

**THE EFFECTS OF METHADONE, AS  
USED IN A METHADONE  
MAINTENANCE PROGRAM, ON  
DRIVING-RELATED SKILLS**

Greg Chesher, Jim Lemon, Michelle Gomel and Glen  
Murphy

**NDARC Technical Report No. 3**



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# CONTENTS

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	PREFACE	i
	ABSTRACT	iii
Chapter 1	INTRODUCTION	1
Chapter 2	OPIOID DRUGS AND THEIR EFFECTS ON HUMAN MOODS AND SKILLS PERFORMANCE	2
	2.1 Pharmacological Differences Between Alcohol and Opioids	3
	2.2 The Opioid Analgesic Drugs	4
	2.3 The Effects of the Opioids on Subjective Mood States	7
	2.4 The Effects of the Opioids on Performance Measures	9
	2.5 Epidemiology of Opioid Involvement in Road Crashes	17
	2.6 General Summary	18
Chapter 3	METHODS	20
	3.1 The Tests of Human Skills Performance	20
	3.2 The Study Population and the Control Group	21
	3.3 Procedure	23
Chapter 4	RESULTS	24
Chapter 5	DISCUSSION	38
	REFERENCES	42

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## PREFACE

In Australia, the primary response to the recent increase in problems associated with illicit opioid use has been to expand the availability of oral methadone as a substitute for intravenously (IV) injected opioids such as heroin. In New South Wales, for example, this has meant an increase from hundreds of places on methadone programmes five years ago to thousands of places today. With the recognition that IV drug use now carries with it the risk of HIV infection, there is pressure to increase the number of positions still further and relax the admission criteria. Such has been the anxiety to adopt a rapid response to illicit drug use in our society, that fundamental questions regarding the potential effects of methadone on the ability to function normally have remained unanswered. The research presented by Dr. Cheshier and colleagues in this report addresses some of these fundamental questions.

It is generally considered that, when provided within the context of a therapeutic program, daily methadone offers the opportunity to adopt a lifestyle which will allow full time employment and the establishment of normal relationships. While it is true that methadone may be associated with as high a degree of dependence as heroin, the way in which methadone is used has an aura of the therapeutic about it. Early views on the use of methadone often employed an analogy with insulin. It was suggested that the hardened illicit opioid user was deficient in some chemical for which heroin was a substitute. Heroin use therefore represented an attempt at normalisation. Hence, like insulin, methadone was a therapeutic replacement and treatment should be regarded as lifelong. While evidence for this notion has not been forthcoming and this view is now held only by a minority, it is nevertheless not uncommon to find individuals

who are maintained on methadone for periods of years. The possibility of cumulative effects of methadone is an important question in itself but is not dealt with in the present report.

The expansion of methadone services has meant that significant numbers of individuals are being placed on a new drug regime. While these individuals can be expected to be tolerant to many of the effects of opioids, daily oral methadone nevertheless represents a different drug, a different route and schedule of administration, and a different dose. In addition, the change in lifestyle made possible by the stabilising effect of daily methadone may mean that the demands on the individual's capacities may be increased. For these reasons, it is important that we understand the extent to which methadone modifies cognition and performance.

To some extent, this research is motivated by immediate, practical issues. Is it, for example, acceptable for individuals on methadone programs to earn a living driving a taxi, or by operating machinery? But it is also essential to know, not least for the benefit of individuals on methadone themselves, the nature and extent of any methadone-induced impairment, no matter how subtle. If the aim of drug treatment programs is not simply to free individuals from dependence on a drug but also to enable that individual to achieve some measure of self fulfilment, then recognition of potential impairment is crucial.

The present report addresses this important question of whether or not methadone when used in a maintenance program, impairs cognitive performance. It is evident that it is not possible to test all aspects of cognition. The tests

selected for this research tap into a variety of cognitive functions, all of which are important for the type of complex skills required in driving a car.

The tests reflect more general abilities than these, however. The ability to attend for extended periods of time (Mackworth Clock), the ability to use rapidly varying sensory feedback to control motor output (Critical Tracking), and the appropriate allocation of cognitive resources between competing tasks (Divided Attention) can be seen not only as examples of the individual skills needed in driving a car, but also, when taken together, as a model for any complex behaviour in which the rapid integration of sensory information is used to guide coordinated, complex motor output.

It is the use of such complex tests of sensory-motor integration that allow us to make inferences about real world function, where a simpler test, e.g. simple reaction time (which is very resilient to drug effects) would not. Moreover, qualitatively different methods of assessment, e.g., psychometric tests, may reflect impairment due to drug effects, but tell us little about the specific cognitive functions which are dynamically involved.

An important aspect of the research was to investigate the possibility of an interaction of methadone with other drugs. It is axiomatic that among illicit drug users, polydrug use is the norm. Alcohol and benzodiazepines were chosen not only because of their widespread usage in the community generally, but also because, individually, both of these drugs have the capacity to impair cognitive function even at relatively low dosages.

A summary of the results obtained is contained in the *Abstract* and will not be detailed here. However, it is important to note that this research provides a clear demonstration that individuals on methadone maintenance programs should not be considered as significantly impaired on the cognitive skills investigated.

This research has provided data of clear practical and theoretical importance. It is hoped that this will encourage further high quality psychopharmacological research programs on the multitude of questions regarding drug effects that remain unanswered. The report also provides a quite comprehensive and detailed review of the effects of opioids, which should prove to be an excellent reference document in itself.

*John Prescott*  
*September, 1989*

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## ABSTRACT

1. A study was undertaken to examine the effects of methadone, as used in the methadone maintenance program, on human performance skills which are related to those required to drive a motor vehicle with safety.
2. The tests used for the study were chosen for their relevance to driving as well as for the distinctive properties of the opioids.
3. Three groups of volunteers from the methadone programs in Sydney were chosen to represent various stages of progress by clients within the program. These were (i) those beginning on the program; (ii) those receiving an increase in dosage of 10 mg methadone; and (iii) those who have been stabilized on a dose of methadone for a period of at least six months.
4. The interaction between methadone and two other drugs commonly used by clients on a methadone program were also examined. These were (i) alcohol, to produce a mean blood alcohol concentration at peak of 0.064 g per 100 ml blood; and (ii) a therapeutic dose of the benzodiazepine, diazepam (15 mg).
5. The mean dose of methadone taken by all of the clients within the study was 70 mg (range 15 to 150 mg). The mean dose for the individual groups was (i) stabilized group, 85 mg (range 40 to 150 mg); (ii) increased dose group, 67 mg (range 40 to 135 mg); and (iii) those beginning the program, 38 mg (range 15 to 60 mg).
6. Two control groups were employed: a group of ex-users of heroin who were drug-free and a group of non-opioid users.
7. Volunteers for the control groups and the stabilized methadone group attended the laboratory on four occasions (days). On days 1 and 2, all subjects after practice on the tests, completed the test battery twice, before and after the methadone clients had received their daily dose of methadone. An interval of one hour was allowed after the methadone dose to allow time for absorption.  
  
On day 3 all clients from the control groups and the stabilized methadone groups received alcohol and on day 4, diazepam.
8. The test battery proved to be sensitive to the effects of alcohol and diazepam at the doses used.
9. **There was no evidence for an effect of the acute dose of methadone on any of the experimental groups of clients on the methadone program.**  
  
**The insensitivity of these tests of skill performance to the acute effect of methadone on the clients within the methadone maintenance program indicates that these clients should not be considered as impaired in their ability to perform complex tasks such as driving a motor vehicle.**
10. Both alcohol and diazepam produced a significant decrement in the performance on the test battery by the control groups and the stabilized methadone clients. However, there was no difference in the intensity of this effect between the groups. **There was no evidence for an interaction between methadone and either**

**alcohol or diazepam in the group of methadone clients stabilized on the program.**

**11.** The overall scores on the test battery showed a trend to poorer performance by the methadone clients. This difference achieved significance for the stabilized group of methadone clients. However, the differences in overall performance between the methadone groups and the controls were considerably smaller than those produced by the acute doses of alcohol or diazepam.

**12.** These differences in overall performance were not attributable to the acute dose of methadone. The possibility that they are related to a chronic effect of methadone was examined. There was a correlation between the methadone dose and the overall performance measure, but this accounted for only 8% of the variance and

was not the most important variable associated with this effect.

**13.** There was no difference in the performance of those stabilized methadone clients who received less than 80 mg methadone, from those who received 80 mg or more per day. The dose of 80 mg methadone is that considered in the National Methadone Guidelines (1988) as being the threshold dose for what is described as a "high dose".

**14.** It is considered that the differences in overall performance between the methadone clients and the controls can be interpreted in a manner which does not involve the pharmacological effects of methadone. It is suggested that factors including unemployment, life-style, social and personality disorders could play a contributory role.

\* \* \*



# Chapter 1

## INTRODUCTION

Methadone is at present the most commonly employed pharmacological therapy for the treatment of opioid dependence, and the extent of its use has greatly increased within the last few years. The major success of methadone therapy rests with the behaviour change which results from a stabilized dosage of opioid. The individual is released from the encapsulated behavioural pattern of drug-seeking and drug-taking and becomes more amenable to other forms of therapy in an attempt to re-enter a more stabilized life-style. Employment is a very important, if not essential, aspect of the rehabilitative process for drug dependent individuals. After stabilization on a methadone maintenance program, many heroin dependent people have been able to return to the work force. However, employment for such people frequently involves driving trucks, buses, taxis or trains or the operation of factory machinery. It is of no little interest therefore to know if methadone, as used in the methadone program, is likely to impair the skills of these people in performing these tasks.

The pharmacological basis for the methadone program rests with two properties of this drug:

- (i) It acts on the same opiate receptors ( $\mu$ ) as does morphine (and heroin<sup>1</sup>) and
- (ii) it has a much longer duration of action than does morphine (or heroin).

The consequence of these properties is that methadone and morphine exhibit complete cross tolerance. This means that should a client stabilized on a dose of methadone choose to self-

administer heroin, the tolerance which has developed to methadone will mean that the effect of the administered heroin will be significantly attenuated if not abolished. In psychological theory, the absence of the reinforcement to the self-administration of heroin, should mean that this behaviour will extinguish.

Another property attributed to methadone as used within the methadone maintenance program is that the stabilized client will experience a reduction of craving for opioids. The mechanism for this property is unclear, as indeed is the mechanism for the phenomenon of craving itself. However, it could be related to the long duration of action of methadone. The plasma concentration of methadone remains quite stable over a period of 12 to 24 hours. This is in marked contrast to that of heroin, a drug with a plasma half-life of only a few hours. It is possible that craving could be associated (in part at least) with the rapid fall in plasma concentration of heroin, and therefore with the concentration presented to the neuronal opiate receptors.

Despite the considerable international concern about the use, distribution and sale of the opiates, there has been remarkably little study of the behavioural effects of this drug group. A review of the literature concerning the behavioural effects of the opiate drugs is given in Chapter 2 of this report. This review is concerned primarily with the effects of the opiate drugs on human mood states and skills performance. It is quite surprising that in spite of the increasingly widespread use of methadone maintenance programs, there has been remarkably little study of the possible effects of this therapy on human skills performance.

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<sup>1</sup> Current evidence indicates that heroin is, in fact, a pro-drug; it more readily crosses the blood-brain barrier than does morphine, but it is as morphine that it acts on the  $\mu$  receptors.

## Chapter 2

### OPIOID DRUGS AND THEIR EFFECTS ON HUMAN MOODS AND SKILLS PERFORMANCE (with emphasis on skills related to driving a motor vehicle)<sup>†</sup>

The study of the effects of drugs on human skills performance was initiated in the first place primarily by the need to understand the role of one drug, alcohol, in road crashes. Indeed, it has been only within the last twenty to thirty years that research, utilizing the techniques of both epidemiology and psychopharmacology, has clarified our understanding of the role of alcohol in road crashes. An understanding of the basic pharmacology of alcohol has defined alcohol as a depressant of the central nervous system, psychopharmacological techniques have described the effects of alcohol on specific tasks which are related to those considered essential for the safe control of a motor vehicle. Laboratory studies have indicated that alcohol induced impairment of these skills shows a dose-response relationship and that an acceptable correlation exists between the blood alcohol concentration and the degree of impairment of skills performance. Finally, the understanding of the pharmacokinetics of alcohol and the knowledge that the determination of the concentration of alcohol in the breath bears an acceptably constant relationship with that in the blood, has facilitated the conduct of the epidemiological studies such as those of Borkenstein et al. (1964), McLean et al. (1971), and Perrine et al. (1971). Using the case-control technique these studies demonstrated that drivers who have consumed alcohol are more likely to be involved in a road crash than those who have not. Furthermore, there is a dose-dependent, logarithmic relationship between crash probability (including the severity of the crash) and the blood alcohol concentration of the driver. As a result of this research, preventive actions such as the drink-driving laws and the program of random breath testing, have been introduced.

The success of this research and in many cases

the success of the methods of intervention, have led to the view in the minds of many that alcohol can be considered the prototype for the effects of any drug on driving performance. It is often assumed therefore that drugs other than alcohol which affect our mood must also affect driving skills and that the same countermeasures as those established with alcohol will be appropriate.

However, the pharmacology and pharmacokinetics of alcohol are in many aspects so significantly different from other drugs that this assumption is not valid. Further aspects of this problem which must be faced before effective approaches to the issue of drugs (other than alcohol) and driving can be made, are discussed by Chesher (1985).

The purpose of this review is to examine the available information on the effects of the opioids on human moods and performance skills. The assessment of these effects should then provide some insight as to the potential of this group of drugs, of which methadone is a member, to adversely affect driver behaviour.

However, before beginning this task it is pertinent to discuss some aspects of the pharmacology of alcohol and to illustrate how this differs from other drugs including the opioids. Both alcohol and the opioids (as opium) have a very long history of social use by man. Both are pharmacologically classified as depressants of the nervous system; both produce euphoria (a reason for their social use) and both with long-term use produce dependence. However, when

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<sup>†</sup> This is a modified and shortened form of a review published in *Alcohol, Drugs and Driving* (1989).

one examines the specific effects produced by these drugs and studies their pharmacology, alcohol and the opioids are more noted for their differences than for their similarities.

## **2.1 Pharmacological Differences Between Alcohol and the Opioids.**

In a previous paper (Chesher, 1985), the differences in the pharmacokinetics of alcohol and other drugs were described. It is the peculiarities of the pharmacokinetics of alcohol which have enabled the collection of the volumes of data which have led to a clearer understanding of the role of this drug in road crashes. The distribution of alcohol in the body is such that its concentration in the blood can be correlated with the degree of performance impairment. The small amount of alcohol which is excreted in the breath bears a fairly constant relationship with alcohol concentration in the blood. Therefore the ability to determine the concentration of alcohol in the blood by the analysis of a sample of breath has greatly facilitated the collection of both test and control data in the epidemiological studies of Borkenstein and those which followed.

