mean 2.85 (±2.4)	
1st	5%
2nd	40%
3rd	10%
4th	10%
5th	10%
6th	15%
7th	5%
8th	5%

Table 6: Participants' psychiatric history, prescribed medication, diazepam prescribed for detoxification and follow up data on who completed detoxification.

		% of Participants
Participants taking any prescribed medication	None	90
	Antidepressants	10
Participants prescribed diazepam for detoxification (alcohol/bezodiazepine)	Yes	55
	No	45
Psychiatric history	Yes	40
	No	60
Completed current detoxification	Yes	50
	No	50

50% of participants had a psychiatric history (and had received formal treatment), although only 10% were taking prescribed psychotropic medication (antidepressants) at the time of admission. Over half were prescribed diazepam as part of their detoxification.

Table 7: Self-reported drug use additional to heroin in the last month.

Drug used in last month	**%**	**(N)**
Alcohol	65	(13)
Amphetamine	10	(2)
Benzodiazepine	40	(8)
Cannabis	95	(19)
Cocaine/crack	45	(9)
Ecstasy	10	(2)
Methadone	95	(19)

Of drugs used additional to heroin, cannabis and methadone were the most widely used. Alcohol was used by a majority, cocaine or crack by nearly half. Benzodiazepines (either temazepam or diazepam) were used by 40%, either prescribed or non-prescribed. Stimulant drugs (amphetamine and ecstasy) were used by fewer participants.(Table 7).

3.2 Generalised Self Efficacy Scale

Figure 2: Graph to show scores of Generalised Self-efficacy Scale

The Generalised Self-Efficacy Scale (GSES; Schwarzer, 1993), assesses an individual's belief in his or her ability to respond to novel or difficult situations, and to deal with any associated obstacles or set backs. The score reflects the strength of an individual's generalised self-efficacy belief. The higher the score, the greater the individual's generalised sense of self efficacy and the range of possible scores is 10-40

The mean score on the GSES was 30 (±4.15). The range of scores for the sample was 21-37. The mean for the normal population is 29.28 (±4.6). Therefore, the generalised self- efficacy beliefs of the participants are similar to those of the normal population.

3.3 Urine sample analysis

Table 8: Results of urine screen to detect additional drug use since admission

Drugs additional to methadone detected	Urine screen (day 3)	Urine screen (day 5)
No additional drug use	40%	45%
Benzodiazepine positive	55%	50%
Missing test	5%	5%

Analysis of one urine sample was not available because it was not sent to the pathology department. The results of the 19 available urine screens, taken on the days of testing show that on day 3, 40% of the sample had no drugs detected since admission except methadone. On day 5, 45% of participants had no additional drugs to methadone. Those urine screens which tested positive for benzodiazepine were all from participants who were taking

prescribed benzodiazepines. Cannabis is detected up to 30 days after last use in heavy users. Most drug screens showed positive for cannabis, and as a result of the extent of use, this would not change over 5 days, due to the residual levels of cannabis detected by the urine screen test. Thus, those urine screens which tested positive for cannabis on admission also tested positive for cannabis subsequently, without indicating subsequent use of cannabis. Therefore, there was no evidence that any participant was taking illicit substances.

3.4 Anxiety and depression

Table 9: Percentages of participants rated as clinical cases by scores on Hospital anxiety and depression scale

Percentage of participants rated as clinical case by anxiety and depression scores			
Non clinical scores	**Anxiety Only**	**Depression only**	**Anxiety and Depression**
45%	25%	5%	25%

Scores for the Hospital Anxiety and Depression scale show that 50% of participants had a score within the range 11-21 which indicates clinical anxiety. 30% of participants had a score within the range 11-21, indicating clinical depression.

3.5 Opiate withdrawal scores

Table 10: Means and standard deviations of opiate withdrawal scores

	Placebo	50% dose	100% dose	Total
Pre drug	26.2 (10.11)	26.3 (7.56)	18.2 (9.11)	24.23 (9.73)
Post drug	22.7 (10.21)	23.3 (9.62)	15.7 (11.15)	21.1 (10.53)
Total	24.45 (10.20)	24.8 (8.56)	16.95 (9.99)	22.67 (10.20)

The scores reported in tables 10, 11, 12 and 13 are based on means across the two testing days.

As shown in table 1b, each participant received 0%, 50%, and 100% doses. The total sample size is 20, therefore 5 participants were assigned to each group (1a,1b,2a,or 2b).

There was a main effect of dose ($F1, 74 = 7.29$, $P<0.01$) whereby the 100% dose was associated with lower withdrawal scores both pre and post treatment.
There was also a main effect of test time (pre vs post drug) ($F1,74 = 4.80$ $P<0.03$) where opiate withdrawal scores were reduced after drug administration. This was regardless of which treatment was given (there was no interaction between test time and dose). There was

also a main effect of test day, whereby scores were higher on day 3 (24.60, ±10.89) than on day 5 (20.72,±8.46) ($F_{1,74} = 10.48$, $P<0.001$).

No significant 2 or 3 way interactions emerged between dose, test time and test day.

ANCOVA showed that years of drug use was a significant covariate, such that withdrawal scores were higher the longer the patient had used opioids ($P<0.023$). Age was not a significant covariate.

3.6 Mood

Table 11: Means and standard deviations of mood factor scores

Mood factor	Placebo		50% daily dose		100% daily dose	
	Pre	post	pre	post	pre	post
Alertness- Drowsiness	53.37 (22.81)	46.99 (21.11)	53.47 (17.51)	43.84 (22.63)	53.09 (18.12)	36.51 (22.24)
Contentedness-Discontentedness	43.54 (25.85)	42.43 (19.52)	43.94 (20.86)	37.52 (24.83)	42.48 (17.24)	43.56 (32.18)
Calmness-Anxiety	38.8 (24.32)	37.7 (20.05)	42.2 (22.29)	28.1 (20.33)	37.15 (19.25)	41 (30.03)

There were no significant main effects (dose or testing time) on the mood factors 'alertness' or 'contented'.

There was a significant day effect on the mood factor 'calm', ($F_{1,74} = 8.36$, $p < 0.005$). The participants were more anxious on day 3 (44.02, ± 22.21) than on day 5 (31.74, ± 19.42), regardless of treatment. Interestingly, years of opiate use was a significant covariate ($F_{1,74} = 6.69$, $p<0.01$). Thus, the more years of opiate use, the more anxious the participants were. Age was not a significant covariate, thus anxiety level was not affected by age.

3.7 Craving

Table 12: Means and standard deviations of heroin craving factor scores.

Heroin craving factor	Placebo		50% daily dose		100% daily dose	
	pre	post	pre	post	pre	post
Desire to use	16.75 (7.91)	15.7 (8.41)	20.5 (10.21)	20.6 (12.41)	13.5 (7.15)	14.9 (10.21)
Intention to use	14.7 (8.03)	15.4 (8.95)	18.3 (11.01)	17.1 (10.44)	18.5 (9.06)	15 (6.23)
Anticipation of positive outcome	23.5 (13.92)	23.75 (13.92)	26.4 (12.39)	25.3 (14.35)	23.6 (17.10)	23.3 (17.34)
Relief from withdrawal	37.2 (13.47)	35 (14.98)	41.4 (13.79)	37.4 (13.43)	38 (9.14)	32 (14.58)
Lack of control	29.8 (11.77)	26.6 (14.37)	31 (12.77)	28.5 (15.74)	32.1 (14.07)	32.5 (14.74)

The craving factor 'desire to use' showed only a significant day effect, ($F1,74 = 4.34$, $p<0.05$). The desire to use was higher on day 3 (18.18, ± 8.37) than on day 5 (15.42, ± 8.23) suggesting that participants had more desire for heroin on day 3.

'Intent to use' showed a significant main effect of dose ($F1,74 = 4.99$, $P<0.05$). Scores on this factor were lower on placebo than on 50 or 100% methadone doses. There was also a trend towards a main effect of day on 'intent to use' ($F1,74 = 3,61$, $P<0.06$). Scores on this factor were rather lower on day 3 (14.92, ± 9.49) than on day 5 (17.3, ± 6.19). There were no significant interactions between dose and pre vs post drug or dose and day.

There were no significant main effects (dose, testing time) on the craving factor 'anticipation of positive outcome'. Thus participants' rating of how potentially more pleasant, happy, satisfied, contented and energetic they would feel if they used heroin, was unaffected by methadone dose or testing time.

The craving factor 'relief from withdrawal' includes participants' ratings of nausea, calmness, concentration, hot and cold flushes, tension and depression. A higher score means that participants attribute feeling better on the above measures if they were to use heroin. The craving factor 'relief from withdrawal' showed a significant main effect of day ($F1,74= 7.65$, $p<0.01$). The 'relief from withdrawal' was lower on day 3(34.3, ±12.29) than on day 5(38.97, ±12.65), suggesting that participants had a greater need for relief from withdrawal on day 5. No other main effects emerged and there were no significant interactions.

Lack of control also showed a significant main effect of day, ($F1,74 = 7.29$, $p<0.01$). Participants rated lack of control more highly on day 5 (31.47, ±13.34), than on day 3 (27.73,

± 12.52), indicating that they were feeling more out of control on day 5. A main effect of pre vs. post drug approached significance ($F1,74 = 3.24$, $p < 0.07$). Ratings were higher pre than post treatment regardless of dose.

3.8 Immediate and delayed recall

Table 13: Means and standard deviations of immediate and delayed recall scores (RBMT)

Rivermead Behavioural Memory Test (RBMT) prose recall scores						
	Placebo		**50% daily dose**		**100% daily dose**	
	Pre	post	pre	post	pre	post
Immediate	8.73 (3.26)	9.6 (2.64)	8.05 (2.39)	8.8 (2.45)	9.6 (2.98)	8.8 (4.61)
Delayed	6.9 (2.85)	7.6 (2.24)	7.0 (2.04)	7.4 (1.67)	8.1 (2.85)	5.9 (3.89)

Scores on immediate recall showed no main effect of dose. Drug order had a significant effect on immediate prose recall scores, ($F1,74 = 4.93$, $p < 0.05$). Scores were significantly better when participants received placebo first than when they received 50% or 100% dose first.

Delayed recall of prose showed a significant interaction of pre and post drug with dose ($F1,74 = 4.54$, $p < 0.03$). As seen in Table 13, delayed recall was significantly impaired by the high dose (100%) of methadone. Indeed, there was a 27% reduction in delayed recall after the

high dose (100%) of methadone. In contrast, participants given placebo or the 50% dose showed a slight improvement. Drug order showed a trend toward significance, ($F_{1,74} = 3.72$, $p<0.054$), again reflecting higher scores when participants received placebo first than when they received methadone first. There were no other significant main effects or interactions.

3.9 Psychomotor performance and attention.

Table 15: Means and standard deviations of tests measuring psychomotor performance and attention.

	Placebo		50% daily dose		100% daily dose	
	pre	post	pre	post	pre	post
Single digit cancellation (time with errors covaried)	2.4 (1.82)	2.2 (2.32)	2.6 (2.32)	1.8 (1.48)	1.6 (1.57)	1.4 (1.71)
Double digit cancellation (time with errors covaried)	4.8 (4.55)	4.9 (3.74)	4.4 (2.84)	6.6 (3.98)	3.7 (3.88)	4.3 (3.97)
Digit symbol substitution (number of symbols correct)	46.3 (11.27)	51.0 (11.8)	45.0 (6.81)	49.0 (7.32)	45.2 (12.1)	52.0 (12.84)
Finger tapping speed (Number of taps)	188.5 (50.77)	180.5 (26.17)	174.8 (44.03)	174.4 (28.03)	192.9 (23.84)	187.3 (23.84)
Simple reaction time (msecs.)	331.6 (59.98)	336.0 (48.81)	323.9 (60.74)	308.0 (40.26)	322.6 (39.21)	307.6 (18.22)

There were no significant main effects of dose, day or test time on the single or double digit cancellation test. There were no significant interactions.

The mean scores for the digit symbol substitution test (DSST) increased post drug with all treatments. There was a significant pre vs. post drug difference ($F_{1,74}= 6.15$, $p<0.05$), probably reflecting a practice effect on this task. There was also a significant main effect of

day on the digit symbol substitution test ($F1,74 = 5.76$, $p<0.05$). Participants scored higher on day 5 (99.20±20.12), than on day 3 (93.25±19.89), again probably reflecting practice effects. There was no significant treatment, test time or day effects on finger tapping speed.

In the simple reaction time test, there was a significant interaction between dose and pre vs. post testing time ($F1,74 = 8.87$, $p < 0.005$). After both the 50% and 100% doses of methadone, participants were faster in reaction times on this test. After placebo, they were marginally slower (table 15).

3.10 Participants' opinion of which dose they were given.

There were a total of forty treatment presentations, i.e. twenty participants tested on two occasions. On the first occasion, 45% of participants correctly identified that they had received methadone, (of these, only 5% correctly identified 100% daily dose) and 20% correctly identified that they had received a placebo. 35% guessed incorrectly. On the second occasion, 35% of participants correctly identified that they had received methadone and 5% correctly identified that they had received a placebo. Then other 60% guessed incorrectly. Chi square tests show no significant association between their prediction and the dose of methadone received. The mean score on participant's self-rating of how sure they were about the treatment they had received was 36.3 (±22.2) on day 3 and 50 (±19.8) on day 5. Therefore, participants could not differentiate between methadone and placebo treatments thus the double blind procedures had been effective.

3.11 Summary of main results

1. Urine sample analysis revealed no evidence of any participant taking illicit substances. Substances detected apart from methadone were benzodiazepines; only in those patients prescribed benzodiazepines.
2. According to self-ratings on HADS 50% participants were clinically anxious and 30% participants were clinically depressed.
3. Opiate withdrawal scores showed main effects of dose, testing time and day. There were no significant interactions. ANCOVA showed that higher withdrawal scores were associated with years of opiate use but were not associated with age.
4. Mood was not affected by dose. The subjective sedation induced by methadone in healthy volunteers and by increased methadone in methadone maintenance patients was not observed in the present detoxification patients. Anxiety levels (mood factor 3) were higher in patients who had used opiates longer.
5. Craving scores revealed no dose x test time interactions and were therefore not affected by treatment.
6. Delayed (but not immediate) recall of prose showed a significant interaction of dose with test time. The higher dose particularly impaired delayed recall.
7. Simple reaction time also showed a significant dose x test time interaction. Participants' mean scores were faster after methadone than after placebo.
8. Participants performed at chance levels when asked to guess whether they had received methadone or placebo.

4.0 Discussion

This study used a placebo- controlled design, and double blind conditions with a population of detoxifying opioid users in an in-patient setting. Years of opiate use varied widely, (mean 10.35(± 6.7) years. Over 50% were additionally prescribed Benzodiazepines as part of their detoxification. The majority of the sample was male, since at the time of testing most women in the treatment setting were pregnant and so excluded from the study. Previous reviews, (Weinreib & O'Brien, 1993; Zacny, 1995), have identified a lack of controlled studies in this under-researched population. Future research should build on this approach to address some of the methodological problems found previously.

The results of this study will be discussed firstly in terms of opiate withdrawals, then mood, craving for heroin. The effects of methadone on cognitive function are discussed in terms of immediate and delayed recall, psychomotor performance and attention. In addition, the clinical implications are considered, both in terms of methadone treatment and psychological therapies for drug dependence.

4.1 Opiate Withdrawal Scale

All participants rated their withdrawals less severely post drug (i.e. results of the Opiate Withdrawal Scale showed a significant pre vs. post drug effect). Interestingly, participants also rated their withdrawals more severely on day 3 than on day 5. That withdrawals were more severe on the first testing occasion than the second, could suggest that participants were more stable on the assessment dose by the 5th day. In

addition, participants receiving 100% (high) dose of methadone rated their withdrawals less severely than either placebo or 50% (normal) of their daily dose. Stizer, Biglowe & Leibson (1984) found increased withdrawals in participants who received a 75% or 100% reduction in dose of methadone, but no difference in participants who received increased doses.

There was no evidence that ratings of opiate withdrawal were changed by treatments (i.e. there were no significant interactions of dose with testing time). Thus my initial hypothesis was not supported.