However, in addition to these pharmacokinetic differences, alcohol also appears to act in a manner which is different from most other drugs. "Appears" is the operative word because the actual way in which alcohol exerts its effects on the nervous system is still not understood. What follows is therefore a speculation, but one which should throw some understanding on some important factors in any comparison between alcohol and other drugs, including the opioids.

### **Drugs and Receptors: the opioid receptors.**

Most drugs show a remarkable degree of structural specificity; that is, the shape of their molecules is of primary importance to their activity. Even a minor change in the shape of the molecule can lead to the drug completely losing its activity or exhibiting a spectacular change in its potency. It can even change a drug from being very active into being an antagonist. The

awareness of these structural requirements for drug activity is the basis for the theory that drugs act at specific binding sites which the pharmacologist calls the "receptor". The oft quoted analogy is that the drug bears the same relationship to its specific receptor as a key does to its lock. There is a structural requirement for the key not only to fit the lock, but also to change the configuration of the lock's tumblers that the lock will open. The interaction of drug and receptor leads to the pharmacological response to the drug; such a drug is an agonist. To pursue the analogy, the agonist not only fits the lock, but opens it as well. However, if the drug-receptor interaction leads no further (but denies access to the agonist), the drug is an antagonist.

The opioid receptors, it is now known, are the physiological means by which the endogenous substances known as enkephalins and endorphins exert their action. Indeed it was because of the studies with morphine and other opioids that the opioid receptors were identified and described. Many opioid receptors have been proposed and currently these are classified within four major groups designated mu, delta, kappa and sigma. The physiological differences between these receptors are still being researched, but it is reasonable to predict that differences in the pharmacological responses to each will exist.

### **Distribution of receptors in the brain**

Another important consideration in a comparison of the actions of the opioids and alcohol is that the distribution of a specific receptor throughout the brain is not necessarily homogeneous. Some receptors might be very widely distributed and are found on all or nearly all nerve cells. Others are far more selectively distributed. The distribution of the opioid receptors throughout the brain is by no means homogeneous. Many nerve cells appear not to bear any receptors for these molecules. Furthermore the distribution for each type of opioid receptor also appears to differ. Most opioids of course will act only on those cells which bear the opioid receptor. These drugs are quite selective of the cells upon which they can act.

### How does alcohol work?

Alcohol (ethyl alcohol), in contrast to the opioids, does not show the same structural specificity. An alcohol receptor has not been described. Rather the alcohols are a group of molecules, with increasing chain length which form a continuum which shows an activity profile which changes rather gradually as the structure changes. The biological activity of the alcohol group was described many years ago as being dependent upon their lipid solubility and on the size of the molecule. The alcohols, it seems, really act as physical agents rather than as agonists for specific receptors. The physical activity alters the state and therefore the function of the cell membrane. This implies that unlike the opioids, or for that matter most other drugs, alcohol is not a selective pharmacological agent.

However, it is well known that alcohol does show a dose-dependency in its effects as well as some degree of selectivity. For example, at low doses it exhibits an apparent stimulatory effect, certainly on mood states, and it will only depress respiration at high doses (whereas respiratory depression with the opioids is apparent even at very low doses). This apparent selectivity of alcohol could be attributed to a number of possible factors including:-

(i) a differential delivery of alcohol to different nerve cells; this in turn depends on the blood supply within the brain. Those cells which receive the better blood supply also receive the highest initial concentration of alcohol.

(ii) The relative size of the nerve cells. Those smaller cells with a relatively larger surface area, might be more affected by a given concentration of alcohol.

(iii) The measurable effect of cell impairment due to alcohol will depend on the state of activity of that cell at the time it is exposed to the drug. An inactive cell, although impaired will not show evidence of this impairment.

It is not surprising therefore, that if carefully

studied with sensitive performance tests, alcohol can be shown to produce impairment on just about any task used. Other drugs such as the opioids will only exhibit their effects on the cells which bear the specific receptor for which they have affinity. The performance tasks affected by the drug will depend upon the functions of these affected cells.

With these basic views and speculations in mind, we can now examine the effects on behaviour of the opioid drugs.

## 2.2 The Opioid Analgesic Drugs.

The term opioid indicates that the drugs are derived from the plant, *Papaver somniferum*, the opium poppy. Opium is the resin produced by the unripe seed capsule of the flower, and contains many alkaloids including three opioids: morphine, codeine and thebaine. Morphine and codeine are the only naturally occurring opioid analgesics. Thebaine is without analgesic activity, but is the parent molecule from which a number of extremely potent opioid analgesics (etorphine and buprenorphine), as well as the opioid antagonist naloxone, have been synthesized. Indeed, the chemical modification of the molecule of the naturally occurring opioids is employed to produce a number of drugs widely used in therapy. Even the world demand for codeine (which is far greater than the licit demand for morphine) is satisfied from the conversion of morphine because there is so little codeine in opium.

In terms of chemical derivation, we can therefore consider the opioid analgesics as falling into three categories:

(i) the naturally occurring opioids (e.g., morphine and codeine);

(ii) the semi-synthetic opioids, derived from the above (e.g., heroin, hydromorphone, oxycodone, dextromethorphan);

(iii) the synthetic opioids, developed completely

in the laboratory and not using the opium alkaloids as precursors (e.g., pethidine, fentanyl, methadone, pentazocine, meptazinol).

### **What do the opioid analgesics do?**

Although derived from various sources and of differing chemical structures, all of the opioid analgesics exert their pharmacological activity on the opioid receptors. There also are differences in the selectivity of each drug for the different opioid receptors. Some of the synthetic opioids also have effects on receptors other than the opioid group. For example, pethidine is an antagonist (atropine-like) of the acetylcholine receptors, and meptazinol has, in some way yet to be understood, an acetylcholine-like effect. There will therefore be differences in the effects produced by each drug. Nevertheless, the general pharmacology of all of the opioid analgesics is basically similar, and all produce to a greater or lesser extent the following effects:

- 1. A modulation of the perception of pain (analgesia),** which is the opioid analgesics' major therapeutic use.
- 2. Modulation of mood-states,** including euphoria or dysphoria; an effect described broadly as "mental clouding"; depression of mentation; and drowsiness. Although really a side effect in the legitimate therapeutic use of these drugs, these properties are undoubtedly the reason for their illicit use.
- 3. Depression of respiration,** a dose-dependent effect, which in overdosage can be fatal.
- 4. Suppression of the cough reflex.** Opioids are used therapeutically, often in combination with other drugs in cough syrups. The drugs used today are less potent and are chosen for their more specific effects on the cough reflex. Many of these preparations are available over-the-counter.
- 5. Reduction of motility of the gastrointestinal tract,** causing constipation. Therapeutic use is made of this property in preparations to treat

diarrhoea. The drugs selected for this effect have very low analgesic potency.

- 6. Constriction of the pupil of the eye,** an effect described as "pin-point" pupils.
- 7. Effects on endocrine functions.** These are unwanted side effects of the opioids and (as yet) have found no therapeutic application.
- 8. Tolerance and dependence.** With careful therapeutic use, these effects can be avoided. Tolerance develops to all of the above effects except 5 and 6. The opioid dependent individual is chronically constipated and has "pin-point" pupils.

The effects described above are those of the presently known opioid analgesics. What is as yet unclear is precisely which of the presently described opioid receptors are responsible for these activities. The properties of the opioid analgesics which are potentially of concern for the skills of driving a motor vehicle are those described in item 2 above. These are broadly the effects on mood, "mental clouding" and drowsiness. Nevertheless, the consequences of drug dependence (item 8) and possibly effects related to the effects on the eye (item 6) could be of some importance.

In the light of the earlier discussion to contrast the pharmacological properties of the opioid analgesics and alcohol, it is appropriate to mention some of the effects that are not produced by the opioid analgesics. The opioids, even in high doses do not produce the gross motor incoordination or slurred speech which are characteristic of alcohol and the hypnotic sedative or the benzodiazepine group of drugs. Nor do the opioids cause the emotionally labile, garrulous and often belligerent behaviour which is frequently observed with other depressants and is typified by alcohol.

### **Variables which may influence responses to the opioids.**

The opioids have both depressant and stimulant

effects on the central nervous system. There are great variations both within people and within species as to which effect is the more prominent. For example, cats and horses are strongly stimulated; the opioid etorphine makes horses run faster and is used illicitly for this purpose. Being an incredibly potent drug, the very small doses used make detection difficult. To date there is no financial incentive to make cats go faster.

The effect of therapeutic doses of opioids in man are more characteristically depressant. However, many of their properties have led to an hypothesis that the opioids produce an arousal of the central nervous system (Jarvik et al., 1981), an arousal which is however quite unlike that observed with the central nervous system stimulants such as the amphetamines or cocaine. There are also idiosyncratic responses to morphine such as that reported by Berryhill et al. (1979) which confirm the notion that some degree of increased arousal may be experienced in man.

In discussing the effects in man there are a number of variables which can affect the response to any given drug. These are (i) the drug used; (ii) the route and manner of its administration and (iii) the drug history of the user.

**(i) The drug used** obviously relates to the response and depends on the potency of the drug as well as the receptors on which it acts.

**(ii) The route and manner of administration.** In the licit, therapeutic context, the drugs are generally administered by mouth and occasionally by subcutaneous or intramuscular injection. For severe pain the drug may be given by cautious, slow intravenous infusion.

When used illicitly, the opioids, usually heroin, are administered by fast intravenous injection. This route is chosen, no doubt, to maximize the effect of an expensive drug. The injection directly into a vein will produce an extremely high concentration of drug in a small volume of blood. The concentration of this "bolus" of drug depends not only on the dose but also on the

speed of its administration. Within about fifteen seconds this drug "bolus" is delivered with very little further dilution to the brain.

The concentration of drug reaching the brain after intravenous administration can be several hundred-fold greater than that achieved by the same dose after oral or subcutaneous administration. In legitimate medicine, intravenous administration of a drug is undertaken with extreme care, with the drug being administered slowly to avoid the extreme concentrations of the drug "bolus".

**(iii) The drug history of the user.** Regular use of opioids leads to the development of tolerance, which can be of remarkable proportions. The effect of a given dose of opioid can therefore be strikingly different in a regular user than it is in a drug-naive individual. There is also evidence that the effect of a dose of opioid on the drug-naive individual will be different from the same dose on an "ex-addict" although the latter might have been drug free for at least several months and would presumably have lost all tolerance.

Should the drug user become physically dependent, the symptoms of the withdrawal syndrome if it occurs must have some effect on driving behaviour. There appears to be a virtual absence of data on these effects, though as pointed out by Seppala and colleagues (1979), they certainly cannot be beneficial.

Therefore whether associated with therapeutic or illicit use, the response to the drug can vary according to the previous drug history of the user. With this in mind four population categories of opioid users can be identified.

**(i) Prescribed therapeutic use.** Those patients receiving the strong analgesics within a hospital setting particularly those attending as outpatients for minor surgical or diagnostic procedures. Many of these might drive a motor vehicle shortly after receiving the drug. These patients are under direct medical supervision and it is the responsibility of the hospital staff to ensure that they are in a safe state to drive before being

discharged. Unfortunately, information to assist the hospital staff with this decision is not always available.

(ii) **“Over the Counter” self-medication.** A much larger population is that which uses codeine or propoxyphene as an analgesic for less severe pains, including headache. Also the users of codeine-containing preparations for treatment of cough should be considered.

(iii) **Illicit opioid use.** A third group is that of the illicit drug users, whose opioid of choice is heroin.<sup>9</sup> For these cases the drug dose is unknown and the frequency of administration and the duration of use varies enormously. A confounding variable within this population is the extent of tolerance and dependence. The latter carries with it the discomfort of the withdrawal syndrome. The dependence phenomenon also greatly structures behaviour towards drug-seeking, which in turn involves criminal activity to gain the money to purchase more of the illicit drug, and may commonly involve the use of a motor vehicle.

(iv) **Methadone maintenance programs.** A fourth, and an increasing population is that undergoing the legal treatment of opioid dependence by the use of methadone maintenance.

It is not possible to provide a comprehensive analysis of data which will clearly demonstrate the differences in responses to opioids of members within each of these populations. Indeed, there are remarkably few studies of the effects of the opioids on human behaviour. Perhaps the reason for this is one of ethics in administering opioids to volunteers.

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<sup>9</sup> The “choice” is, of course, dictated by the market. When given by intravenous injection, heroin is more potent than morphine. However, if morphine and heroin are offered in equi-effective doses, the user cannot tell the difference. Gram for gram, heroin is the more potent drug and is therefore the preferred opioid for trafficking.

## 2.3 The Effects of the Opioids on Subjective Mood States.

### **Morphine, heroin, codeine, methadone: agonists of the mu receptor**

Much of the literature of the effects of the opioids in man concerns the subjective, mood effects of these drugs. Most of these studies were published in the 1950s and 1960s. The precise role of subjective mood changes on skills performance is unclear. Nevertheless, a review of these studies will illustrate the quite often striking differences in drug effects which occur between different user populations and so indicate the complex nature of the psychopharmacology of the opioid drugs.

Perhaps the earliest study of this type was that conducted by Lasagna et al. (1955) who, in a double blind study, compared the mood changes induced by the drugs amphetamine, pentobarbitone, morphine and heroin in human volunteers. With the exception of pentobarbitone, which was given intravenously, all drugs were administered by subcutaneous injection.

A most interesting aspect of this study was that it involved three populations of volunteers; healthy volunteers (n = 20), chronically ill patients (n = 30) and “postaddicts” (n = 30). The latter group were drawn from a group described as “incurable addicts” some of whom had used opioids as recently as two days prior to the experiment.

These authors used a series of bipolar horizontal analog mood scales having descriptive adjectives with opposite meanings at either end of the scale, such as “sad.....happy”. A quantitative estimate can be given by the volunteer indicating on the scale, that point which most appropriately indicates the best description of their present mood state within the two descriptors at either pole. The score can then be transformed into the positive or negative mood effects and described as euphoric (e.g., “happy”) or dysphoric (“sad”). The general topics covered in the 54-item questionnaire were descriptors of “thinking and

concentration"; "mood or feelings"; "degree of wakefulness"; as well as "physical effects" such as palpitations, nausea or dizziness.

The most striking finding was the distinct difference in reporting of mood states between the "normal" and the "ex-addict" groups. The scales describing mood states indicated a ratio of "euphoric" to "dysphoric" was 1.0 : 2.3 for the "normal" volunteers and 4.3 : 1.0 for the "ex-addicts". The "sedation : stimulation" ratio was 34 : 1 for the "normals" and only 2 : 1 for the "ex-addicts" whilst the scales describing either an "improvement or impairment" of mentation indicated that all of the "normal" group reported an impairment with an almost 2:1 ratio of the "ex-addicts" reporting an improvement.