Years of drug use was approaching significance as a covariate, showing that the more years of use the more severe the reported opiate withdrawals. This accords with an association between severity of dependence and severity of withdrawals. (Ghodse, 1995). The order in which the doses were given (ie placebo first or methadone first) did not affect opiate withdrawal scores.

4.2 Mood

Mood was not affected by treatment, but was significantly affected by day of testing whereby participants were calmer (less anxious) on day 5 than on day 3. Participants also had higher desire for heroin, and more severe opiate withdrawals on day 3 than day 5 These effects may well be inter-related. Presumably participants would be more anxious if their desire for heroin and withdrawals were higher on day 3. This may also be influenced by being in a detoxification unit in the first few days of a four week stay. Anxiety may diminish, after being in the treatment setting longer.

Anxieties about taking part in the research (the possibility of receiving a placebo caused some concern) may also have contributed to differences in testing days. Interestingly, years of opiate use (but not age) was a very significant covariate in that the more years of opiate use, the higher the level of anxiety. Therefore, years of use is affecting anxiety, irrespective of age (i.e. a younger person with many years of opiate dependency will be more anxious than an older person, who is dependent on opiates for a shorter time). An additional point to consider is that half of the sample had ratings which indicated clinical levels of anxiety. Comorbid anxiety problems are often found in substance using populations (Gossop et al, 1991). There were no treatment effects on the other 2 mood factors: alertness or contented, implying that methadone had no sedative effect in this highly opioid tolerant population. (c.f. summary of results 4)

4.3 Craving

Craving scores showed no significant interactions between dose and test time and therefore the initial hypothesis predicting increased craving following methadone was not supported. There are several reasons why the results of the present study did not support my hypothesis and why results divergent to Curran et al were obtained. In the present study the population was inpatient, for detoxification from opiates. As such, their motivation to abstain from opiates may be substantially different from a population who have no intention to abstain, rather are obtaining stable continuing prescriptions of methadone for maintenance. The doses given to stabilise participants prior to commencing detoxification treatment were lower than those given to the out patient maintenance population of the previous study. In addition, the Heroin Craving Questionnaire is a self-report measure, and the limitations of such measures are

discussed more fully later. However, of note is the issue of confidentiality; in this suspicious and anxious population it is possible that the assurance of confidentiality was insufficient to facilitate honesty about the amount that they were craving heroin at this time, due to concerns about implications for detoxification treatment.

The craving category desire to use had a significant day effect and participants had more desire for heroin on day 3 than day 5. This suggests that patients were craving heroin more on day 3, perhaps because they did not feel 'held' by the assessment dose of methadone. This effect was commonly reported by participants, especially if their additional drug use immediately before admission had been heavy.

'Intent to use' was higher with participants receiving methadone (50% and 100%) than placebo but this was regardless of treatment (i.e. there was no dose x test time interaction). There was a trend in the effect of day whereby participants had higher scores on 'intent to use heroin' on day 5. 'Lack of control' was also significantly affected by day whereby, participants felt more out of control on day 5. This latter finding perhaps reflects participants anticipation the imminent start of their detoxification. In addition, they had been in the treatment centre for 5 days, often reporting lack of sleep and associated negative feelings. Lack of control was rated higher pre than post drug by all participants which suggests that taking a linctus, (regardless of whether it contained an active drug) reduces lack of control, at least in the few hours immediately after it is taken.

The craving category relief from withdrawal revealed a significant day effect whereby participants had a greater need for relief from withdrawals on day 5. This supports

the trend towards higher levels of intent to use heroin and feeling more lack of control on day 5. However, the opiate withdrawal scores suggest that participants have less severe withdrawals on day 5, so one could expect that the craving scores would reduce in a similar way. However, they do not so suggest that craving is independent of withdrawal symptoms. Methadone did not significantly affect anticipation of positive outcome of using heroin. Desire to use heroin approached significance.

The action of methadone is thought to be twofold, firstly reducing the craving for heroin per se, and secondly by blocking the euphoric effects of other drugs, if used in conjunction with methadone. This effect is thought to occur at doses of between 80-120mg. However, previous studies have reported that doses of 80mg reduce craving (Ball & Ross, 1991), and other reports (eg de Vos, 1996) of craving for heroin in a patient receiving 700mg methadone daily. In Curran et al the mean methadone dose was 43.5ml (±16.2ml), range 20-80ml. In the present study, the mean dose was 37ml (±10.42), range 20-50ml.

Burton & Tiffany (1997) report a definite link between cigarette smoking and drinking alcohol. They report that alcohol acts as a primer for cigarette smoking. Methadone could be acting as a primer for heroin in the same way that alcohol acts as a primer for cigarette smoking but this will depend on several factors including dose, population and motivation for abstinence, as discussed previously.

Interestingly, desire to use was the only category of craving which reduced on day 5. This could be as a result of longer time in the treatment setting, with opportunity to

affirm motivation for entering treatment, in a similar way that length of stay appears to reduce anxiety.

4.4 Delayed and Immediate recall

The order in which participants received the dose (0%, 50% or 100% daily dose) significantly affected immediate recall, with better scores if placebo was the first treatment. Methadone impaired immediate recall scores. The high dose of methadone also impaired delayed recall such that in the 100% group there was a 27% reduction in delayed recall. The placebo and 50% groups by contrast improved slightly. These findings are contrary to Zacny's (1995) review of the few previous studies which have been carried out, that single doses of methadone in chronic users (compared with healthy controls) are devoid of cognitive effects. In the present study, the methadone dose was increased by 100%, compared with a 33% increase in Curran et.al. (1999), which also reports that methadone does not appear to significantly affect cognitive function. As such it could suggest that it is only at high doses that the detrimental effects of methadone on cognitive function are evident in chronic opiate users.

4.5 Psychomotor, performance and attention

Methadone had a few performance effects. It did not impair finger tapping, DSST, single or double digit cancellation. Dose of methadone significantly affected simple reaction times. Patients were faster to react following 50% and 100% doses, whereas those receiving placebo were slightly slower. This supports Gordon's (1970) report that reaction time in methadone maintenance out patients was equal to or faster

compared with non-drug controls, (non-drug users or recently detoxified opiate users). The finding of faster reaction times may appear paradoxical given that methadone has known sedative effects. However, sedation is more frequently observed in patients who are less tolerant to opiates than this population of highly heroin dependent patients. Methadone may have counteracted withdrawal symptoms in this population to enable more focus on the reaction time task and resulting in faster reaction times. Thus change on the opiate withdrawal scale and on simple reaction times may be related. Mean scores on the digit symbol substitution test improved post drug, reflecting a practice effect on this task. Participants also scored better on day 5, again probably reflecting practice effects. The lack of effects of methadone on DSST, finger tapping and digit cancellation accords with previous research findings (Rothenberg, et al 1977; Curran et al 1999).

4.6 Detection of dose

Participants were unable to guess whether they received methadone or placebo (time 2, 65% correct, time 4, 40% correct). There was no significant association at all between actual dose and prediction of dose received. This is similar to the findings of Stizer, Biglowe & Leibson (1984) who studied detectability and symptoms associated with a single-day alteration of methadone dose. They found no reliable detection of increase in dose of up to 50%. However, they did find accurate detection of decreases in dose. Curran et. al. (1999) also found methadone maintenance patients could not differentiate between when they received a 33% increase in daily dose or matched

placebo. Thus, the double-blind procedures used in the present study were effective: participants could not distinguish between methadone and placebo.

4.7 Urinalysis

The results of urine sample analysis revealed no evidence of any participant taking illicit substances. This in itself is an impressive result. Previous studies have been unable to achieve this (Weinreib et al, 1993; Curran et.al. 1999). Especially high levels of additional illicit drug use was found in methadone maintenance out-patients, with only 27% of the sample providing a negative urine screen for illicit drugs (Curran et. al. 1999).

In the research setting, clients are required to give a supervised urine sample every day. The rationale is that the unit is a detoxification unit and no drug use is allowed. If there is evidence of drug use the client is discharged. Samples are supervised to ensure that each person provides their own sample, not one from someone else or which has been adulterated in some way. This study therefore achieved one of its main aims by ensuring that methadone challenges occurred in the absence of additional illicit drug use by participants.

Urine sample analysis was carried out on both testing days to screen for illicit substances. Urine testing needs to be considered with the knowledge that different drugs are metabolised in different ways and therefore are detectable in urine for different amounts of time. For example, cocaine is detectable for up to 3 days while cannabis may be detected up to 30 days after last use, long after there would be any

likely clinical effects. 95% of the sample was positive for cannabis on admission and this did not change. However, this was assumed to not indicate re-use during admission. 55% of the sample was positive for benzodiazepines. These samples were all from participants who were receiving prescribed benzodiazepines as part of their detoxification. Therefore, in this sample there was no evidence that any of the participants were taking any illicit substances.

In the treatment of opiate dependence, the policy regarding urine screening in relation to the overall treatment philosophy is an important part of the client-therapist relationship. For example, the overall treatment philosophy may be one of abstinence, therefore urine screens are used to detect and monitor other drug use and as a tool for changing treatment if other illicit drug use is detected. Such policies can foster an atmosphere of non-disclosure of illicit drug use and craving which makes therapeutic interventions limited in their usefulness to deal with the client's current issues. However, in this setting, daily urine samples are a requirement of admission, and clients are aware of this requirement before admission. As such, the impact on the therapeutic relationship is not an issue in the same way it would be in, for example, methadone maintenance clinics.

4.8 Poly-drug abuse

As reported previously, many studies have encountered polydrug use among participants as a block to obtaining clear, interpretable data in opiate dependent populations. In this study, over half of participants were prescribed diazepam as part of their detoxification. Conjunct use of benzodiazepines and heroin is common with many opiate users who claim that benzodiazepines prolong the 'high' of heroin. It

could also be that benzodiazepines reduce the level of anxiety they experience as levels of opiates in the blood drop. Drug users with complex polydrug use and physical and psychological deterioration are candidates for in patient treatment , because their cases are too complex to manage easily in an out patient setting. (DoH,1997)

An additional consideration for research in this area is the scarcity of a heroin only dependent patient, since almost all drug dependent patients have some degree of polydrug use. It is possible that drug using patterns vary according to where research is conducted. It is possible that different cities 'favour' different drugs. This is one reason for the variations in reporting of additional drug use. Dupont and Saylor, (1989) found 51% of their sample had urine samples that contained evidence of cannabis. In this sample, 95% of the participants regularly smoke cannabis.

In an inner city area such as where most of the sample lives, it could be speculated that as in this study, additional drug use is for none of the above reasons. It is possible that the sample is poorly motivated and their admission to detoxify is as a result of social situations. The majority of the sample is unemployed and report that for them drug use is a consequence of life stresses (including boredom resulting from unemployment). The associated forensic activity means that some are forced into treatment to avoid custodial sentencing or that they need to be seen to be addressing their drug problem to receive social security benefits or to keep custody of their children.

In clinical terms such feelings are attributed to the pre-contemplation or contemplation stage of motivation (Prochaska & DiClemente, 1992). For example, the user wants to continue heroin use but methadone is a legal alternative and the user has not yet decided on whether the adverse consequences of their heroin use means that they want to give up. Alternatively, contemplation means the patient has considered the consequences and wants to give up heroin, but is not yet ready to act. It is important to consider that drug use is difficult to give up without awareness of the role it fulfils in the individuals' life. For some it is an escape from trauma and or the reality of everyday life, for others it is just a normalised part of everyday life.

Further research should investigate further the role of polydrug abuse in the history of those seeking treatment for opiate dependency.

Tiffany et al (1998) propose an alternative view of the function of compulsive drug use: that compulsive drug use is similar to other automated over-learned behaviour, in that it is stimulus-bound, stereotyped, effortless, difficult to control and regulated mostly unconsciously. Many of the sample reported, in the absence of any other reason, that they "just do" (take heroin), thus giving anecdotal support Tiffany et al's proposal.

Studies show that most opiate users spend a longer time in treatment, compared with stimulant users who present for treatment at a younger age and are discharged from treatment sooner (The Department of Health review of drug services 1996).

4.9 Generalised self-efficacy

Mean GSES scores were 30(±4.15)(range 21-37). The mean score for the standardised population is 29.28(±4.6). Therefore, the GSES scores for the sample are not significantly lower than the norms. Possible reasons for this unexpected result are that participants are feeling an enhanced sense of self-efficacy by virtue of being in the detoxification treatment centre. If this is so, GSES scores for participants who do not complete detoxification would perhaps be lower than those who detoxify successfully. An additional consideration is the previously discussed limitations of using self-report measures in this population. Since Self-efficacy has been identified by Marlatt & Gordon (1985) as central to relapse, despite the findings of no difference in this study, further research into the self-efficacy beliefs of addicts may aid treatment.

4.10 Clinical implications

What constitutes adequate methadone dosage is a matter of debate. Dole & Nyswander (1966) stated that:

> "At present, the most that can be said is that there seems to be a specific neurological basis for the compulsive use of heroin by addicts and that methadone, taken in optimal doses can correct this disorder. The proper methadone dose is one that prevents ongoing heroin use."

The DoH task force (1997) recommends doses of between 50-100mg daily. However, it advises caution in prescribing methadone at such levels for detoxification.

Wolff et al. (1991) found a linear relationship between methadone dose and methadone concentration in blood plasma, i.e. the mean plasma level at the 80mg dose are very close to the 400ng/ml suggested as ideal for effective treatment. The study recommends that individual doses are calculated as shown in table 15.

Table 16: Recommended methadone dose range over the treatment course

Phase	Purpose	Range
Initial dose	Relieve abstinence symptoms	20-40mg
Early induction	Reach tolerance threshold	±5-10mg (3-4 hours)
Late induction	Establish adequate dose (desired effects)	±5-10mg (5-10 days)
Maintenance	Maintain desired effects	Usually 80±20mg (may be >100 or < 50)

In the present study, mean methadone doses were smaller (36.75 ±10.42ml) than those of the methadone maintenance population in the Curran et.al.(1999) study (43.5± 16.2ml), reflecting these recommended doses.

One of the main obstacles to clinicians' adequately prescribing methadone is the fear of overdose if the client continues to take other drugs. There is also the potential increase in amounts of methadone available illicitly, if clients sell their methadone to obtain heroin. There is a particular risk since the introduction of 10mg in 1ml methadone liquid, which is ten time more concentrated than previously available

methadone. This is the obvious increase in the risk of accidental fatal overdose, especially in children.

4.10.1 Implications for psychological therapies

Craving is an important part of cognitive-behavioural interventions such as relapse prevention Marlatt & Gordon (1985). It is assumed that craving for heroin leads to heroin use and relapse. It is not possible to attribute craving to an entirely physiological or psychological effect, it is likely to be the interaction between the two. Craving is similar to many aspects of addiction treatment in that there is often a separation between the behavioural and medical consequences and therefore the subsequent treatment adopted varies, according to what the craving is attributed to and originating from. For example, if a dealer moved in next door to a patient and their cravings increased, therapeutic intervention would focus on resolving the situation rather than increasing methadone. It is possible that in addition to the situational context, the client's attributions as to the origins of their craving affect their ability to deal with it. Therefore, if methadone is the source of the craving, coping with it could be qualitatively different than if craving is attributed to observing drug taking or seeing a dealer, for example.

4.11 Methodological issues and suggestions for further research

Representativeness of the sample

The majority of the sample is male. The DOH (1996) reports that the women are a minority in treatment settings, so the sample was representative in this respect. Reasons for this include fewer women IV users so possibly fewer associated problems, child care issues which may prevent mothers accessing services for practical reasons or for fear of repercussions form Social Services of openly addressing a drug problem. However, the number of women in the sample is not representative of the proportion of women in treatment, since at the time, most were pregnant and thus excluded from the study. The mean age of participants was 33.3(±8.1) (range 19-51). Over half were in detoxification for the 3rd time or more which is representative of in-patients, (DoH, 1996) p58:

"It is not unusual for detoxification to take place several times in the context of a drug use career of several years that leads to eventual abstinence."

Half of the participants subsequently completed their detoxification. Previous studies (Gossop et al. 1986, 1995,) report completion rates of 78% and 38%.