Subsequent studies from this same research group (Gravenstein et al., 1956; von Flesinger et al., 1955; Smith and Beecher, 1959; 1962) with normal, "non-addict" volunteers have convincingly confirmed that the mood effects of morphine or heroin administered subcutaneously, in an experimental setting to normal volunteers are unpleasant. These effects have been described as "mental clouding", a descriptor for effects of being "groggy", "drowsy" and "mentally slow". Other subjective effects noted in normal volunteers were described as "physical and mental inactivity". It is interesting therefore to contrast these responses to those obtained from the "ex-addict" population studied by Lasagna et al 1955 who reported a far more positive subjective response to these drugs.

Further light on these population differences in subjective responses is revealed by the studies using the Addiction Research Centre Inventory (ARCI), an inventory of drug-related mood scales developed by Haertzen et al. (1963). The ARCI resulted from a series of studies using a population of "ex-addict" prisoners. Different types of drugs were studied in order to develop and classify subjective drug effects. Drugs used included the opioids, the hallucinogens such as LSD, stimulants such as the amphetamines and depressant drugs such as the barbiturates as well as the neuroleptics such as chlorpromazine.

These studies led to the development of a series of mood-related questions which were correlated by factor analysis into three main drug-mood categories:

1) Mood questions which are considered to describe feelings of **euphoria and well-being or general pleasant stimulatory effect**. These correlated with the drugs of the morphine group as well as those of the benzedrine (amphetamine) group. The mood scale is referred to as the MBG scale.

2) Questions which related to feelings of **sedation, tiredness, grogginess and drunkenness** which were correlated with the drugs pentobarbitone, chlorpromazine and alcohol. This scale shows a weaker correlation with morphine in the group of "ex-addict" volunteers. These mood scales were termed the PCAG.

3) Questions which described feelings of **dysphoria, irritability, delusions, hallucinations and an inability to concentrate** were correlated with the hallucinogen Lysergic acid diethylamide and were termed the LSD scale.

Most subsequent studies using these scales have indicated that in an "ex-addict" population morphine produces a dose-related increase in the MBG scale. Similar results have been obtained with heroin, methadone, dilaudid, pethidine and codeine; all drugs with a predominant affinity for the mu receptor.

The effect of these drugs on the PCAG (sedation) scale did not show such a consistent dose-dependent effect between studies, suggesting that in an "ex-addict" population sedative effects are more variable.

A recent and very comprehensive study (Jarvik et al., 1981) addressed the question of the correlations which might exist between subjective assessments of the effects of morphine and an objective measure of tolerance to pain. The volunteers were ten pairs of non-dependent



male monozygotic twins. Using subjective mood scales (which included subscales from the ARCI, and scales from the NIMH) the authors found that morphine (10 mg/70 Kg, intramuscularly), whilst it did increase the 'euphoric' scores, decreased the perception of 'clear thinking'. Interestingly, they found positive correlations between scores of both 'hostility' and 'anxiety' with the measures of the increased threshold and tolerance to the perception of a painful stimulus (plunging the hand into ice water at 0 - 1° C). The authors interpreted these findings as suggesting a relationship between decreased pain sensitivity and an increased arousal of the nervous system. This hypothesis is consistent with others concerning the physiology and pharmacology of pain and further serves to highlight the differences between the actions of the opioids and those of the general depressants of the nervous system such as alcohol, the barbiturates and the benzodiazepines.

To summarize the mood effect of the opioids, it first must be remembered that all of these studies were conducted in a laboratory under obviously experimental conditions. The considerable role of "set" and "setting" (expectancy and environment) in drug effects reminds one that these results should be interpreted with caution. Nevertheless, it seems that the effects of opioids in naive, non-dependent volunteers are predominantly unpleasant and sedative, whilst in habitual users, the effects are predominantly euphoric. The effects however, seem to change in opioid users once dependence develops. When "ex-addicts" have received the drug on a regular basis, such as to develop tolerance and become physically dependent, the subjective responses change somewhat. From the initial acute responses of predominant euphoria, the sedative effects become more prominent. Scores on the PCAG scale of the ARCI become significantly increased and subjects become tired and withdrawn (Haertzen and Hookes, 1969; Martin et al, 1973). The atropine-like effects of pethidine, as well as the toxicity of its metabolite, provide this drug with the additional psychotomimetic effects in high doses. The psychotomimetic

effects reported with pentazocine are presumably related to its affinity for the sigma receptors.

## 2.4 The Effects of the Opioids on Performance Measures.

### Morphine, heroin, codeine, methadone.

The effects of the opioids on mood, reviewed above would lead one to expect that these drugs would impair performance skills in non-tolerant volunteers. However, results of performance studies have not been consistent, some reporting no effect at all and others demonstrating some measurable impairment. For example, some studies with either opioid naive or "ex-addict" volunteers have failed to demonstrate any significant performance impairment with morphine (Bauer and Pearson, 1956; Christie et al., 1958; Fraser et al., 1963; Jarvik et al., 1981; Bourke et al., 1984) whilst others (Wikler et al., 1965; Smith et al., 1962; Linnoila and Hakkinen, 1974; Rothenberg et al., 1977; Bradley and Nicholson, 1986) have shown some evidence of impairment.

#### (i) Studies involving opioids administered intravenously.

A very important early study and one in which the mode of administration most closely resembles the illicit "street" use of opioids is that of Fraser et al (1963). It is one of only very few studies which have administered the drug intravenously. Using "ex-addict" volunteers the investigators provided a regular administration of heroin on an increasing dosage schedule to a point of development of tolerance and physical dependence. During this period several measures of physical activity as well as performance on a tracking task were recorded.

Five "ex-addict" volunteers, who were in prison for narcotic offences were used. They had a history of between 12 and 15 years of previous opioid dependence and had been opioid free for several months before the study began.

All volunteers were given an intravenous injection, four times per day throughout the experiment though the nature of the drug (placebo or heroin) or its dose were not revealed to the volunteers. The study began with the intravenous administration of only saline (as a placebo) for the first 30 days. However, on day 17 one dose of heroin (8 mg) was given. Beginning on day 31 heroin administration began with a dose of 10 mg per day (2.5 mg four times per day). This was gradually increased to an average of 95 mg per day. The high dose was then maintained over a period of 45 days.

The data collected predominantly concerned aspects of physical activity but also included performance on a pursuit rotor and clinical observations of temperature, pulse rate respiratory rate and blood pressure. At regular half hour intervals observers recorded the time subjects spent lying horizontal on the bed, hours of sleep and hours off the research ward. In addition, over each day between 6 am and 10 pm, measurements of general activity as determined by a pedometer were recorded.

With this design it was possible to compare the changes of activity under the placebo condition with the heroin condition. The initial effects of heroin within the first four days were in the direction of an increase in activity. The effect of the single 8 mg dose on day 17 was conspicuous for a "sudden display of energy in cleaning their rooms ..." This increase in activity was also observed in pedometer recordings for that day.

These effects on activities were consistent with those of acute heroin or morphine on subjective mood states described above. Similarly, the effects of the continued (chronic) heroin administration then showed a significant reduction in activities; a result which also is consistent with the studies on mood effects. The prolonged use, and dependence upon, opioids produced an apparent tolerance to the euphoric, mood-stimulatory effects and the dominance of the subjective feelings of sedation.

The results on the pursuit rotor indicated a

tendency for a slight though non-significant reduction in performance (compared with the plateau reached in the placebo condition) at the beginning of heroin administration, an effect which lasted about 12 days. After this time there was a gradual improvement in the daily scores. The authors concluded that the evidence for the increase in physical activity is consistent with the frequent reports by the illicit users of opioids that the drug produces a "drive". This effect however, is short lived and is followed by a depression of activity. However, the depression of physical activity is attributed by the authors to a reduced responsiveness to ambient stimuli rather than to any effect on psychomotor performance or to any physical debility. The effects of the drug on the pursuit rotor suggested that there were no effects of chronic heroin on psychomotor performance

Bauer and Pearson (1956) also administered morphine intravenously, but did so by slow infusion over a two minute period. This method is not as closely associated with the "street" methods as that used by Fraser et al. (1963), nor was their volunteer population. Unlike the "ex-addict" population used by Fraser et al. (1963), Bauer and Pearson (1956) used volunteers recruited from those undergoing basic training in the US Air Force, and who, one would assume, were drug-naive. A dose of 8 mg morphine was used and the performance measure was the perceptual motor task of the United States Air Force, the SAM Multidimensional Pursuit test. This task required the subjects to manipulate throttle, stick and rudder controls to compensate random movements of four instrument pointers from the null position. There were no effects of this dose of morphine on the performance of this task. Performance under morphine was no different from that of the group given saline.

A more recent study which delivered morphine by intravenous infusion to normal, healthy, drug-free volunteers has added further evidence for an absence of effect on performance measures by morphine given by this route (Bourke et al., 1984). The dose was higher than that used by

Bauer and Pearson (1956) being 0.21 mg/Kg (15 mg/70 Kg). The rate of the drug infusion was, however not stated. The study was primarily concerned with the respiratory depression caused by morphine and diazepam during anaesthesia and the possible antagonism of this effect by physostigmine (an inhibitor of the enzyme cholinesterase). As part of the investigation, two performance tests were administered to the volunteers, the Trieger Dot Tests (TDT) and the Continuous Performance Test (CPT). The TDT is a test of psychomotor function commonly used by anaesthetists and the CPT, especially as used in this study, a measure of choice reaction time.

When tested twelve minutes after the delivery of morphine there was no change in either of the performance measures when compared with pre-drug scores or those after the administration of the placebo (saline). There was, however, a significant deterioration of performance on the CPT when the volunteers had been given diazepam 0.29 mg/Kg (i.e. about 20 mg/70 Kg). There was a strong trend, though not achieving significance, for diazepam to affect performance on the TDT. A comment by the authors worthy of note is that the dose of morphine (15 mg/70 Kg) is seldom associated with changes in the level of consciousness, whereas diazepam, 20 mg/70 Kg, may have considerable effect on the level of consciousness.

#### **(ii) Administration of opioids by intramuscular or subcutaneous injection.**

In a study which was concerned primarily with peculiarities of the differences in reaction time measures in schizophrenic patients and normal controls, Wikler et al. (1965) administered drugs, including morphine, to a group of ten "ex-addicts". Interestingly, when compared with the "normal" control group which consisted of ten members of staff (physicians, technicians and medical aids) of the Addiction Research Center (Lexington, Kentucky), the reaction times of the "ex-addict" group before being given the drug were "supernormally" short. Nevertheless, morphine (15 and 30 mg) significantly prolonged

measures of (simple) auditory reaction time when tested one hour after the drug had been given by intramuscular injection. As the drugs were given only to the "ex-addict" group, no post-drug group comparisons could be made. The same observation of "supernormally" short reaction times in "ex-addicts" or in chronic opioid users was later reported by Gordon (1970) and Rothenberg et al., (1977) and are discussed below.

The study by Jarvik and colleagues (1981) included with their battery of subjective mood tests, two timed psychomotor tasks, the digit-symbol substitution test (DSS) from the Wechsler Adult Intelligence Scale, and a test of tapping speed. After morphine (10 mg/70 Kg intramuscularly) had been given to the "non-addict" volunteers, scores on the DSS were faster, and those on the tapping test were slower. Both values were significant at  $p < 0.05$ . However, the authors considered that these values cannot be attributed to morphine *per se*, as practice and fatigue effects were apparent.

The effects of the administration of morphine or heroin by subcutaneous injection to "normal" volunteers was reported by Smith et al. (1962). Two separate experiments were conducted, each using a group of 24 male college and graduate students who were described as non-addicted. The first study compared the effects of morphine with placebo; the second compared morphine, heroin and placebo.

In experiment 1, the volunteers were tested under placebo (saline) or morphine (10 mg s.c.) conditions on a randomized basis, with testing conducted at intervals of at least one week. The test battery, which had a duration of 2 hours and twenty minutes, was presented to each subject twice; first beginning 40 mins and secondly 5 hours after the administration of the drug or saline. The test battery comprised eleven tests designed to appraise the mental functions of perception, learning and memory, and reasoning. Comparisons of scores achieved in the placebo or morphine condition were made by two-tailed t test. Significant impairment was reported for

scores taken under the morphine condition for four of the tests ( $p=0.1$  to  $p=0.01$ ).

Experiment 2 used a battery of five tests, only two of which were common to experiment 1. Morphine (10 mg), heroin (4 mg) or saline were administered subcutaneously and the test battery was begun 75 mins and again 3 hours 15 mins after the drug had been given. In this case morphine produced an effect ( $p = 0.05$ ) only on one test (coding). Strangely, the results of the second testing period which began 3 hours 15 mins after morphine, showed a significant impairment ( $p = 0.01$ ) in two of the tests (written addition and coding).

The interpretation of these data as presented is rendered difficult in view of the multiple comparisons made; twenty two in the first experiment and twenty in the second. Corrections for the possibility of an inflated Type I error associated with multiple comparisons were not made. However, it does seem extremely likely that if the data were to be examined using a composite of measures for each experiment, and the data for heroin and morphine were to be combined, there would be a significant effect of these drugs on the tests of mental performance.

In the studies reported above of the effects of morphine and heroin, we have a curious situation in which the effects of the drugs are most obvious only when given by the intramuscular or subcutaneous routes. This is somewhat surprising from a pharmacological point of view. For example, the recommended therapeutic doses of morphine vary according to the route of administration such that the dose recommended for subcutaneous or intramuscular use is 10 mg/70 Kg; when given orally, 10 to 30 mg; and the intravenous dose is 2.5 to 5 mg (Jaffe and Martin, 1985).

Variables other than the route of administration which could affect these results are the dose, the drug experience of the volunteers and the nature of the tests used. The study of Bauer and Pearson (1956) used sensitive measures, drug-naive volunteers and the intravenous administration

of 8 mg morphine and did not demonstrate performance deficits. The study which did demonstrate morphine and heroin effects on drug-naive volunteers by the subcutaneous administration of 10 mg morphine (Smith et al., 1962) used tasks of cognitive and higher order functions which proved sensitive.

### **Methadone and the methadone maintenance program.**

Since the introduction of the methadone maintenance program for the treatment of opioid dependence, there is now a substantial population of people ("addicts") taking a daily dose of methadone in a dose averaging 60 - 80 mg, but varying between 30 to 120 mg or more. One of the features of the methadone program is that within a very short time the "addicts" are able to re-enter society and often maintain stable employment. Certainly a very high proportion of them regularly drive a motor vehicle, either privately or for their employment. It is of obvious importance therefore that a complete understanding of the effects of methadone on driving skills, as well as on abilities to operate machinery, should be available.

Methadone is an agonist of the mu opioid receptors, in the same way as morphine. It shows cross tolerance with morphine and therefore can substitute for this drug in a morphine (or heroin) dependent individual. In fact, the only notable difference between the two drugs in this context is that methadone has a longer duration of action. In view of the cross-tolerance with morphine and its longer duration of action, methadone is often used in the detoxification of heroin-dependent persons. The dose can be slowly reduced and, because of the longer duration of action of methadone, the symptoms of the withdrawal syndrome are extended over a longer period of time and are therefore less severe.