A main problem in conducting this study was recruitment. In order to take part, participants were required to extend the assessment period before their detoxification started, from 3 days to 5 days. This was to ensure that participants were taking the same amount of methadone on both testing days. All new admissions to the unit between December 1998 and March 1999, who fulfilled the inclusion criteria were asked to participate. Research in this client population is very difficult for a variety of reasons, including unreliability and lack of co-operation. The majority of those approached about participating were enthusiastic about the research, giving the subjective opinion that "methadone makes matters worse", but did not agree to participate. Of 167 approached, 24 agreed and of those, 20 completed testing on both

day 3 and day 5. Those who refused all stated not wanting to extend the time on assessment as the reason for refusal. They wanted to begin detoxification as soon as possible, and did not like taking methadone, however briefly. It is possible that recruitment may have improved if participants received payment. However, this raises ethical concerns. Since this sample were patients, it was not possible to pay them. There were also organisational difficulties around the dispensing of the methadone, which delayed the data collection and reduced the time available for data collection considerably.

The use of a double-blind placebo controlled cross over design is very sensitive to any effects of drugs and has been used in many other drug studies.

In terms of measures, the limitations of self-report measures are well documented (Nelson, 1981, Barker, Pistrang & Elliott, 1995). There are a number of potential validity problems associated with self-report measures. People are not always truthful, so the 'reality' of what they tell you is often quite different to the objective reality. This is a particularly relevant problem in the area of drug and alcohol research. Other factors, such as denial of problems to themselves, or telling the researcher what they think they want to hear, may affect the 'reality' of what is reported. However, the main advantage of self-report, that it gives you the respondent's views directly, was considered to be more important in this study. The participants were reminded of confidentiality when completing the self-report measures. All participants appeared to be very honest when giving their views, and there was little evidence of socially desirable responses! However, in addition to

earlier considerations about the limitations of self-report measures, The Heroin Craving Questionnaire (Tiffany, 1996) was not standardised on an in- patient detoxification population. It was psychometrically assessed on a population not attempting to stop opiate use).

Future research

Of obvious concern for future research is the link between methadone and craving. Previous research (Curran et al, 1999) questions the efficacy and indeed ethics of prescribing methadone when it potentially increases craving for heroin. However, this study did not find increased craving in a detoxification population receiving a mean 36.75±10.42ml dose.

The cognitive effects of methadone should be investigated further, with consideration of the limitations of the previous research, as so far results have been, at best inconclusive (Zacny, 1995). My finding that delayed recall of prose is impaired by the doses of methadone administered is of concern. This task taps episodic memory, a function of crucial importance in day to day life. Episodic memory, our memory for personally experienced events, is also involved in treatment, since approaches such as Cognitive Behavioural Therapy involve memory and learning.

Future research into cognitive effects associated with opiate dependency may assess the potential impact of cognitive deficits on treatment. Currently, there is little known about cognitive effects of opiates, and thus current assessment and treatment of opiate dependency does not acknowledge any cognitive deficits. This is despite anecdotal

evidence from participants that methadone reduces their attention, concentration and memory.

The inpatient setting improved control over additional drug use and enabled a larger increase in dose to be investigated, which were improvements on Curran et al's (1999) out patient study. However, any future research in this population will encounter the practical difficulties of non-compliance and unreliability, which makes research into this population so challenging. Previous studies have largely involved service evaluation that have potential impact on clinical practice, and so are understandably threatening for staff. A common understanding between clinicians and the purpose of research - the goal of improving treatment in this population - would therefore facilitate research.

References

Adams, K.M., Rennick, P.M., Schoof, K., & Keegan, J., (1975) Neuropsychological measurement of drug effects: Polydrug research. *Journal of Psychedelic drugs* **7:** 151-160

Annis H.M., & Davis, C.S. (1986) A relapse prevention model for treatment of alcoholics, In W.R. Miller & N.Heather (Eds) *Treating Addictive Behaviours: Processes of change.* New York, Plenum Press.

Annis, H.M., & Davis, C.S., (1988) Self-efficacy and the prevention of alcoholic relapse: Initial findings from a treatment trial. In T.B. Baker & D. Cannon (Eds) *Addictive disorders: psychological research on assessment and treatment.* New York: Praeger Publishing Company

Appel, P.W., & Gordon, N.B. (1976) Digit-symbol performance in methadone treated ex-heroin addicts. American Journal of Psychiatry. **133** 1337-1339.

Ball,J.C., & Ross, A.(1991) *The Effectiveness of Methadone Maintenance Treatment.* New York, Springer-Verlag.

Baker, T.B. Morse, E. & Sherman, J. (1987) The motivation to use drugs: A psychobiological analysis of urges. In P.C. Rivers (Ed.) The Nebraska symposium on motivation. *Alcohol use and abuse.* Lincoln: University of Nebraska Press.

Barker. C., Pistrang, N., & Elliott, R, (1995) *Research Methods in Clinical and Counselling Psychology.* John Wiley & Sons Chichester.

Bandura, A. (1977) Self-efficacy: Toward a unifying theory of behaviour change. *Psychological Review*, **84,** 191-215.

Bandura, A. (1986) The social foundation of thought and action: A Social Cognitive Theory. Englewood Cliffs, N.J. Prentice-Hall.

Bell, J., Bowron, P., Lewis, J. & Batey, R. (1993). Serum levels of methadone in maintenance clients who persist in illicit drug use. *British Journal of Addiction* **85** 1599-1602.

Bond, A.J., Lader, M. (1974) The use of visual analogue scales in rating subjective feelings. *British Journal of Medical Psychology.* **47** 211-18.

Bond, A. Silveira, J. & Lader, M.(1991) Effects of single doses of Alprazolam and alcohol alone and in combination on psychological performance. *Human Psychopharmacology* **6** 219-228.

Brockmuhl, M. & Ehrhart, G. (1949) The use of methadone, cited in Preston, A.(1996) *The Methadone Briefing,* ISDD.

Burton, S.M. & Tiffany, S. T. (1997) The effect of alcohol consumption on craving to smoke,

Addiction **92,**15-26.

Christie, G., Gershon, S., Gray, R., Shaw, F.H., McCance, I., Bruce, W. (1958) Treatment of certain side effects of morphine. *British Medical Journal,* **1** 675-680.

Cockburn, J., & Smith, P.T. (1989) *The Rivermead Behavioural Memory Test.* Thames Valley Test Company.

Coda, B.A., Hill, H.F., Hunt, E.B., Kerr, E.B., Jacobson, R.C., & Chapman, C.R. (1994) Cognitive and motor function impairments during continuous opioid infusions. Human *Psychopharmacology*, **8**, 383-400.

Crawford, J.R., Moore, J.W., Cameron, I.M. (1992) Verbal fluency: A NART-based Equation for the estimation of Premorbid Performance. *British Journal of Clinical Psychology* **31** 327-329.

Curran, H.V., Bolton, J., Wanigaratne, S., Smyth, C. (1999) Additional methadone increases craving for heroin: a double blind, placebo controlled study of chronic opiate users receiving methadone substitution treatment. *Addiction* **94,** 665-674.

Curran, H.V.(1991) Benzodiazepines, memory and mood: A review. *Psychopharmacology* **105** 1-8.

Dawe, S. & Gray, J.A. (1995) Craving and drug reward: a comparison of methadone and clonidine in detoxifying opiate addicts, *Drug and Alcohol Dependence* **39** 207-212.

De Vos, J.W., Ufkes, J., van Brussell, G., van der Brink, W. (1996) Craving despite extremely high methadone dosage. *Drug and Alcohol Dependence* **40** 181-184.

The Department of Health (1996) The Task Force To Review Services For Drug Misusers: Report of an Independent Review of Drug Treatment Services in England.

Dole V., Nyswander M., (1966) Narcotic Blockade. *Archives of Internal Medicine*. **118** 304-309.

Drummond, C., Tiffany, S., Glautier, S., & Remington, B. (Eds) (1995) *Addictive Behaviour: Cue Exposure theory and practice* Wiley, Chichester.

DuPont, R.L., & Saylor, K.E. (1989) Marijuana and benzodiazepines in patients receiving methadone treatment. *Journal of the American Medical Association* **261** 3409.

Dyer, K.R. & White, J.M. (1997) Patterns of symptom complaints in methadone maintenance patients, *Addiction*, **92** 1445-1455.

Folli, D., Mutti, A., Van der Venne, M.T., Berlin, A., Gerra, G., Cavazzini, S., Maninetti, L., & Vescovi, P. (1992) Neuroendocrine response to psychological performance testing. *Psychoneuroendocrinology,* **17** 467-474.

Frith, C.D. (1967) The effects of nicotine on tapping. *Life Science* **6**, 321-326.

Ghodse, H. (1995) *Drugs and Addictive Behaviour* 2nd Edition Blackwell, London.

Gordon, N.B. (1970) Reaction-times of Methadone Treated ex Heroin Addicts *Psychopharmacologia* **16:** 337-344.

Gossop, M. Green, L.,Phillips, P., Bradley, B. (1987) What happens to opiate addicts immediately after treatment: A prospective follow-up study. *British Medical Journal.* **294** 1377-1380.

Gossop, M. (1988) Clonidine and the treatment of the opiate withdrawal syndrome. *Drug and Alcohol Dependence* **21**, 253-259.

Gossop, M. Griffiths, P, Bradley, B. & Strang, J. (1989) Opiate withdrawal symptoms in response to a 10- day and 21-day methadone withdrawal programmes. *British Journal of Psychiatry,* **154** 360-3.

Gossop, M., Grant, (1991) A six country survey of the content and structure of heroin treatment programmees using methadone, *British Journal of Addiction,* **86** 1151-1160.

Gossop, M.(1994) Prescribing Heroin and Other Injectable Drugs to Addicts: A British Perspective. Schut **5:**322-333. Cited in: The Department of Health (1996) The Task Force To Review Services For Drug Misusers: Report of an Independent Review of Drug Treatment Services in England.

Gossop, M., Marsden, J., Edwards, C., Wilson, A., Segar, G., Stewart, D., Lehmann, P. (1995) The October Report . The National treatment Outcomes Study. A Report prepared for the Task Force.

Grant, I., Adams, K.M., & Carlin, A.S. (1978) The collaborative neuropsychological study of polydrug users. *Archives of General Psychiatry,* **35**, 1063-1064.

Grant, I.,Reed, R., Adams, K.M., & Carlin, A.S. (1979) Neuropsychological function in young alcoholics and polydrug users. *Journal of Clinical Neuropsychology* **1**, 39-47.

Gritz, E.R., Shiffman, S.M., Jarvick, M.E., Harber, J., Dymond, A.M., & Coger, R.(1975) Physiological and psychological effects of methadone in man. *Archives of General Psychiatry.* **32** 237-242

Hartnoll, R.L., Mitcheson, M., & Battersby, A. et al. (1980) Evaluation of heroin maintenance in controlled trial. *Archives of General Psychiatry,* **37** 877-84

Heather, N., Stallard, A., & Tebbutt, J. (1991) Importance of substance cues in relapse among heroin users: Comparison of two methods of investigation. *Addictive Behaviours.* **16**, 41-49

Higgins, S.T., Preston,K.L., Cone, E.J., Henningfield, J.E., & Jaffe, J.H. (1992)

Supersensitivity to naloxone following acute morphine pre-treatment in humans: Behavioural, hormonal and physiological effects. *Drug and Alcohol Dependence,* **30** 13-26.

Hill,S.Y., Mikhael, M.A. (1979) Computerised Tomographic and neuropsychological evaluations in chronic alcoholocs and heroin abusers. *American Journal of Psychiatry* **136:** 598-603.

Hiltunen, A., Lafoile, P., Martel, J. et al (1995) Subjective and objective symptoms in relation to plasma methadone concentrations in methadone patients. *Psychopharmacology* **118** 122-126.

Home Office (1986) Statistics of drug addicts notified to the Home Office, United Kingdom, 1985. *Home Office Statistical Bulletin, 40/86.* London.

Horns, W.H., Rado, M. & Goldstein, A. (1975) Plasma levels and symptom complaints in patients maintained on a daily dosage of methadone hydrochloride. *Clinical Pharmacology and Therapy* **17** 636-649.

Isbell, H., Wikler, A., Eisenman, A.J., Daingerfield, M., & Frank, K. (1948). Liability of addiction to 6-dimthylamino-4-4-diphenyl-3-deptanon ('methadon', 'amidone' or '10820') in man. Archives of Internal Medicine, **82** 362-375.

Jarvick, L.F., Simpson, J.H. Guthrie, D. & Liston, E.H. (1981) Morphine, experimental pain and physiological reactions. *Psychopharmacology,* **75,** 124-131.

Jellinek (1955) The 'craving' for alcohol. *Quarterly Journal of The Study of Alcoholism* **16** 35-38.

Kanof, P.D., Handelsman, L., Aronson, M.J., Ness, R., Chochrane, K.J., & Rubinstein, K.J. (1992) Clinical characteristics of naloxone precipitated withdrawal in human opioid dependent subjects. *Journal of Pharmacology and Experimental Therapeutics,* **260** 355-363.

Kelley, D., Welch, D., & Mcknelley, W. (1978) Methadone maintenance: An assessment of potential fluctuations in behaviour between doses. *The International Journal of Addictions,* **13** 1061-1068.

Kerr, B., Hill, H., Coda, B., Calogero, M., Chapman, C.R., Hunt, E., Buffington, V., &

Kozlowski, L.T. & Wilkinson, D.A. (1987) Use and misuse of the concept of craving by alcohol, tobacco and drug researchers. *British Journal of Addiction.* **82** 31-6

Koob, G. (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways, *Trends in Pharmacological Sciences,* **13** 177-184.

Kreek, M.J. (1992) Rationale for maintenance pharmacotherapy of opiate dependence, *Research Publications of the Association for Research into Nervous and Mental Disease* **70** 205-230.

Lamas, X., Farre, M., & Camik, J. (1994) Acute effects of pentazocaine, naloxone and morhine in opioid dependent volunteers. *Journal of Pharmacology and Experimental Therapeutics.* **268** 1485-1492.

Liappas, J.A., Jenner, F.A., & Vicente, B. (1988) Literature on Methadone Maintenance Clinics *International Journal of Addiction* **23** 927-940.

Lombardo, W.K., Lombardo, B., & Goldstein, A. (1976) Cognitive functioning under moderate and low dosage methadone maintenance. *The International Journal of Addictions.* **11** 389-401

Lorimer, N., & Schmid, R., (1992) The use of plasma levels to optimise methadone maintenance treatment. *Drug and Alcohol Dependence* **30** 241-246.

Mackie, A. (1991) Concentration-related effects of morphine on cognition and motor control in human subjects. *Neuropsychpharmacology*, **5** 157-166.

Marlatt, G.A. & Gordon, J.R. (1985) Relapse *Prevention: Maintenance Strategies in the development of Addictive Behaviours.* New York: Guildford Press.

Marlatt, G.A.(1987) Craving notes. *British Journal of Addiction*, **82**, 42-3.

Marsden, J., Gossop, M., Stewart, G., Best, D., Farrell, M., & Strang, J. (1998) *Maudsley Addiction Profile* National Addiction Centre /Institute of Psychiatry, London.

Milby, J., Sims, M.K., Khuder, S., Schumacher, J., Huggins, N., Mclellan, A., & Woody, G. (1996) Psychiatric comorbidity: prevalence among methadone maintenance treatment. *American Journal of Drug and Alcohol abuse*, **22** 95-107.

Miller, N.S. & Gold, M.S. (1994) Dissociaton of 'conscious desire' (craving) from and relapse in alcohol and cocaine dependence. *Annals of Clinical Psychiatry.* **6** 99-106.

Mirin, S.M., Meyer, R.E., McNamee, H.B. & McDougle, M. (1976) Psychopathology, Craving and mood during heroin acquisition: an experimental study. *International Journal of Addiction* **11**, 525-544.

Musselman, D.L. & Kell, M. (1995) Prevalence and improvement in psychopathology in opioid dependent patients participating in methadone maintenance, *Journal of Addictive diseases* **14** 67-82.

Nelson, H.E. (1991) The National adult reading Test (2nd Edition): Test Manual. Windsor, Berks, U.K.: NFER-Nelson.