The pharmacological basis for the use of methadone in the treatment of the heroin dependent individual rests primarily on these two facts; the cross tolerance of methadone with morphine (or heroin) and the fact that methadone

can effect this substitution on a stable basis for in excess of twenty-four hours. The maintenance of high blood opioid concentration so achieved is to be contrasted with the fluctuations of heroin blood levels which occur with its illicit street use. These fluctuations are associated with the strong stimulus to seek and to take another dose of the drug at frequent intervals. This stimulus is often called the "narcotic hunger". The attenuation of the "narcotic hunger" is a major advantage of methadone. Another consequence of methadone maintenance is the degree of tolerance to opioids which is developed. This often is far greater than the "addict" ever was able to achieve in their illicit use of heroin. It means that if the "addict" on the methadone program uses heroin again, the dose is usually insufficient to surmount the methadone tolerance. The absence therefore of drug reinforcement leads to the extinguishing of the drug using habit. Although this ideal is not always attained (Martin et al 1973), treatment within the methadone program usually produces a marked change in behaviour of the "addicts". They are far more amenable to counselling, and very commonly they are able to gain useful employment. The fact that the methadone is taken by mouth, usually as a syrup, avoids the very powerful reinforcing stimuli associated with the preparation for an intravenous injection or "hit".

An important feature of the methadone program is that once a stable dosage has been achieved, the individual is tolerant to most of the effects of the drug. In theory, therefore, they should be able to handle machinery or drive a motor vehicle as efficiently and safely as a non-user of opioid drugs. The studies of the effect of methadone on people under treatment within the methadone maintenance program have tended to confirm this hypotheses. There is even some interesting evidence that some aspects of their performance skills are even enhanced. For example, the methadone program client has shorter reaction times than the non-addicted opioid naive controls (Gordon, 1970; Rothenberg, 1977). Other studies have reported that no difference in performance

can be demonstrated between populations of methadone patients and control groups (Appel and Gordon, 1976; Lombardo et al., 1976; Kelley et al., 1978; Moskowitz & Robinson, 1985; Robinson and Moskowitz, 1985).

Appel and Gordon (1976) used the digit symbol substitution task (DSST) to assess differences between two groups of high dosage (80 - 120 mg/day) methadone maintenance patients, one with jobs, the other unemployed; and two control groups, one of drug-free former heroin users, and another drug-free group which had no history of opioid use. There were no indications that the attentional functions of methadone patients (as determined by the DSST) were adversely affected by the schedule of methadone dosage. The analysis of the correlations of the duration of methadone treatment within the methadone groups indicated that increasing duration of methadone treatment did not adversely affect attentional functions. However, the scores for the unemployed group of methadone patients were significantly lower than those of the other group, although they were within normal range for the task. The authors suggested a possible reason for the differences might be associated with the psychological problems which accompany unemployment.

A similar study by Lombardo et al. (1976) was designed to assess the differences in possible impairment between two (very similar) dosage groups (50 mg and 80 mg /day) of methadone maintenance patients. Testing on the Wechsler Adult Intelligence Scale failed to show any significant differences between these groups.

Kelley et al. (1978) administered a battery of tests designed to assess "the ability of subjects (methadone maintenance patients) to engage in necessary everyday activities". The experimental design compared the test performance one hour or twenty four hours after the last dose of methadone. The tests were of auditory threshold, distance perception, simple and differential reaction time, time perception, digit span (short term memory) and attention span. Thirty subjects who had been on a stable dosage for at least two

weeks and whose doses ranged from 20 to 120 mg (mean: 63 mg) were used. Duration of stay in the program was between 24 to 874 days (mean 240 days). The methadone dosage was given in orange juice and a placebo containing quinine in orange juice also employed. The volunteers were given an oral medication both before and after the tests were administered and were told that each contained half of their daily dosage. In fact, some received their total daily dose in the first juice and others received the placebo at this time. In this way a cross-over design was employed in which volunteers were tested on two occasions, either 24 hours after their previous dose or at one hour after. The design tested for any differences which might be associated with the increase or decline in blood concentration of methadone over the intervals between two successive doses.

Rothenberg et al. (1977) reported the relative stability of cognitive perceptual and perceptual-motor capacities of the methadone patients over the two testing times after dosage. There was a small, but significant, difference between the two testing times for the perception of distance. There were no treatment effects for auditory threshold, simple reaction time, time perception or digit span. For attention span, there was an interaction between treatment time and the gender of the patient; for differential reaction time there was an interaction between testing time and the preparatory interval. The interpretation of these results is difficult as the effects are subtle. Whether there is any decrement in the perception of distance might however warrant further investigation. The effects of methadone on visual mechanisms has been the most clearly defined measure and has been demonstrated in the studies of Rothenberg et al. (1980a,b) and Bradley and Nicholson (1986).

#### **Effect of methadone on oculomotor functions.**

The reaction time deficit to a visual signal which was produced by methadone in "non-addict" volunteers (Gordon 1970; Rothenberg et al., 1977) was interpreted by the latter authors as involving visuomotor mechanisms. These

authors have published the results of two studies to investigate this hypothesis both using "non-addict" volunteers. Two aspects of oculomotor functions have so far been examined, saccadic and smooth pursuit eye movements. Saccadic eye movements are rapid, and are made to follow rapidly moving targets; smooth pursuit movements are slow and continuous and are made to follow slow moving targets. Under normal conditions, saccadic movements incorporate basically two periods of delay. First is a delay between the rapid movement of the target and the time the eye begins to move to follow it. The second delay is the fixation of the fovea onto the target. Saccades to targets which move more than 10 degrees from the fovea are usually inaccurate and require a further adjustment for "fixation". These saccades more commonly fall short of the target. The delay in correcting for this inaccuracy is usually shorter than that between the movement of the target and the initiation of the saccade. Methadone at doses of 5 or 10 mg delayed both the initiation of the saccade and caused an increasing undershoot of the saccades as the magnitude of the target displacement increased (Rothenberg et al., 1980a). The effect of these doses of methadone on smooth pursuit movements indicated that the drug reduced the gain of smooth pursuit tracking without changing target-eye movement phase relationship. The nature of the effects on saccadic eye movements were such as to indicate that the effect was not on the motor component of eye movement but rather on a central sensory mechanism.

The implications of these findings are that under the influence of an acute dose of methadone, a non-tolerant, non-dependent individual will obtain less information about the target and will suffer a loss of visual acuity. These determinations were made using one dose of methadone on non-addict volunteers. Therefore, the effect of methadone on these measures in the methadone-tolerant patient stabilized in a methadone maintenance program has yet to be determined. The differences in the effect of acute methadone on "addicts" and "non-addicts"

on other performance measures lead one to expect that tolerance develops also to the drug effects on oculomotor function. However, this hypothesis remains to be tested. Related to this is the ability of the methadone maintenance patient to perform tasks which are more directly related to the skills required when driving a motor vehicle. Should the oculomotor deficits be affected, they should be apparent in driving-related abilities.

### **The methadone maintenance patient and driving-related abilities**

The studies of Rothenberg et al. (1980 a,b) involved the collection of sensitive measures of eye movements. The implication of the changes produced by acute methadone, or indeed of the improvements observed in the "addict" groups in the actual task of driving, is difficult to assess. In a series of studies Robinson and Moskowitz (1985) and Moskowitz and Robinson (1985) investigated the effect on driving-related skills of methadone in a population of patients in a methadone maintenance program. In a very comprehensive series of studies these authors have examined a range of human abilities important for handling a motor vehicle or industrial machinery.

#### **(i) Methadone maintenance: effects on visual acuity**

In their first study, Robinson and Moskowitz (1985) examined aspects of visual function with tests of static and dynamic visual acuity, rate of accommodation, peripheral field of vision and a divided attention task involving two visual detection tasks as well as a tracking task. The volunteers were 15 males who had been receiving for at least six months a stabilized dose of between 60 to 110 mg per day of methadone. The control group comprised 16 male, drug-free "ex-addicts". All but one of the tests (the peripheral field test) involved the recognition of the position of the break in Landolt C-rings. The subject recorded this position by means of a four way lever to indicate up, down left or right. Static visual acuity was measured at seven acuity

levels; dynamic acuity at 6 levels with the target moving at the rate of 60 degrees per second. The rate of accommodation was determined by the subjects viewing three Landolt C-rings presented in succession at three distances and with five different intervals between presentations. After the presentation of all three targets, the subject was required to indicate the position of the break in order of their presentation. The peripheral field test involved the subject viewing a central fixation light and responding to the illumination of other lights placed in an arc around the subject's peripheral vision at locations from 45 to 75 degrees from centre.

The divided attention task required subjects to respond to the peripheral lights at 25 and 45 degrees of centre as well as responding to changes in position of two C-rings within the central visual field whilst at the same time undertaking a tracking task. Performances on these tests were recorded on two occasions which coincided with the times before and after the daily methadone dose of the methadone program patients. The controls received no medication.

The results produced from this quite extensive assessment of visual functions as they might apply to the task of driving, indicated that there were no differences between the methadone group and the no-drug using controls. There were no differences within each group in performance at testing times 1 and 2 (before and after the daily methadone dose). The authors concluded that there was no evidence to suggest that patients stabilized on the drug within a methadone maintenance program were impaired in aspects of visual functioning which are likely to be important in the safe operation of automobiles or industrial equipment.

#### **(ii) Methadone maintenance: effects on visual search rate and on divided attention**

Robinson and Moskowitz (1985) followed this investigation by examining a more specific aspect of skills performance. Driving has been demonstrated by Stephens and Michaels (1963) as being a task which requires skill in the

performance of tasks of visual search and recognition and in compensatory tracking, and both of these tasks must be undertaken on a time-sharing basis. Robinson and Moskowitz therefore compared the abilities of a group of patients in a methadone program with those of a control group on a task of visual search and recognition.

The search and recognition task presented the subject with a series of numeral sets of two, four or six digits which were projected on to a screen. Each set size was presented as 48 trials (i.e. a total of 144 trials). The task was to determine as quickly as possible if the numeral "2" was a member of each set. Half of each set contained this numeral. Subjects were tested on two occasions, before and after the methadone maintenance group had received their daily dose of methadone. There were no differences between groups or within groups across testing times in either errors of detection or in the mean response times to detect the target stimulus.

The divided attention task comprised the simultaneous presentation of the search and recognition task and a compensatory tracking task. There were no significant differences between groups or between testing times on either the tracking task or on the response times to recognition of the target stimuli in the visual search task.

### **(iii) Methadone maintenance: effects on rate of information processing**

Within the same study the subjects were also tested on a task which measures the rate of information processing. In this test, a target is presented by a tachistoscope and, after a brief and variable interval (the inter-stimulus interval; ISI), is followed by a masking stimulus. The subject's task was to identify and record the stimulus (a series of four consonants). A total of 120 trials was presented at ISIs of between 30 and 75 msec. If the interval between stimulus and mask is brief enough it will interfere with the processing of the target stimulus. The time available for the transfer of the information from

the sensory storage system into short term memory is the effective duration of the visual image, before the onset of the masking stimulus.

There were significant between group differences in the rate of information processing when the ISI was greater than 60 msec., the methadone group taking longer to process the information. However, the results also indicated that there were no significant differences between testing times 1 or 2 for either group. The methadone group appeared not to be affected by the acute effects of the daily dose. More research is needed to understand the implications of this finding. It would be necessary for example to determine the effect of methadone on this measure using "non-addicts" or on "addicts" when given a dose significantly higher dose of methadone than that on which they have been stabilized. The reported slowing of information processing time is also of interest in the light of the evidence for the shorter reaction times to both simple and complex reaction times of "addicts" and "ex-addicts" described by Wikler et al. (1965), Gordon (1970), and Rothenberg et al. (1977). The inference from this is that the mechanism which is responsible for the shortening of the reaction times in "ex-addicts" (and which one might propose is excitatory) is being opposed by the mechanism which is responsible for the slowing of the rate of information processing (which one might assume is depressant). It would be interesting to know if any differences exist in the speed of information processing between groups of "ex-addicts" or "addicts" and a group of non-dependent, non-drug using volunteers.

### **(iv) Methadone maintenance: effects on tracking tasks**

Moskowitz and Robinson (1985) further examined the possible effects of chronic methadone by examining performance on three different tracking tasks. In two experiments, methadone maintenance patients and "ex-addict" controls were tested before and 2 hours after the methadone patients had received their daily dose of methadone. The three tasks were compensatory, pursuit and critical tracking task.



The compensatory task might be compared with the task of maintaining a vehicle on the road in windy conditions, when compensatory movements must be made to allow for the wind. The pursuit task is similar to the tracking of a vehicle through a continuous winding road. The critical task is a compensatory task which gradually increases in difficulty as the trial progresses. It was designed to be sensitive to the effects of stressors, and it forces the operator to their maximum level of performance.

The results for each of these tracking tasks indicated that there were no significant differences in performance across treatment sessions or between groups.

Moskowitz and Robinson (1985) and Robinson and Moskowitz (1985) have undertaken a comprehensive series of studies of the effects of methadone on patients who had been stabilized on a regular daily dose of the drug, and in which ten tests of performance skills covering a very wide spectrum of driving related abilities were used. These authors demonstrated that the patient stabilized on a methadone program does not show any significant impairment of these skills after the acute daily dose of the drug. Furthermore, the methadone patient shows skills which are not significantly different from those of the matched control group. The exception was in the test which measures the speed of information processing. Methadone patients appear to process information at a slower rate than the control group. The significance of this observation is unclear in the light of the significantly shorter reaction times demonstrated by the "addict" and "ex-addicts" as outlined above.

The authors concluded that "the apparent insensitivity of aspects of skilled performance to methadone effects indicates that such patients should not be considered as impaired in terms of their ability to perform complex tasks such as driving a motor vehicle."

The effects of methadone in relation to the methadone maintenance program may be

summarized:

1. The acute effect of methadone on an opioid naive subject is to produce a dose dependent increase in reaction time. Effects on eye movements indicate that there is some degree of reduction in visual acuity. It is also likely that there will be a reduction in the speed of information processing.

The degree of opioid tolerance of the new patient in a methadone program is difficult to determine. The initial effect of methadone on these individuals is therefore uncertain. Some methadone programs, such as those in prisons, often treat with methadone those prisoners considered to be at-risk of drug taking even though they may be drug-free at the time. It is prudent therefore to regard the newly inducted clients to the program with caution and advise them not to drive or to operate machinery. It is suggested that a period of 3 to 4 weeks of methadone be allowed to establish a stable dosage before they drive a vehicle or operate machinery.

2. Once on a stabilized dosage of methadone, there is no evidence to suggest that a patient is in any way impaired. Nor is there any evidence that such a patient will be impaired if the dose has to be increased, though some caution should be exercised until further data are available.