Nelson, H.E., & O'Connell, A. (1978) Dementia: The estimation of premorbid intelligence levels using the National Adult Reading test. *Cortex*, **14** 234-344.

Nelson, R.O. (1981) Realistic dependent measures for clinical use. *Journal of Consulting & Clinical Psychology* **49**, 168-182.

Niaura, R.S. Rosenhowe, D.J., Binkoff, J.A. Monti, P.M, Pedraza, M. & Abrahams, D.B. (1988) Relevance of cue reactivity to understanding alcohol and smoking relapse. *Journal of Abnormal psychology* **97:** 133-152.

Oliveto A.H., Bickel, W.K., Kamien, J.B., Hughes, J.R., & Higgins, S.T. (1994) Effects of Diazepam and hydromorphone in triazolam trained humans under a novel-response drug discrimination procedure. *Psychopharmacology* **114**, 417-423.

Paxton R., Mullin P., & Beattie, J. (1978) The effects of methadone maintenance with opioid takers: A review and findings from one British city. *British Journal of Psychiatry*, **132** 473-81.

Payte, J.T. (1881) A brief history of methadone in the treatment of opioid dependence: A personal perspective. *Journal of Psychoactive Drugs*, **23**, 103-7.

Poulos C. Hinson, R. Siegel (1981) The role of Pavlovian processes in drug tolerance and dependence: Implications for treatment. *Addictive Behaviour* **6**, 205-211.

Prescott, F. & Ransome, S.G. (1947) Amidone (miadone) as an obstetric analgesic. *Lancet* **2** 501.

Preston, K.L., Liebson, I.A. & Bigelow, G.E., (1992) Discrimination of agonist-antagonist opioids in humans trained on a two-choice saline-hydromorphone discrimination. *Journal of Pharmacology and Experimental Therapeutics*, **261**, 62-71.

Preston, K.L., Bigelow, G.E., & Leibson, I.A. (1988) Buprenorhine and naloxone alone and in combination in opioid dependent humans. *Psychopharmacology*, **94,** 484-490.

Preston, K.L., Bigelow, G.E., & Leibson, I.A. (1989) Antagonist effects of nalbuphine in opioid dependent humans. *Journal of Pharmacology and Experimental Therapeutics* **248,** 929-937.

Preston, A (1996) *The Methadone Briefing.* Available from ISDD, Tel: 0171 928 1211

Prochaska, J.O. & DiClemente, C.C., (1992) In Search of How People Change: Applications to addictive behaviours. *American Psychologist* **47:** 1102-1114.

Rankin, H. Hodgson, R. & Stockwell (1979) The concept of craving and its measurement. *Behaviour Research and Therapy*. **17** 389-396.

Roache, J.D., (1991). Performance and physiological measures in abuse liability evaluation. *British Journal of Addiction*, **86** 1595-1600.

Robinson, T.E. & Berridge, K.C. (1993) The neural basis of drug craving: an incentive sensitization theory of addiction. *Brain Research Review* **18** 247-291.

Rothenberg, S., Schottenfield, S., Meyer, R.E., Krauss, B., & Goss, K.(1977). Performance

differences between addicts and non-addicts. *Psychopharmacology*, **52,** 299-306.

Rounsaville, B.J. Novelly, R.A. (1980) Neuropsychological impairment in opiate addicts: Risk factors. *Annals of New York Academy of Science.* **362,** 79-80.

Russell M.A.H. (1976) Smoking and nicotine dependence In R.J.Gibbins et al (Eds) Research Advances in Alcohol and Drug Problems, Vol. 3 New York: John Wiley.

Saddler, J.M., James, M.F., & Hartington, A.P. (1985) Naloxone does not reverse ethanol analgesia in man. *Clinical and Experimental Pharmacology and Physiology,* **12** 359-364.

Schuster, C.R., & Thompson, T., (1969) Self administration of and behavioural dependence on drugs. *Annual Review of Pharmacology* **9:** 483-502.

Schwarzer & Jerusalem (1993) Measurement of perceived self efficacy. In Weinman, J., Wright, S. & Johnstone, M. *Measures in Health Psychology: A users portfolio.* NFER-Nelson publishing company, Windsor, UK.

Singleton, E.G. Tiffany, S.T. & Henningfield, J.E. (1994) Development and validation of a new questionnaire to assess craving for alcohol. Paper presented at 56th Annual Scientific Meeting, College on problems in drug dependence, Florida.

Spear, B. (1969) The growth of heroin addiction in the United Kingdom. *British Journal of Addiction,* **64** 245.

Stimson, G.V. & Oppenheimer, E. (1982) *Heroin Addiction: Treatment and control in Britain.* Tavistock, London.

Stitzer, M.L., Bigelow, G.E. & Liebson, A. (1984) Single day methadone: detectability and symptoms *Clinical Pharmacology and Therapeutics* **14:** 123-139.

Strain, E.C., Preston, K.L., Leibson, I.A., & Bigelow, G.E. (1992) Acute effects of buprenorphine, hydromorph and naloxone in methadone-maintained volunteers. *Journal of pharmacology and Experimental Therapeutics* **261,** 985-993.

Strain, E.C., Preston, K.L., Leibson, I.A., & Bigelow, G.E. (1993) Precipitated withdrawal by pentazocine in methadone-maintained volunteers. *Journal of pharmacology and Experimental Therapeutics* **267,** 624-634.

Tenant, F., (1987) Inadequate plasma concentrations in some methadone maintenance patients, *American Journal of Psychiatry* **114** 1349-1350.

Tiffany, S.T. (1990) A cognitive model of drug urges and drug abuse behaviour: role of automatic and non-automatic processes. *Psychological Review* **2** 147-168.

Tiffany, S.T., Field, L., Singleton, E.G., Haertzen, C., & Henningfield, J.E (1991) The development and initial validation of a questionnaire of smoking urges. *British Journal of Addiction* **86** 1467-1476.

Tiffany, S.T. (1992) A Critique of contemporary urge and craving research: methodological, psychometric and theoretical issues. *Advances in Behaviour Research and Therapy.* **14** 123-139.

Tiffany, S.T., Field, L., Singleton, E.G., Haertzen, C., & Henningfield, J.E (1993) the development and initial validation of a cocaine craving questionnaire. *Drug and Alcohol Dependence* **34** 19-28.

Tiffany, S.T. (1997) New perspectives on the measurement, manipulation and meaning of drug craving, *Human Psychopharmacology: Clinical and Experimental* **12** S103-S113.

Tiffany, S.T. & Carter, B.L. (1998) Is Craving the source of compulsive drug use? *Journal of Psychopharmacology* **12(1)** 23-30.

Tiffany S.T. Field, L., Singleton, E.G., Haertzen, C., & Henningfield, J.E. (1998) The development of a heroin craving questionnaire (In preparation).

Weinreib, R,. & O'Brien, C.P., (1993) Persistent cognitive deficits attributed to substance abuse. *Journal of Drug and Alcohol Abuse,* **11** 663-691.

Weschler, D. (1958) *The measurement and appraisal of adult intelligence.* (4^{th} ed.) Baltimore: William & Wilkins.

West, R.W., & Kranzler, H.R., (1990) Craving for cigarettes and psychoactive drugs In D.M. Warburton et al. (Eds) *Addiction Controversies* Harwood Academic Publishers, London.

Westerling, D., Frigren, L., & Hoglund, P. (1993) Morphine pharmacokinetics and effects on salivation and continuous reaction times in healthy volunteers. Therapeutic Drug Monitoring, **15** 294-299.

Wieland, W.F., & Chambers, C.D. (1971) Narcotic substitution therapy *International Journal of Clinical Pharmacology, Therapy and Toxicology* **4** 462-466.

Wolff, K., Sanderson, M. & Ralstrick, D. (1991) Methadone concentrations in plasma and their relationship to drug dosage. *Clinical Chemistry* **37:** 205-209.

Zacny, J.P., Lichtor, J.L., Flemming, D., & Thompson, W.K., (1994a) A dose-response analysis of the subjective, psychomotor and physiological effects of intravenous morphine in healthy volunteers. *Journal of Pharmacology and Experimental Therapeutics.* **268** 1-9.