## **2.5 Epidemiology of Opioid Involvement in Road Crashes.**

As pointed out by Simpson (1986;1987), interpretation of epidemiological data requires the convergence of evidence obtained from epidemiological studies and experimental investigations. The experimental studies reviewed in this chapter suggest that the effects of opioids on skills performance are slight.

For reasons outlined earlier (Chesher,1985; Consensus Report,1985; Simpson, 1987), a correlation between the blood concentration of opioid with any degree of impairment has not

yet been reported, such a task being fraught with difficulties associated with the pharmacokinetics of the drugs. To date no study has collected blood from a control group of non-crash involved drivers, so the data available do not tell us very much. Alternative methods for data collection such as described by Terhune and Fell (1981), MacPherson et al., (1984), Perl et al. (1985; 1987), and Donaldson et al. (1986) which analyse other aspects of cause and culpability are being devised to overcome these methodological problems.

It is no doubt due to an awareness of these difficulties that there does not appear to have been any report of a controlled epidemiological survey to investigate the role of the opioids in road crashes this decade. Indeed, the studies reported in the 1960s and 1970s offer quite conflicting evidence for the role of the opioid drugs in road crashes. For example, Crancer and Quiring (1968), Edwards and Quartano (1978), and Smart and Fejer (1976) found a higher incidence of road crashes in populations defined as opioid users. On the other hand, Babst et al. (1973), Blomberg and Preusser (1974), and Maddux et al. (1975) all found there to be no difference in road crash incidence or in driving offences between clients enrolled in a methadone program and control groups.

It is instructive to note the differences between these studies as far as the selection of the test population is concerned. Those who reported a higher incidence of road crashes selected populations of opioid users from those who had been arrested for heroin use (Cancer and Quiring, 1968), or heroin addicts referred to a hospital (Edwards and Quartano, 1978), or opioid users from a high school student population (Smart and Fejer, 1976). On the other hand, the studies which found no reliable correlation between opioid use and road crashes or violations, selected populations from those enrolled in methadone maintenance programs (Babst et al., 1973; Blomberg and Preusser, 1974; Maddux et al., 1975).

Several factors require consideration in interpreting these data, one of which is the

consideration that the methadone program is a therapeutic intervention for opioid dependence. In addition, the pharmacological property of long duration of action of methadone would exert an influence on the well-being and general behaviour of those on the methadone program.

## 2.6 General Summary.

1. The specificity of the actions of the opioid drugs for the opioid receptors was noted. Some differences were also noted in both the specificity and actions of different opioids on the different opioid receptors. These differences appear to be of more importance in determining side effects of the drugs than in any differences in effects on psychomotor skills, though some dysphoric side effects could influence driving behaviour.

2. Evidence presented suggests that the effects of opioids on skills performance are slight in comparison with those of other receptor-specific drugs such as the benzodiazepines. The activity of the opioids is confined to those nerve cells which bear the opioid receptors. Therefore the effects of the opioids will depend upon the function of those opioid receptor-bearing cells. The nerve cells which respond to the benzodiazepines are presumably, therefore functionally more important in motor skills control than are those which bear the opioid receptors.

3. The precise mode of action of alcohol (ethyl alcohol) is still not understood, though evidence suggests a non-specific action (possibly on cell membrane function) which does not involve specific receptors. It is speculated therefore that alcohol may be capable of affecting all nerve cells. Any selectivity of action on specific nerve cell groups could be dependent on the rate of delivery of this drug to those cells. This in turn depends upon the nature of the cerebral circulation. The effects of alcohol on skills performance are much more obvious and severe than those of the opioids.

4. The actions of opioids show striking differences on different population groups with differing history of opioid use. The habitual opioid user develops a remarkable degree of tolerance to the drug's effects; drug free "ex-addicts" respond differently to an acute dose of opioid than do entirely opioid-naive individuals. Contrary to pharmacological expectation, the route of administration of the opioid does not seem to influence the effects of the drug on skills performance.

5. The effects on human mood and skills of the opioids are considered in relation to the drug and the populations using them. The strong analgesics are used legally and illegally. The legal use is essentially confined to hospitalized patients who are not likely to drive or operate machinery until after their discharge. The illicit opioids, notably heroin, are difficult to research because of variability in purity, potency, the dosage used and the frequency and duration of its use. However, studies on the acute effects of opioids in populations of "addicts" and "ex-addicts" suggest that psychomotor performance impairment is slight.

6. Changes in medical practice dictated by economic difficulties has seen the increasing use of short acting opioids for outpatients undergoing surgical or diagnostic procedures. Fentanyl is an opioid which is commonly employed in these cases because of its short duration of action. However, recent studies have demonstrated significant impairment which would be experienced by the patient at the time they would normally be discharged.

7. Opioids such as codeine and propoxyphene, although much weaker than morphine and other opioids, deserve special consideration because of their much wider use in the population and their easy availability, frequently without prescription. These drugs are used only sporadically and by non-dependent individuals. Tolerance would be an uncommon occurrence. Evidence currently available indicates that impairment with these drugs is slight, but more research is indicated.

8. The use of methadone in the treatment of opioid dependence is also discussed. The doses used produce a high degree of drug dependence and the patients on the program do drive vehicles and operate machinery. There is no evidence to suggest that the psychomotor performance skills of an individual stabilized on methadone within the program can be considered to be impaired. However more information is required to be confident that new patients on the program, who are receiving their first few doses of methadone, are safe to drive or to operate machinery.

9. The difficulty or even impossibility of determining the degree of impairment of an individual by the analysis of a sample of blood means that properly controlled epidemiological surveys cannot at present be undertaken. Until this difficulty can be overcome, the true role of opioids as causative agents in road crashes cannot be determined. However, in view of the evidence reviewed in this paper, it is doubtful if these drugs can be considered to constitute a threat of anything near the proportions of that produced by alcohol.

\* \* \*

## Chapter 3

### METHODS

#### 3.1 The Tests of Human Skills Performance.

The purpose of the study is to examine the effect of methadone on the skills performance of those enrolled in a methadone program. The practical significance of the investigation is concerned primarily with skills related to driving a motor vehicle, though skills associated with the operation of machinery also deserve attention. Therefore, the selection of tests was directed to those skills related to driving.

Other factors considered in the selection of the tests were:

a) Consideration of the present knowledge of the behavioural effects of the opioids and specifically of the drug methadone. The current status of knowledge as to these effects are reviewed in Chapter 2. The evidence from this review suggests that the most likely property of opioids to adversely affect performance could be associated with the subjective, mood altering effects of the opioids. Included in these effects is drowsiness, and the response referred to by methadone clients as "nodding". An effect of the opioids on eye movements and visual acuity also deserves attention.

b) Consideration of the fact that those on the methadone program frequently use drugs other than opioids such as alcohol and the benzodiazepines. The study will include the investigation of the possible interaction between methadone and the benzodiazepines and alcohol. For this reason, the tests used should be of known sensitivity to these drugs.

b) Consideration of the specific population to be studied. The population is defined as those who

became involved in the use of heroin to the point that such use became destructive. Such people then presented for admission to the State Methadone Maintenance program.

Three tests were chosen for the study:

1. **Divided attention task** (Southern California Research Institute).

This comprises two tasks which are conducted simultaneously: a compensatory tracking task (CTT) and a visual search task (VST).

The complete task is computer presented on five separate viewing screens placed in the form of the five spots on a die. The tracking task appears on the central screen.

The tracking task takes the form of a fixed reference mark (a divided narrow vertical bar) in the screen centre and a horizontally moving cursor (a smaller bar fitting between the fixed bars) which moves randomly back and forth. Subjects use a control stick located at their preferred hands to attempt to maintain the moving cursor level with the reference bar.

Simultaneously with the tracking task, a search task (VST) is presented in the form of a matrix of 24 numerals shown on the four separate peripheral screens, 6 numerals to a screen. The numerals are changed randomly, but from time to time a "target" numeral appears (the numeral "2"). When the target numeral is detected by the subjects on any of the screens, they are required to press one of the four corresponding response buttons located at their non-preferred hands. If the correct response is made the target numeral changes to a "0". If a response is incorrect, no change in the display occurs. The duration of

each test run is 12 minutes plus a 15 seconds warm-up period (during which responses are not recorded). There are 48 visual search "targets" during each trial with an inter-stimulus interval mean of 15 seconds; range between 7 and 23 seconds.

The computer samples and maintains a record of the tracking error, which is the difference between the stimulus signal and the response. At the end of a trial the absolute tracking error is calculated. This is the error of the response from the zero position. The mean response time to correct target stimulus responses was taken as the measure for the visual search task.

## **2. Critical tracking task (Systems Technology Inc. California)**

A critical tracking task is a form of compensatory tracking which continually increases in instability and difficulty during the trial. The rate of increase in the instability of the task is directly related to the number and extent of errors made by the subject. At some point the instability of the system is beyond the capacity of the subject to control, and at that point the trial ends. The basic theory and validation of this task is provided by Jex et al. (1966), McDonnell and Jex, (1967), and Kelly, (1968). One measure ( $\lambda$ ) is recorded, being an index of the ability of the subject to stabilize the controlled instability of the system.

## **3. Vigilance task (The Mackworth clock).**

Vigilance is obviously an important factor in driving, particularly in light traffic when attentional demands on the driver are lower.

The Mackworth Clock test presents on the screen, twenty four dots in a circle like the digits on a clock. Each dot 'flashes' in clockwise sequence. A target stimulus occurs when the flashing skips a dot. The subject must press a key on the response board when a target occurs. The task has a duration of forty five minutes. The reaction time for each hit is recorded, as are misses and false positives. During the 45 min of the test, 20

stimuli are presented.

## **3.2 The Study Population and the Control Group.**

There are a number of variables which are associated with the behaviour of an individual enrolled on the methadone program, only some of which are related to the pharmacological effect of the drug methadone. The selection criteria for volunteers in the study rests solely on their membership of the methadone program. Membership is dependent upon a history of destructive use of heroin.

However, this criterion will embrace subjects with different degrees of exposure to methadone. Therefore, it was decided to include three groups of methadone clients according to their exposure to the drug. These groups also provide the opportunity to examine the effect of an acute dose of methadone on individuals with differing degrees of opioid tolerance.

### **(a) Stabilized clients**

As indicated in Chapter 2 (Review), the fundamental principles of the methadone program are that of the cross-tolerance between methadone and morphine, and the long duration of action of methadone in maintaining this cross tolerance with relatively stable plasma concentrations of drug.

As methadone programs have been underway in this State for some years, the greater proportion of clients enrolled in a program will have been stabilized on a dose of the drug and will exhibit a substantial degree of tolerance to most of the effects of methadone and of other opiates. Earlier studies (see review) have indicated that the skills performance of stabilized methadone clients are not affected by the drug.

However, cross tolerance to the opioids does not extend to other central depressant drugs. Clients in the methadone program commonly use alcohol and benzodiazepines and the possibility of an

interaction between these drugs and methadone was investigated.

The stabilized group comprised those clients who had been maintained on the same dose of methadone for at least six months. Members of this group attended the laboratory on four occasions. On occasions 1 and 2, the test battery was completed before and after the daily methadone dose. On the third and fourth occasions, tests were conducted before and after methadone as well as a dose of alcohol (on occasion 3) and diazepam (occasion 4).

**(b) Clients beginning on the program: their first dose.**

If methadone is to exhibit an acute effect on skills performance, one would expect it to be most noticeable after the first dose, or when the dose taken is increased. The acute effect of the drug would be expected at this time, before tolerance had been developed to the dose taken.

Volunteers for the second experimental group were drawn from those clients beginning the methadone program. Members of this group were given their first and third dose of methadone at the laboratory. These volunteers attended the laboratory on two days only, and were tested before and after taking their first and third daily dose of methadone.

Naturally, other factors would influence behaviour and performance on the tests of the volunteers in this group. One of these is the initial dose of methadone prescribed by the physician who must assess the degree of opiate tolerance already developed by the subject. This, it would be expected, would show considerable variation from subject to subject.

Another variable is the fact that by the time the volunteers attend the laboratory, it is very likely that they will be suffering, to various degrees, withdrawal from their last dose of heroin. One therefore might expect to observe an improvement in the performance on the tests after the first dose of methadone.

**(c) Methadone maintenance clients undergoing a dosage increase.**

Clients in the earlier stages of their treatment frequently require an upward adjustment of their dose of methadone. Volunteers for this group were those who were receiving an increase in their dose of methadone of 10 mg per day.

These volunteers attended the laboratory on two occasions, the first when they were tested before and after their usual dose, and the second occasion, before and after their increased dose.

**(d) The control groups.**

**(i) Ex-user controls.**

In view of the findings of Hagland and Furland (1978) and Kleinman (1978) that people who use heroin differ in a number of significant respects from those who do not, it is necessary to use as controls a group of volunteers who are ex-opiate users and who currently are drug free. These were recruited by a "snowball" technique by asking each volunteer to encourage a friend who had been a user of heroin, to participate in the study.

**(ii) Non-user controls.**

In view of an initial difficulty in recruiting ex-user controls who were willing to participate in the study, we included a group of non-user controls. These volunteers were recruited from University students and from those enrolling for unemployment benefits.

**Urinalysis**

A control for the possibility of use of drugs other than methadone by clients participating in the study was undertaken by the analysis of a urine sample collected before the each day of the experiment. In order to avoid the problems associated with the collection of urine samples at the laboratory, these were routinely collected at the methadone centres. The samples were analysed at the Oliver Latham Laboratories.

### 3.3 Procedure.

Volunteers were recruited from the following methadone centres in the Sydney metropolitan area: Rankin Court, Darlinghurst, and the Parramatta, and Chatswood Methadone Centres.

The purpose of the study, the nature of the treatments and the tests were explained to all volunteers and their informed consent obtained.

All subjects were conveyed to and from the laboratory by taxi. Upon arrival at the laboratory the tests were demonstrated to them and a practice run on each was given as described below. The tests were conducted in the same order throughout the experiment, with divided attention first, the critical tracking next and the Mackworth clock, the task of longest duration, was last.

#### Practice on the test battery.

Each test was fully described to the volunteers who then had a brief practice run under supervision to ensure that the task was fully understood. A complete run on the task was then completed before continuing with the description of the next test.

For the volunteers of Group 1 (the stabilized clients) who attended the laboratory on four occasions, the data for the first testing occasion was regarded as practice on the test battery and was not used in the analysis. However, as the clients in Groups 2 and 3 had not reached a stable dosage of methadone and could not be described as being in a stable state, we could not, for ethical reasons, ask these clients to defer their first dose or their increased dose of methadone

more than necessary for the sake of the experimental design. For this reason, we did not devote a full days testing to practice on the tests. The practice on the test battery for Groups 2 and 3 was, as described above, a complete run on each test after they had shown a full knowledge of the nature of the test.

#### Test schedule.

Each volunteer received their designated dose of methadone at the laboratory and after a wait of one hour to allow for drug absorption, the tests were repeated.