Zacny, J.P., Lichtor, J.L., Flemming, D., & Thompson, W.K., (1994b) Comparing the subjective, psychomotor and physiological effects of intravenous butorphanol and morphine in healthy volunteers. *Journal of Pharmacology and Experimental Therapeutics.* **270** 579-588.

Zacny, J.P., (1995) A Review of the Effects of Opioids on Psychomotor and Cognitive Functioning in Humans. *Experimental and Clinical Psychopharmacology,* **3** 432-466.

Zigmond, A.S. & Snaith, R.P. (1983) The Hospital Anxiety and Depression *Scale Acta Psychaitrixca Scandinavica* **67**, 361-70

THE MAUDSLEY
Advancing mental health care

Maudsley Hospital

Denmark Hill
London
SE5 8AZ

Telephone: 0171 703 6333
Fax: 0171 919 2171

ETHICAL COMMITTEE (RESEARCH)

Tel: (0171 919) 2892

27 July, 1998

Dr J Bearn
Wickham Park House
Bethlem

Dear Dr Bearn

Re: An investigation of the effects of methadone on concentration and mood (125/98)

The Ethical Committee (Research) considered and approved the above study at its meeting on 17 July 1998. **This approval is subject to the removal of the phrase 'and permission has been granted ....' at the end of the Information Sheet. Please send the revised sheet to this office.**

Initial approval is given for one year. This will be extended automatically only on completion of annual progress reports on the study when requested by the EC(R). Please note that as Principal Investigator you are responsible for ensuring these reports are sent to us.

Please note that projects which have not commenced within two years of original approval must be re-submitted to the EC(R).

Please let me know if you would like to nominate a specific contact person for future correspondence about this study.

Any serious adverse events which occur in connection with this study should be reported to the Committee using the attached form.

Please quote Study No. 125/98 in all future correspondence.

Yours sincerely,

Margaret M. Chambers

Margaret M Chambers
Research Ethics Coordinator

ECRMC96

Appendix 2: Information For Participants

An Investigation of the effects of methadone on concentration and mood

Information Sheet

We are inviting you to participate in a research study that is designed to assess the effects of methadone on concentration and mood.

After you are admitted to Wickham Park House you will be stabilised on methadone. After 3 days you will be asked to fill in some questionnaires about your mood and do some straight forward tests of concentration. In addition, you will be asked to take part in a brief interview with the researcher about your use of drugs. Altogether these will take 1-2 hours. Two days later you will be asked to do the questionnaires, and concentration tests again.

On one day this will be after you have taken your normal dose of methadone in full; on another it will be after half your normal daily dose. On each day you will get your full dose, by the end of the day. Some people will get the full daily dose at one point; and others will get half their dose in the morning and half at night. Each dose will look the same as placebo linctus (inactive substance) may be added. The order in which you get the doses is randomised. You will need to give a urine sample so that levels of methadone can be monitored.

Neither you nor the researcher will know whether you get your full dose all at once or in two halves. This is important to stop the results being biased. You can request the balance of your daily dose early, if it is required.

Participation in this study is voluntary and your decision to take part or not does not affect your treatment. You are able to withdraw from the study at any point and this decision will not affect your current treatment, or any subsequent treatment you may need.

The study has been reviewed by the ethical committee at the Bethlem and Maudsley NHS Trust.

All information collected for the study will be totally confidential and anonymous. Please ask if you would like more information. The Researchers involved in this study are: Dr. Bearn 0181 776 4116
Dr. Wanigaratne 0171 740 5745
Julia Kleckham 0171 740 5745

Appendix 3: Consent form

A Study of the effects of methadone on concentration and mood

Patient Consent Form

Consent to take part in the study.

Name:----------

Address:

I understand the nature and purpose of the study. I understand that participation in the study is entirely voluntary, that I may withdraw from the study at any point in time and that this decision will not affect my treatment, either now or in the future.

Signed:

Signature of witness:

Date:----------

Appendix 4: Randomisation Codes for test versions and drug

GROUP	Am dose	Pm dose	Am dose	Pm dose
A	PLACEBO	100%	50%	50%
B	50%	50%	PLACEBO	100%
C	PLACEBO	100%	100%	PLACEBO
D	100%	PLACEBO	PLACEBO	100%

PLACEBO = VEHICLE
50% = half the patients' daily dose of methadone
100% = the patients' full daily dose of methadone

Randomisation codes for 4-version tests

Subject	Day 3		Day 5	
	Predrug	Post drug	Predrug	Post drug
1	A	B	C	D
2	A	B	C	D
3	A	B	C	D
4	A	B	C	D
5	B	C	D	A
6	B	C	D	A
7	B	C	D	A
8	B	C	D	A
9	C	D	A	B
10	D	A	B	C
11	C	D	A	B
12	C	D	A	B
13	C	D	A	B
14	D	A	B	C
15	D	A	B	C
16	D	A	B	C
17	D	C	B	A
18	D	C	B	A
19	D	C	B	A
20	A	D	C	B

Appendix 5: Non standardised Measures

Opiate Withdrawal scale

Over the last 24 hours, to what extent have you been:

1. Yawning	10. Felt sick
2. Had muscle cramp	11. Had stomach cramps
3. Had a pounding heart	12. Had difficulty sleeping
4. Had a runny nose	13. Felt aches in bones or muscles
5. Been sneezing	14. Felt twitching and shaking
6. Experienced pins and needles	15. Felt irritable/bad tempered
7. Had hot/cold flushes	16. Been sweating
8. Had diarrhoea	17. Had runny eyes
9. Had gooseflesh	18. Felt craving

0 = not at all
1 = slightly
2 = moderately
3 = continuously

DATE_____

Indicate how much you agree or disagree with each of the following statements by placing a single tick (like this: ✓) along each line between STRONGLY DISAGREE and STRONGLY AGREE. The closer you place your tick to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling right now as you are filling out the questionnaire.

RIGHT NOW

If there was heroin right here in front of me, it would be hard not to use it.

RONGLY DISAGREE ___ : ___ : ___ : ___ : ___ : ___ : ___ :STRONGLY AGREE

Using heroin would not be pleasant.

RONGLY DISAGREE ___ : ___ : ___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would feel less sick now if I used heroin.

RONGLY DISAGREE ___ : ___ : ___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

If I had the chance to use heroin right now, I don't think I would use it.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Using heroin would not sharpen my concentration.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Even if it were possible, I probably wouldn't use heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

PLEASE TURN OVER

RIGHT NOW

I am not missing using heroin now.

'RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I am going to use heroin as soon as possible.

'RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

My aches and stiffness would not go away if I used heroin right now.

'RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

) Using heroin would make things seem just perfect.

'RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I My desire to use heroin seems overpowering.

[RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

2 Right now, I am not making plans to use heroin.

[RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

3 I could control things better right now if I could use heroin.

[RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

4 Using heroin right now would make me feel less tired.

[RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

GO TO NEXT PAGE

I could not stop myself form using heroin if I had some here now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

If I tried a little heroin now, I would not be able to stop using more of it.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I want heroin so much I can almost taste it.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Nothing would be better than using heroin right now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would do almost anything for heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would feel so good and happy if I used heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I don't want to use heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would be less irritable now if I could use heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

PLEASE TURN OVER

RIGHT NOW

All I want to use now is heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

It would be difficult to turn down heroin this minute

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Starting now, I could go without using herion for a long time.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Using heroin would not be very satisfying now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

If I used heroin right now, it would not help me calm down.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would not enjoy using heroin right now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would not be able to control how much heroin I used if I had some here.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I would feel energetic if I used heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

GO TO NEXT PAGE

RIGHT NOW

If I had some herion with me right now, I probably would't use it.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

My hot and cold flushes would not get better if I used heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I do not need to use herion now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I will use herion as soon as I get the chance.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I have no desire for heroin right now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

If I were using herion, I would not feel less tense.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Using herion now would make me content

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

It would be easy to pass up the chance to use heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

PLEASE TURN OVER

RIGHT NOW

I crave heroin right now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

If I were offered some heroin, I would use it immediately.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

Using heroin would make me feel less depressed.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I have an urge for heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I am thinking of ways to get heroin.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I could easily control how much heroin I used right now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE

I think that I could resist using heroin now.

RONGLY DISAGREE ___ : ___ :___ : ___ : ___ : ___ : ___ : STRONGLY AGREE