On the third test day, when alcohol was consumed by the stabilized methadone group and both of the control groups, the procedure after the completion of the pre-drug test run was as follows:

*Methadone taken ..... 0 mins*

*Wait ..... 0 to 20 mins*

*Alcohol consumed ..... 20 to 40 mins*

*Wait ..... 40 to 60 mins.*

Subjects were then submitted to breath analysis after which they completed the post-drug run on the test battery.

On the fourth day of the experiment, when the dose of diazepam was given, both methadone and diazepam were administered (by mouth) at the same time. Testing began after an absorption period of one hour had elapsed.

\* \* \*

## Chapter 4

### RESULTS

The dependent variable used in all comparisons was a composite score reflecting overall performance. The individual test scores were standardized and combined as follows:-

*[Divided Attention (mean absolute tracking error) + Divided Attention (visual search reaction time)] - [Critical tracking (lambda) + Mackworth clock misses]*

A numerical increase in the composite score therefore represents poorer performance.

#### Planned analyses

The initial analyses were planned to compare the performance of the various methadone groups before and after their prescribed dose of methadone with that of the control and ex-user groups.

There were two between-subject (group) effects of potential interest :

- (i) the presence or absence of methadone, and
- (ii) the subject's history of drug use.

Comparisons were planned on the first effect, and post-hoc analyses were to be conducted if the performance of the ex-users differed reliably from that of the controls who reported no regular use of opiates.

There were also three within-subject effects :

- (i) Pre-dose versus post-dose;
- (ii) The presence or absence of alcohol;
- (iii) The presence or absence of diazepam.

All planned analyses were conducted using a groups x repeats ANOVA program based on the regression model.

The results of the study fall into two groups :-

**Analysis : Group 1.** The comparison of the performance of the **stabilized** group with that of the normal controls and the ex-user groups.

Performance for these groups are compared for the second third and fourth days of testing, i.e. the effects before and after (a) methadone alone, (b) methadone with alcohol, and (c) methadone with diazepam.

**Analysis : Group 2.** The comparison of the performance of the **new clients** group and the **increased dose** group with the normal controls and the ex-user groups. These comparisons were of the effects of methadone only, or in the case of the control groups, no drugs at all, and were of the performance measure on the two days these clients attended the laboratory.

**Variability of the data.** The variance of the data was not equally distributed throughout the groups. Table 1 presents the mean of the performance measure for both testing occasions on Day 2 of testing. On this day, the only drug involved was the dose of methadone for the groups receiving this drug.

Table 1.  
*Mean of the pre- and post-dose performance scores of day 2 (S.E.M. = Standard Error of the Mean)*

GROUP	MEAN	±S.E.M.
ALL GROUPS	-0.0359	0.45
METHADONE	0.1104	0.71
INCREASE	0.1690	0.89
STARTERS	2.4275	1.79
EX-USERS	-1.8414	0.48



Table 2.

*Group 1 analysis: Stabilized methadone clients compared with normal controls and the ex-user group.*

---

**(a). Between Subjects Contrasts**

<u>Controls</u>	<u>Stabilized</u>	<u>Ex-Users</u>	
1	0	-1	Control v Ex-users
-1	2	-1	Stabilized v All Others

These between-group contrasts examine any differences between the groups over the six testing occasions on Days 2, 3 and 4.

**(b). Within Subjects Contrasts**

<u>No drug</u>		<u>Alcohol</u>		<u>Diazepam</u>		
<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	
1	-1	0	0	0	0	Pre v Post (repetition)
1	-1	-1	1	0	0	Pre v Post x No drug v ethanol
1	-1	0	0	-1	1	Pre v Post x No drug v diazepam

---

**Blood alcohol concentrations.**

The mean blood alcohol concentration measured twenty minutes after the completion of drinking, which in turn had been undertaken over a period of twenty minutes were as follows:

(a) For all 64 volunteers : 0.064 g per 100 ml blood ( $\pm 0.015$  S.D.);

(b) For the controls: 0.062 g% ( $\pm 0.012$  S.D.);

(c) For the methadone maintenance group: 0.060 g% ( $\pm 0.012$  S.D.);

(d) For the ex-user group: 0.072 g% ( $\pm 0.016$  S.D.).

The contrasts used in the Group 1 analysis are listed in Table 2. Contrast 1 examines for effects on Day 2 (no drugs other than methadone in stabilized group), e.g. practice effects, fatigue or boredom. Assumption is that this will represent pre-post practise fatigue effects on days 3 and 4.

Contrast 2: effects of ethanol on performance controlling for repetition effects (as in contrast 1).

Contrast 3: as for contrast 2, though effect of diazepam.

The interaction of these three (within group) contrasts with the first four between-group contrasts indicates whether the repetition or the drug effects differed between the groups.

Since there was no clear prediction as to the outcome of the study, a post-hoc analysis of the data was conducted. This involved defining critical F values for each family of contrasts using the method recommended by Hall and Bird (1986).

**Analysis: Group 1. Stabilized methadone group, controls and ex-users.**

Subjects used in this analysis comprised 26 stabilized methadone clients, 19 normal controls and 19 ex-users. The results of this analysis, with obtained and critical F values are shown in Table 3.

Table 3.

*Stabilized methadone clients compared with normal controls and the ex-user group. Obtained and critical F ratios. \* Significant,  $p < 0.05$*

EFFECT	Obtained F	Critical F
<b>I. Group</b>		
(a) Controls v ex-users	0.05	6.3
(b) Stabilized v all others	6.39 *	6.3
<b>II. Repetition</b>		
Day 2 : pre v post test	0.94	13.1
<b>III. Group x Repetition</b>		
(a) Controls v ex-users x pre v post	0.03	17.25
(b) Stabilized v all others x pre v post	0	17.25
<b>IV. Repetition x Drug</b>		
(a) Pre v post test x no drug v ethanol	41.01 *	13.1
(b) Pre v post test x no drug v diazepam	31.92 *	13.1
<b>V. Group x Repetition x Drug</b>		
(a) Controls v ex-users x pre/post x ethanol	0	17.25
(b) Stabilized v others x pre/post x ethanol	0.2	17.25
(c) Controls v ex-users x pre/post x diazepam	1.27	17.25
(d) Stabilized v others x pre/post x diazepam	0.83	17.25

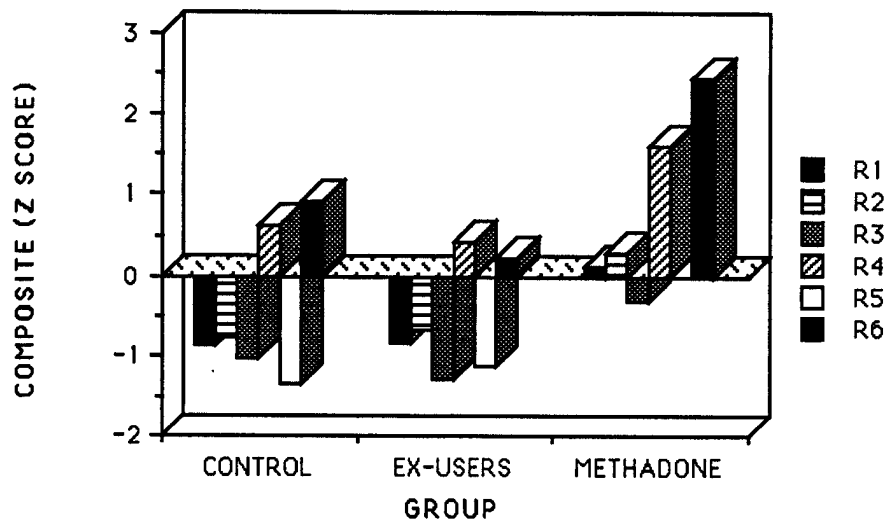
As there was no difference in the group comparison between the normal control group and the ex-users (Group I a), the comparison between the stabilized group scores and that of the combined control groups was examined (Table 3. I b; III a; V a and c).

The contrast Group I (b) (Table 3) indicates that there was a difference in the overall performance scores between these groups over the six testing occasions on Days 2, 3 and 4 which just achieved significance ( $F=6.39$ ; critical  $F=6.3$ ). This indicates that both the normal controls and the ex-user groups performed better overall than did the stabilized methadone group. However, an examination of the other contrasts indicates that this difference cannot be explained by the effect

of the acute dose of the drug methadone.

In the within-subject contrasts, that comparing pre-post baseline performance, neither the repetition effect (Table 3. II), nor the group x repetition interaction (Table 3. III b) approached significance. These results indicate that the acute dose of methadone to the stabilized group was without effect on the performance measure when compared with the combined control and ex-user groups, which did not receive methadone. All groups, of course, received alcohol and diazepam on the appropriate testing occasions as described in Methods.

The repetition x drug contrasts (Table 3. IV a and b) reveal that very strong effects in the



*Figure 1.* Analysis group 1. Results for the performance measure for control, ex-user and the stabilized methadone groups. R1 to R6 are repeats on days 1 to 3. The effects of alcohol and diazepam are represented in repeats 4 and 6 respectively.

direction of impaired performance were seen over all groups for both ethanol ( $F= 41.01$ ; Critical  $F= 13.1$ ) and diazepam ( $F= 31.92$ ; Critical  $F= 13.1$ ). However, neither the group  $\times$  repetition  $\times$  ethanol (Table 3. V b), nor the group  $\times$  repetition  $\times$  diazepam (Table 3. V d) interaction approached significance. This indicated that although both ethanol and diazepam significantly impaired performance of all groups tested, there was no difference in the extent of this impairment between the methadone and the control groups.

These results are depicted in Figure 1.

#### **Analysis: Group 2. New clients and increased methadone dose groups.**

The performance of the groups of new clients and those taking an increased dose of methadone were compared with the performance of the normal controls and the ex-users, as for the first analysis. However, in these comparisons, the

first two days of testing of the control groups were used to assess the relative performance measures. The two methadone groups of course were only tested on two days.

Subjects used in this analysis comprised 10 new clients taking their first and third doses of methadone, 22 taking an increased methadone dose on the second day, 18 normal controls and 17 ex-users. These numbers were those for whom a complete set of data were available for analysis. The contrasts examined for these groups are shown in Table 4.

#### **(a) Between subject contrasts.**

The first between group contrast examines differences between the two control groups.

The second and third between group contrasts examine differences between the combined controls and the new and increased dose clients.

Table 4.

*Group 2 analysis: The new clients and increased dose clients, controls and ex-users.*

---

(a) **Between subjects contrasts**

New	Incr.	Contr.	Ex-users	
0	0	1	-1	Control v Ex-users
2	0	-1	-1	New v control & ex-users
0	2	-1	-1	Increase v control & ex users

(b) **Within subjects contrasts**

First day		Second day		
<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	
1	-1	0	0	Pre v Post - first day
0	0	1	-1	Pre v Post - second day
1	-1	-1	1	Pre v Post x first v second

---

(b) **Within-subject contrasts.**

First and second within-subject contrasts examine pre/post test differences on the first and second days of testing respectively.

The third contrast examines any difference in the pre/post change between the two days.

As with the Group 1 data, a post-hoc analysis was conducted. The results and the critical F value for each family of contrasts are shown in Table 5.

As can be seen from Table 5, the following points are emphasized. The group difference contrasts indicated that there were no differences between performance measures of the two control groups (Table 5: I a; IV a and b; V a). The data for both control groups were therefore combined for subsequent analysis for differences between the control groups and the two methadone groups (Table 5. I b and c). These contrasts indicated that there were no significant difference in the overall performance, i.e. across all testing

occasions, between the controls and the methadone groups. There was however a trend (non-significant) suggesting that both of the methadone groups performed less well overall on the tests than did the control groups.

The repetition contrasts examining the pre-post differences of all groups (i.e. both controls and both methadone groups) on days 1 and 2 indicated that there were no effect on day 1, but a significant effect on day 2 ( $F=14.61$ ; Critical  $F=8.57$ ). However, examining the interaction of group x repetition and their pre/post scores both for day 1 (Table 5. IV c and d) and day 2 (Table 5. IV e and f), it can be seen that none of the interactions was anywhere near achieving significance. These analyses indicate that the effect described above for the day 2 pre/post differences (Table 5. II b) could not be attributed to the effect of the daily dose of methadone. This effect is clearly illustrated in Figure 2 in which it can be seen that, in all groups, the pre/post differences were observed in the direction of worsened performance of the post scores for all

Table 5.

*Group 2 analysis: The new clients and increased dose clients, controls and ex-users. Obtained and critical F ratios \* Significant at  $p < 0.05$  † p/p = pre/post.*

EFFECT	Obtained F	Critical F
<b>I. Group</b>		
(a) Controls v ex-users	0.02	8.28
(b) New clients v all others	4.26	8.28
(c) Increase dose v all others	5.77	8.28
<b>II. Repetition</b>		
(a) Day 1 -pre v post test	0.4	8.57
(b) Day 2 -pre v post test	14.61 *	8.57
<b>III. Repetition x test day:</b>		
Pre- v post test x first v second day	8.47	8.57
<b>IV. Group x Repetition</b>		
(a) Controls v ex-users x pre/post (day 1)	0.03	15.09
(b) Controls v ex-users x pre/post (day 2)	0.3	15.09
(c) New clients v all others x p/p † (day 1)	0.03	15.09
(d) Increase v all others x p/p (day 1)	2.68	15.09
(e) New clients v all others x p/p (day 2)	2.22	15.09
(f) Increase v all others x p/p (day 2)	1.38	15.09
<b>V. Group x Repetition x Test day</b>		
(a) Controls v ex-users x p/p x days	0.08	15.09
(b) New clients v others x p/p x days	1.46	15.09
(c) Increase v others x p/p x days	0.11	15.09

groups.

Finally, from this analysis, the group x repetition x test day x pre/post scores interaction (Table 5. V b and c) showed that there were no differences between methadone groups and the combined control groups which even approached significance. There was therefore, no effect of the acute dose of methadone for either the new client or the increased dose groups, when compared with the control groups, neither of which received any drug.

These results are depicted in Figure 2.

#### **Overall Performance of the methadone groups.**

Due to the difference in overall scores noted between the groups taking methadone (in particular, the stabilized group) and those not taking methadone (the controls and ex-users), it was decided to further analyse this difference post-hoc. A difference between the groups on overall scores might be due to a number of

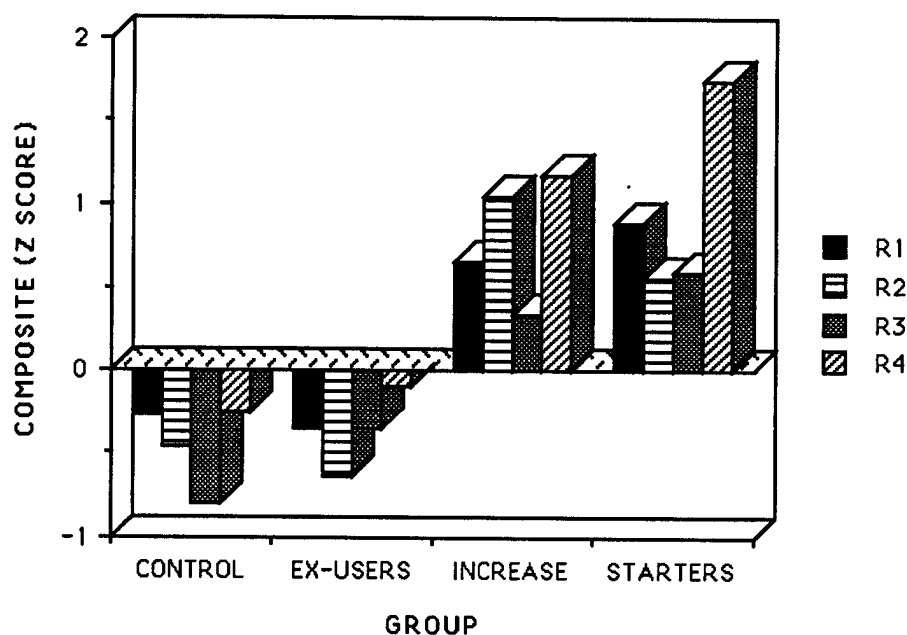


Figure 2. Analysis group 2. Results for the performance measure for control, ex-user and the methadone groups receiving an increase in dose or starting on the program. R1 to R4 are repeats on days 1 to 2.

factors which were in practice impossible to balance. To determine this, the educational attainment of the subjects, defined as the highest year of schooling successfully completed, was sought. This was obtained for 43 of the subjects whose scores were included in the previous analysis. It was not possible to obtain educational attainments for any of the control subjects whose scores were complete, but scores for approximately 81% of the stabilized subjects, 79% of the ex-users, 30% of the starters and 36% of the increased dose subjects were obtained.

The overall score for day 2 was used as an indication of performance. This score was available for all subjects, and should represent a more stable measure of performance than that observed in day 1. Four possible variables were

tested for their ability to predict the overall score on day 2: educational attainment, sex, age and the dose of methadone. The overall score for day 2 was used as the dependent variable in a regression equation in which all three potential predictors were entered. The results were as follows:

$$\text{Multiple } R^2 = .148 \quad (F_{4,38} = 1.65, p=0.181)$$

	Beta	t	p
Education	.26	1.47	.15
Dose	.41	2.30	.03
Age	-.15	-.97	.34
Sex	.10	.64	.53

Eliminating sex resulted in the following regression equation:

$$\text{Multiple } R^2 = .139 \quad (F_{2,40} = 2.10, p=0.12)$$

	Beta	t	p
Education	.25	1.42	.16
Age	-.16	-1.05	.30
Dose	.41	2.30	.03

Finally, eliminating age resulted in the following regression equation:

$$\text{Multiple } R^2 = .115 \quad (F_{2,40} = 2.59, p=.09)$$

	Beta	t	p
Education	.26	1.46	.15
Dose	.40	2.30	.03

The only variable included in the regression equation which was significantly related to overall score on the second day was the dose of methadone.

However, as none of the members of the two control groups were taking any methadone, this result really identifies the variable which correlates most closely with performance on the test battery as being the membership of a methadone group and not specifically the actual dose of the drug. It is of some importance therefore to determine if the actual value of the dose of methadone was correlated with performance skills. For this reason, the same analysis as above was conducted using only the results on day 2 of those groups which received methadone.

Four variables were identified which might be expected to influence overall performance on the tests. These were subject's age, sex, educational attainment and the dose of methadone. These were entered into a hierarchical multiple regression (using the SPSSX program) in which overall performance on day 2 was the criterion variable. This score

was calculated in the same way described earlier, except that both pre- and post- dose scores were summed to form the overall composite score. The order of entry of the potential predictor variables is shown in Table 6.

The sex variable indicated that females performed less well overall than males. Increasing years of education was associated with a slight decrease in overall performance. Age was not reliably associated with performance. The dose variable showed that increasing dose of methadone was associated with somewhat lower overall performance. However, dose was clearly not the most important variable associated with poor performance and it explained only a very small proportion of the variance in overall scores.

Given that the dosage level of 80mg is considered as clinically significant in dividing "high dose" from "medium dose" within the National Methadone Guidelines (1988), a comparison was made between these two groups. No reliable difference in overall performance on day 2 was found when the dose variable was dichotomized in this way.

The mean dose for all of the methadone clients was 70 mg (range 15 to 150 mg). The mean for the stabilized group was 85 mg (range 40 to 150 mg); the group receiving a dose increase, 67 mg (range 40 to 135 mg); and the group beginning on the program, 38 mg (range 15 to 60 mg).

### Performance on individual tests.

For purely descriptive purposes the results on each of the specific tests are depicted in Figures 3 to 10. The visual examination of these data suggests that the only test where the effect of the acute dose of methadone could have been of some intensity was that for missed targets on the Mackworth Clock (Figures 6 and 10). A post-hoc analysis was made of the scores on this test. The data for all of the groups which had received methadone were compared with those of the combined control groups. No reliable differences were found on this measure (see Table 7).

Table 6.

*Variables reliably associated with overall performance on day 2 in all subjects receiving methadone. The proportion of the total score variance explained by the entry of each variable is shown in the right-hand column.*

Variable	beta	t	p	prop. of variance
Sex	.57	3.94	.0004	.30
Dose	.32	2.31	.028	.08
Education	.29	2.12	.042	.06

Table 7.

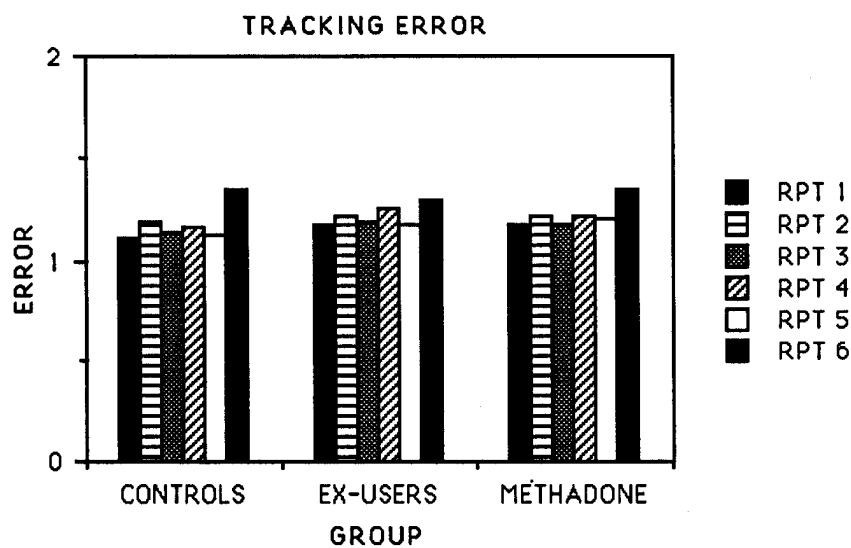
*Analysis of Mackworth Clock misses for day 2, pre- and post- trials.*

*\* Significant at  $p < 0.05$ .*

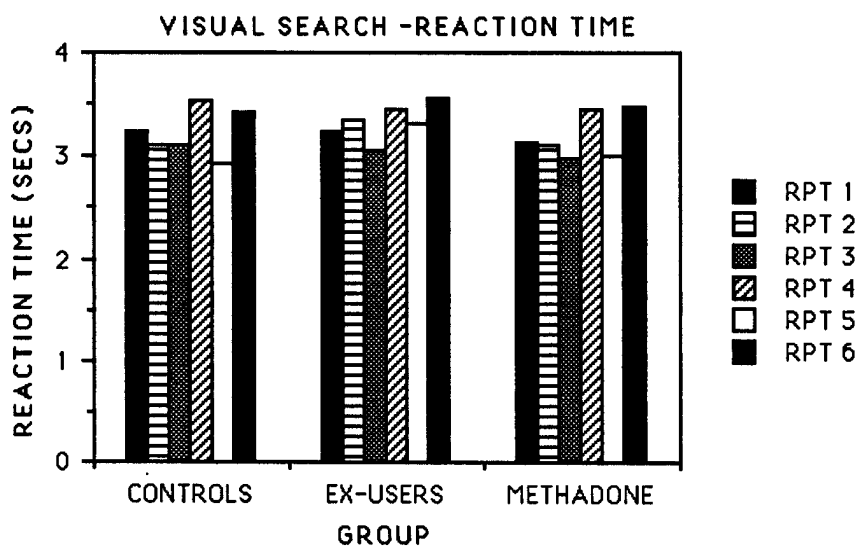
EFFECT	OBTAINED F	CRITICAL F <sup>+</sup>
<b>Group</b>		
Stabilized v Controls	1.05	8.28
Starters v Controls	0.61	8.28
Increase v Controls	1.14	8.28
<b>Repetition</b>		
DAY 2 Pre- v Post-	9.09*	8.60
<b>Group X Repetition</b>		
Stabilized v Controls x Pre- v Post-	0.89	14.92
Starters v Controls x Pre- v Post-	0.53	14.92
Increase v Controls x Pre- v Post-	1.38	14.92

<sup>+</sup> Critical F ratios were calculated using the number of repeats (4) which were recorded for all four groups.

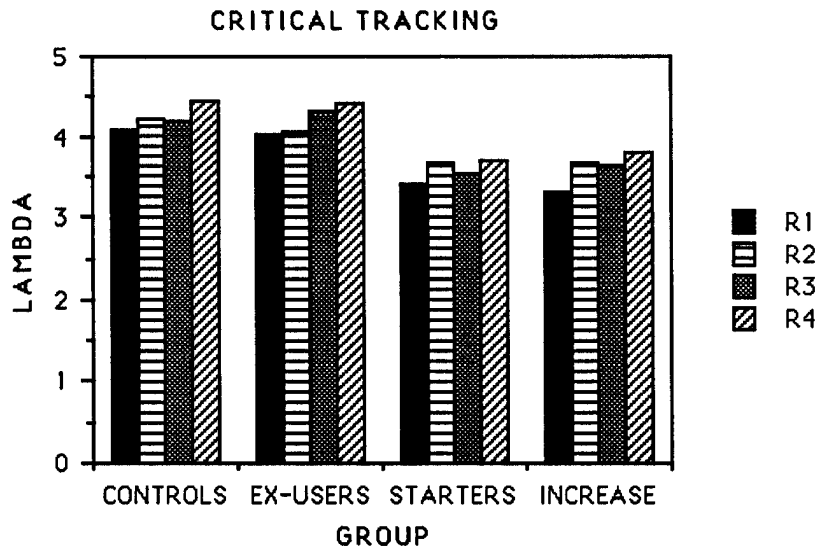




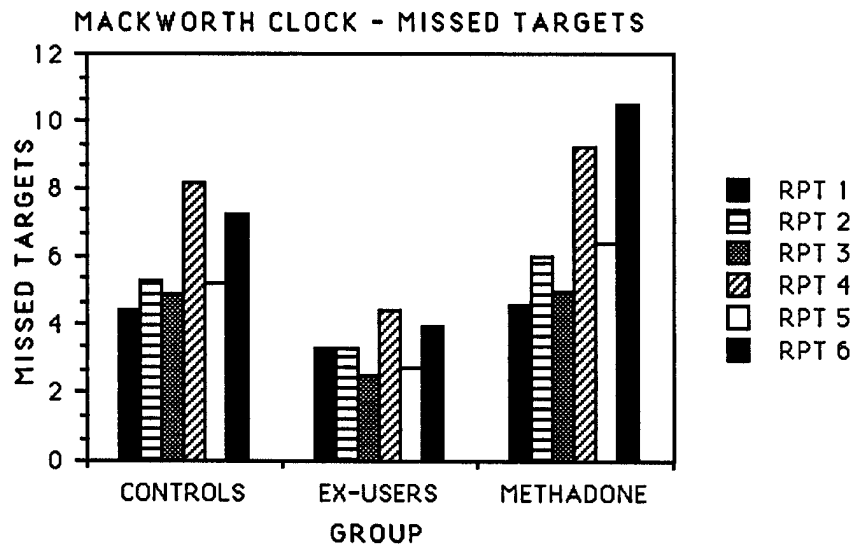
*Figure 3.* Analysis group 1. Tracking error for the divided attention task. Repeats 4 and 6 are results after alcohol and diazepam respectively.



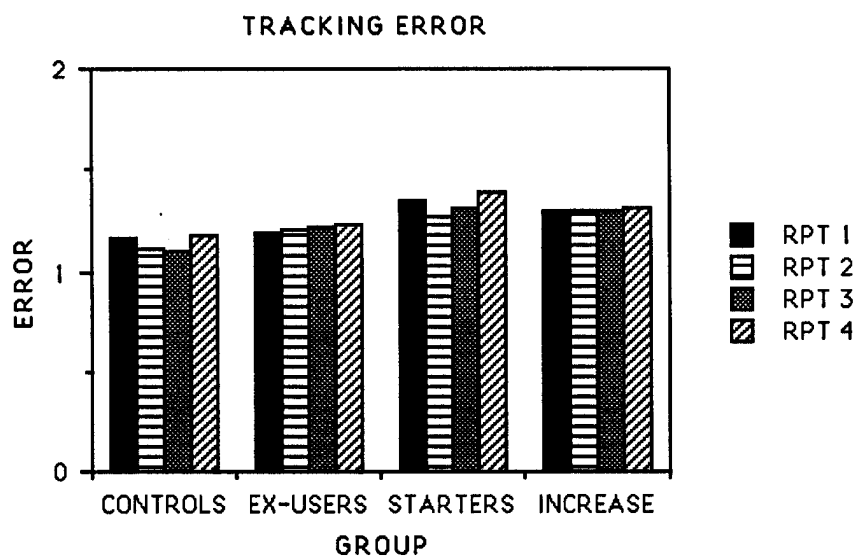
*Figure 4.* Analysis group 1. Visual search reaction time for the divided attention task. Repeats 4 and 6 are results after alcohol and diazepam respectively.



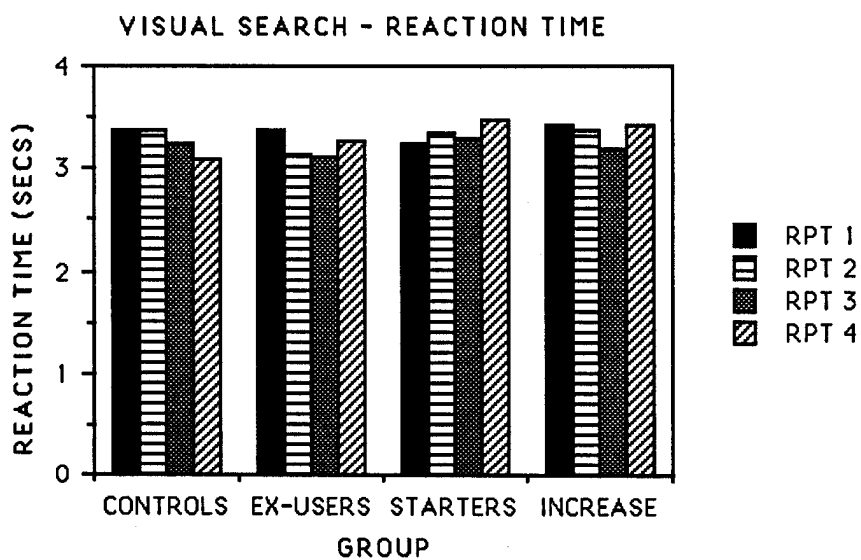
*Figure 5.* Analysis group 1. Critical tracking lambda. Repeats 4 and 6 are results after alcohol and diazepam respectively.



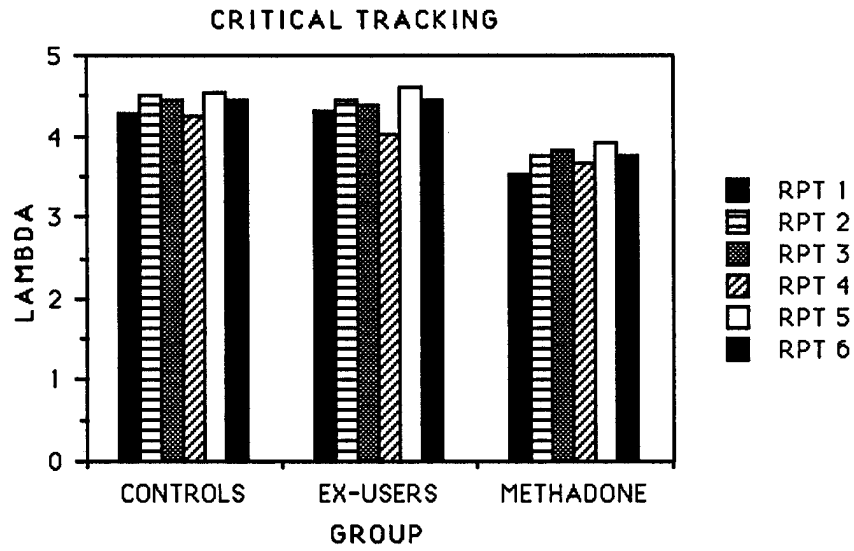
*Figure 6.* Analysis group 1. Mackworth Clock missed targets. Repeats 4 and 6 are results after alcohol and diazepam respectively.



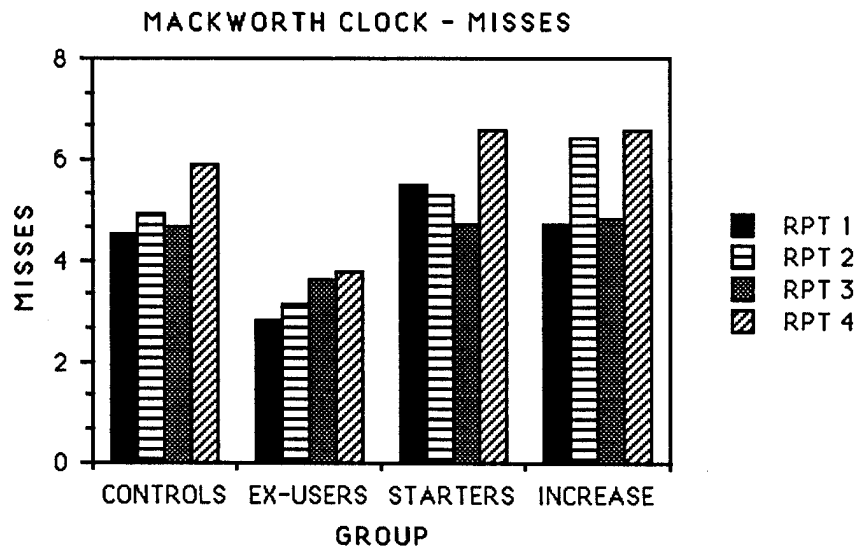
*Figure 7.* Tracking error for the divided attention task.



*Figure 8.* Analysis group 2. Visual search reaction time for the divided attention task.



*Figure 9. Analysis group 2. Critical tracking lambda.*



*Figure 10. Analysis group 2. Mackworth clock missed targets.*

## **Urinalysis.**

### **(a) Methadone maintenance group**

Urine samples from two of the methadone maintenance volunteers were morphine positive, both for two of the four days they attended the laboratory. Six volunteers were taking benzodiazepines on prescription and their urines were positive for these drugs on all four occasions of testing. One volunteer was taking tricyclic antidepressant and was positive for this drug on all four occasions.

All other urines from this group were positive for methadone but negative for other drugs.

### **(b) The ex-user group**

One volunteer was taking benzodiazepines on prescription and was positive for the drug on all four testing occasions. Three volunteers were positive for a benzodiazepine on one of the four

testing occasions. The concentrations were within the therapeutic range. One volunteer was, on one testing occasion, positive for dextromethorphan, an antihistamine.

### **(c) The control group.**

No drugs were detected in the urines of the control group.

### **(d) The new client group**

All new clients showed morphine positive urines on the first day of testing, though only six were morphine positive on the second testing day. One volunteer, although negative for morphine on day two, was positive for a benzodiazepine.

### **(e) The dose increase group.**

Six clients were positive for morphine on both testing occasions and one was positive for a benzodiazepine on the second testing occasion.

\* \* \*

## Chapter 5

### DISCUSSION

The tests employed in this study were chosen to examine those skills which are related to driving a motor vehicle as well as to be sensitive to the peculiar behavioural properties of the opioids. Of the pharmacological properties of the opioids reviewed in Chapter 2, those which one would expect to interfere with the ability to drive a motor vehicle, are the effects on mood states. These include drowsiness and an effect described as 'mental clouding'. These subjective states should be detected by the vigilance task, the Mackworth Clock. An effect of the opioids on eye movements has also been reported (Rothenberg et al., 1980a,b) and, if of sufficient severity within the context of driving, might be expected to adversely affect the peripheral visual search task.

The task of driving is in fact one which requires the division of attention between the task of tracking and a continuous visual search of the environment. The skills of tracking are tested at two levels within the test battery. The compensatory tracking test of the divided attention task is representative of the skills required to maintain the vehicle on the road during routine driving; and the critical tracking test is an indirect laboratory correlate of the more demanding skills of controlling the vehicle in an emergency. The test of divided attention, being the task which requires the subject to perform a tracking task at the same time as the visual search and recognition task is representative of the skills required to drive a motor vehicle. The Mackworth Clock, conducted over a period of forty minutes with only twenty target stimuli, is a sensitive test of vigilance. Driving a motor vehicle at night, with very light traffic, and where attentional demands are low,

is itself a task requiring the exercise of vigilance.

#### **The Volunteers: Methadone clients and controls.**

The methadone groups were chosen to represent the various sections of the methadone program. Broadly stated, the clients within a methadone program may be considered within three groups: those beginning on the program and taking their first dose of methadone; those for whom the dose is increased until a satisfactory dose has been attained. A third group which would comprise the greatest proportion of clients enrolled in the program are those who have achieved a stabilised on a dose of methadone and who have been on this dose for at least six months. The volunteers used in the study comprised representatives from each of these groups.

The controls, as discussed in the Methods section, included a group of ex-users of heroin and a group of non-opioid users. As was noted in the analysis, there were no differences between the two control groups on the performance measures, so the data for these two control groups were combined for comparisons with the methadone groups.

#### **Sensitivity of the test battery.**

In the analysis, the maximum sensitivity of the test battery is attained by the use of a composite, standardized measure from all tests. The test battery proved to be sensitive to the effects of alcohol, at a mean blood alcohol concentration of 0.064 g per 100 ml. The magnitude of this effect is illustrated by the magnitude of the obtained F ratio indicated in Table 3 (IV a). The

battery was also sensitive to a therapeutic dose (15 mg) of diazepam, as is also indicated in Table 3 (IV b). The concentration of alcohol (0.064 g%) is, in this country, within the low range of proscribed alcohol concentrations for driving a motor vehicle. In many other countries it is lower than the legal limit for blood alcohol concentration for driving a motor vehicle.

With this degree of impairment by alcohol and diazepam on the test battery in mind, it is important to note the absence of any reliable decrement in the effect of the acute dose of methadone for any of the three groups which received the drug. Furthermore, there is no evidence provided by this study that clients stabilized on a methadone program are affected by either alcohol or a benzodiazepine (represented by diazepam) in a manner which differs from that of the control groups. Both control groups and the stabilized methadone clients were significantly impaired by alcohol and diazepam, but the extent of this impairment did not differ between the groups. There was no evidence for an interaction between methadone and either alcohol or diazepam in this study.

It would seem reasonable to expect that those subjects receiving their first dose of methadone, or those receiving an increase in dosage would be more likely to exhibit an effect of the drug on performance skills. However, the present study provided no evidence for an effect of methadone in either of these groups (Table 5. IV c,d,e and f; V b and c). The starting dose for the first dose group ranged between 15 to 60 mg with a mean of 38 mg methadone. The increase in dose was, in all cases an increment of 10 mg. The findings are therefore in accord with those of Rothenberg et al. (1977) who reported that chronic exposure to methadone as in a methadone program will render a tolerance to the effects of the drug such that clients can take *"up to half again their usual daily maintenance dose without a reduction in performance on the tasks of their study."*

Examining the trends of performance change for the individual tests suggests that missed targets for the Mackworth Clock may show the

greatest sensitivity to the effects of the acute dose of methadone. This after all may seem appropriate in view of the reported effects of this drug in producing drowsiness or "nodding". However, a post-hoc analysis of the scores on this test showed no reliable differences between groups.

### Overall Performance on Tests.

The absence of an effect of an acute dose of methadone to clients who had been stabilized on a constant dose in a methadone maintenance program is in complete agreement with the previous study by Moskowitz and Robinson (1985) and Robinson and Moskowitz (1985). It is also consistent with the evidence outlined in the review of the literature of the effects of the opioids on skills performance (Chapter 2). In populations of opioid users, such as those enrolled in a methadone program, the effects of the opioids on skills performance appear to be slight.

However, in both analyses (Groups 1 and 2) of data in the present study, a difference between the overall performance in the tests between the methadone groups and the control groups was apparent. In the case of the group 1 analysis, the difference between the stabilized methadone group and the controls achieved statistical significance. In the case of the groups taking their first methadone dose and those receiving an increase in dose, the trend was apparent, but did not achieve statistical significance.

It is clear from the analysis that these differences were not due to the acute dose of methadone given during the test days of the study. In the light of these findings, there are many possible variables which might be considered in an attempt to explain these differences in performance skills. The only drug related variable within all of the test groups which was significantly related to the overall performance score was the dose of methadone. However within this population, which included both of the control groups (which of course did not receive any methadone at all), this finding indicated only that membership of a methadone group rather than the specific dose of

methadone was correlated with the poorer performance.

The second analysis indicated that sex, dose, and educational attainment all correlated reliably with the performance score. The gender variable indicated that the females of these test groups performed less well overall than did the males. The impression gained from discussion with the subjects was that the females reported less experience with "video games" which closely approximated the concept of the tests used. However, data for this measure were not collected and this conclusion rests only on conversation with the volunteers. This variable accounted for 30% of the variance.

If chronic methadone exposure were to have influenced the performance of the clients in the methadone program, one would expect there to be a correlation between dose of the drug and the performance measure. The dose of methadone did show a correlation with test performance, but accounted for only 8% of the variance. Furthermore, there was no significant difference in the comparison of test scores between the clients which received less than 80 mg methadone from those who received more than 80 mg per day. The dose of 80 mg is that considered in the National Methadone Guidelines (1988) as being the threshold dose for what is described as a "high dose". The guidelines state that "Doses above 80 mg per day are usually not required". The mean dose of methadone for all of the clients in the study was 70 mg with a range of 15 to 150 mg. There were 23 subjects who were receiving 80 mg or more per day of methadone.

It is clear from these analyses that dose, whilst being reliably associated with a somewhat lower overall performance on the tests, was not the most important variable associated with this, nor did it explain a substantial proportion of the variance. Furthermore, it is worthy of mention that the effects found in the present study with alcohol and diazepam were both larger in magnitude and statistically more reliable than those associated with the prescribed dose of methadone.

It is entirely arguable that the differences in overall performance between methadone clients and the controls can be interpreted in a manner which does not involve the consideration of any impairment of skills by methadone or any of the opioid drugs used by these individuals. Those who become heroin-dependent have been shown to differ in a number of ways from those who do not (Hagland and Furland, 1978; Kleinman, 1978). There has also been an increase in the evidence that personality disorders play a possible aetiological role in opioid dependence. For example, Craig (1988) using DSM-III criteria, considered that "*drug addicts have an array of personality disorders concomitant to their substance abuse*". The role of unemployment as a factor in skills performance was examined by Appel and Gordon (1976) who compared performance of high dosage methadone maintenance clients on the digit symbol substitution task of the WAIS with employed and unemployed clients. They noted, unexpectedly, that the scores of the unemployed group, although within the normal range, were significantly lower than those for the employed group. The authors discussed possible reasons for the differences.

Proceeding from this evidence we sought to determine the employment status of as many subjects as possible. It was quite striking to find that 21 of the 31 stabilized clients, whose overall performance was significantly poorer than the controls, were unemployed. The status of unemployment with associated factors of possible depression and personality disorders within this population could have been a contributory factor with the finding of poorer performance.

### **Methadone and opioids on the road.**

For reasons outlined in Chapter 2, the currently available data for the role of methadone and other opioids in road traffic accidents are not necessarily very reliable. However, the indications from the epidemiological studies of the road crash records of clients enrolled in a methadone program (Babst et al., 1973;



Blomberg and Preusser, 1974; and Maddux et al., 1975) are that these clients do not differ in the incidence of road crashes or in driving offences from those of a control group. Within these studies, the driving records of the methadone clients during the period before they were enrolled on the methadone program was also examined by Blomberg and Preusser (1974), who found that during their period of heroin involvement, and although they travelled more mileage than the national average, their road traffic record was still no different from that of the control group. The studies which did exhibit a correlation between opioid use and road crash incidence, also determined on a post-hoc basis, were for those heroin users selected from police

arrest records (Crancer and Quiring, 1968) or heroin addicts referred to a hospital (Edwards and Quartarno, 1978) or opioid users from a high school student population (Smart and Fejer, 1976).

If the role of factors such as personality disorders and unemployment are taken into account, the selection of the populations of opioid users for the epidemiological studies cited above must also be considered. There could indeed be a confusion of the factors which have been interpreted to be causally associated with road crashes. There is therefore some doubt on the interpretation that the opioid use is directly associated with the poor driving performance.

\* \* \*

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